ESC European Society of Cardiology

European Heart Journal (2021) **00**, 1–94
doi:10.1093/eurheartj/ehab364

ESC GUIDELINES

2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy

Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC)

With the special contribution of the European Heart Rhythm Association (EHRA)

Authors/Task Force Members: Michael Glikson * (Chairperson) (Israel), Jens Cosedis Nielsen* (Chairperson) (Denmark), Mads Brix Kronborg (Task Force Coordinator) (Denmark), Yoav Michowitz (Task Force Coordinator) (Israel), Angelo Auricchio (Switzerland), Israel Moshe Barbash (Israel), José A. Barrabés (Spain), Giuseppe Boriani (Italy), Frieder Braunschweig (Sweden), Michele Brignole (Italy), Haran Burri (Switzerland), Andrew J. S. Coats (United Kingdom), Jean-Claude Deharo (France), Victoria Delgado (Netherlands), Gerhard-Paul Diller (Germany), Carsten W. Israel (Germany), Andre Keren (Israel), Reinoud E. Knops (Netherlands), Dipak Kotecha (United Kingdom), Christophe Leclercq (France),

* Corresponding authors: Michael Glikson, Jesselson Integrated Heart Center, Shaare Zedek Medical Center and Hebrew University Faculty of Medicine, Jerusalem, Israel, Tel: +972 2 6555975, Email: mglikson@szmc.org.il.

Jens Cosedis Nielsen, Department of Clinical Medicine, Aarhus University and Department of Cardiology, Aarhus University Hospital, Aarhus N, Denmark, Tel: +45 78 45 20 39, Email: jenniels@rm.dk.

Author/Task Force Member affiliations: listed in Author information.

ESC Clinical Practice Guidelines Committee (CPG): listed in the Appendix.

ESC subspecialty communities having participated in the development of this document:

Associations: Association for Acute CardioVascular Care (ACVC), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council for Cardiology Practice, Council on Basic Cardiovascular Science, Council on Cardiovascular Genomics, Council on Hypertension, Council on Stroke.

Working Groups: Adult Congenital Heart Disease, Cardiac Cellular Electrophysiology, Cardiovascular Regenerative and Reparative Medicine, Cardiovascular Surgery, e-Cardiology, Myocardial and Pericardial Diseases.

Patient Forum

The content of these European Society of Cardiology (ESC) Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the *European Heart Journal* and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oup.com).

Disclaimer: The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy, and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgement, as well as in the determination and the implementation of preventive, diagnostic, or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

This article has been co-published with permission in the *European Heart Journal* and *EP Europace*. © the European Society of Cardiology 2021. All rights reserved.
The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article. For permissions, please email journals.permissions@oup.com.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Béla Merkely (Hungary), Christoph Starck (Germany), Ingela Thylén (Sweden), José Maria Tolosana (Spain), ESC Scientific Document Group

Document Reviewers: Francisco Leyva (CPG Review Coordinator) (United Kingdom), Cecilia Linde (CPG Review Coordinator) (Sweden), Magdy Abdelhamid (Egypt), Victor Aboyans (France), Elena Arbelo (Spain), Riccardo Asteggiano (Italy), Gonzalo Barón-Esquivias (Spain), Johann Bauersachs (Germany), Mauro Biffi (Italy), Ulrika Birgersdotter-Green (United States of America), Maria Grazia Bongiorni (Italy), Michael A. Borger (Germany), Jelena Čelutkienė (Lithuania), Maja Cikes (Croatia), Jean-Claude Daubert (France), Inga Drossart (Belgium), Kenneth Ellenbogen (United States of America), Perry M. Elliott (United Kingdom), Larissa Fabritz (United Kingdom), Volkmar Falk (Germany), Laurent Fauchier (France), Francisco Fernández-Avilés (Spain), Dan Foldager (Denmark), Fredrik Gadler (Sweden), Pastora Gallego Garcia De Vinuesa (Spain), Bulent Gorenek (Turkey), Jose M. Guerra (Spain), Kristina Hermann Haugaa (Norway), Jeroen Hendriks (Netherlands), Thomas Kahan (Sweden), Hugo A. Katus (Germany), Aleksandra Konradi (Russia), Konstantinos C. Koskinas (Switzerland), Hannah Law (United Kingdom), Basil S. Lewis (Israel), Nicholas John Linker (United Kingdom), Maja-Lisa Løchen (Norway), Joost Lumens (Netherlands), Julia Mascherbauer (Austria), Wilfried Mullens (Belgium), Klaudia Vivien Nagy (Hungary), Eva Prescott (Denmark), Pekka Raatikainen (Finland), Amina Rakisheva (Kazakhstan), Tobias Reichlin (Switzerland), Renato Pietro Ricci (Italy), Evgeny Shlyakhto (Russia), Marta Sitges (Spain), Miguel Sousa-Uva (Portugal), Richard Sutton (Monaco), Piotr Suwalski (Poland), Jesper Hastrup Svendsen (Denmark), Rhian M. Touyz (United Kingdom), Isabelle C. Van Gelder (Netherlands), Kevin Vernooy (Netherlands), Johannes Waltenberger (Germany), Zachary Whinnett (United Kingdom), Klaus K. Witte (United Kingdom)

All experts involved in the development of these guidelines have submitted declarations of interest. These have been compiled in a report and published in a supplementary document simultaneously to the guidelines. The report is also available on the ESC website www.escardio.org/guidelines

For the Supplementary Data which include background information and detailed discussion of the data that have provided the basis for the guidelines see *European Heart Journal* online

Keywords Guidelines • cardiac pacing • cardiac resynchronization therapy • pacemaker • heart failure • syncope • atrial fibrillation • conduction system pacing • pacing indications • alternate site pacing • complications • pacing in TAVI • bradycardia • temporary pacing

Table of contents

1 Preamble 6
2 Introduction 8
2.1 Evidence review 8
2.2 Relationships with industry 8
2.3 What is new in these guidelines 8
2.3.1 New concepts and new sections 8
2.3.2 New recommendations in 2021 9
2.3.3 Changes in cardiac pacing and cardiac resynchronization therapy guideline recommendations since 2013 13
3 Background 13
3.1 Epidemiology 13
3.2 Natural history 14
3.3 Pathophysiology and classification of bradyarrhythmias considered for permanent cardiac pacing therapy 14
3.4 Types and modes of pacing: general description 15
3.4.1 Endocardial pacing 15
3.4.2 Epicardial pacing 15
3.4.3 Cardiac resynchronization therapy (endo-and/or epicardial) 16
3.4.4 Alternative methods (conduction system pacing, leadless pacing) 16
3.4.4.1 Conduction system pacing 16
3.4.4.2 Leadless pacing 16
3.4.5 Pacing modes 16
3.4.6 Rate-responsive pacing 16
3.5 Sex differences 16
4 Evaluation of the patient with suspected or documented bradycardia or conduction system disease 16
4.1 History and physical examination 16
4.2 Electrocardiogram 18
4.3 Non-invasive evaluation 18
4.3.1 Ambulatory electrocardiographic monitoring 19
4.3.2 Exercise testing 19
4.3.3 Imaging 19
4.3.4 Laboratory tests 20
4.3.5 Genetic testing 20

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

4.3.6 Sleep evaluation ... 21
4.3.7 Tilt testing ... 21
4.4 Implantable monitors ... 21
4.5 Electrophysiology study ... 22
5 Cardiac pacing for bradycardia and conduction system disease ... 23
5.1 Pacing for sinus node dysfunction ... 23
5.1.1 Indications for pacing ... 23
5.1.1.1 Sinus node dysfunction ... 23
5.1.1.2 Bradycardia—tachycardia form of sinus node dysfunction ... 24
5.1.2 Pacing mode and algorithm selection ... 24
5.2 Pacing for atrioventricular block ... 26
5.2.1 Indications for pacing ... 26
5.2.1.1 First-degree atrioventricular block ... 26
5.2.1.2 Second-degree type I atrioventricular block (Mobitz type I or Wenckebach) ... 26
5.2.1.3 Second-degree Mobitz type II, 2:1, and advanced atrioventricular block (also named high-grade atrioventricular block, where the P:QRS ratio is 3:1 or higher), third-degree atrioventricular block ... 26
5.2.1.4 Paroxysmal atrioventricular block ... 26
5.2.2 Pacing mode and algorithm selection ... 27
5.2.2.1 Dual-chamber vs. ventricular pacing ... 27
5.2.2.2 Atrioventricular block in the case of permanent atrial fibrillation ... 27
5.3 Pacing for conduction disorders without atrioventricular block ... 28
5.3.1 Indications for pacing ... 28
5.3.1.1 Bundle branch block and unexplained syncope ... 28
5.3.1.2 Bundle branch block, unexplained syncope, and abnormal electrophysiological study ... 28
5.3.1.3 Alternating bundle branch block ... 29
5.3.1 Bundle branch block without symptoms ... 29
5.3.1.4 Patients with neuromuscular diseases ... 29
5.3.2 Pacing mode and algorithm selection ... 29
5.4 Pacing for reflex syncope ... 30
5.4.1 Indications for pacing ... 31
5.4.2 Pacing mode and algorithm selection ... 32
5.5 Pacing for suspected (undocumented) bradycardia ... 32
5.5.1 Recurrent undiagnosed syncope ... 32
5.5.2 Recurrent falls ... 32
6 Cardiac resynchronization therapy ... 32
6.1 Epidemiology, prognosis, and pathophysiology of heart failure suitable for cardiac resynchronization therapy by biventricular pacing ... 32
6.2 Indication for cardiac resynchronization therapy: patients in sinus rhythm ... 33
6.3 Patients in atrial fibrillation ... 35
6.3.1 Patients with atrial fibrillation and heart failure who are candidates for cardiac resynchronization therapy ... 35
6.3.2 Patients with uncontrolled heart rate who are candidates for atrioventricular junction ablation (irrespective of QRS duration) ... 35
6.3.3 Emerging novel modalities for CRT: role of conduction system pacing ... 36
6.4 Patients with conventional pacemaker or implantable cardioverter defibrillator who need upgrade to cardiac resynchronization therapy ... 37
6.5 Pacing in patients with reduced left ventricular ejection fraction and a conventional indication for antibradycardia pacing ... 38
6.6 Benefit of adding implantable cardioverter defibrillator in patients with indications for cardiac resynchronization therapy ... 38
6.7 Factors influencing the efficacy of cardiac resynchronization therapy: role of imaging techniques ... 39
7 Alternative pacing strategies and sites ... 40
7.1 Septal pacing ... 40
7.2 His bundle pacing ... 40
7.2.1 Implantation and follow-up ... 40
7.2.2 Indications ... 40
7.2.2.1 Pacing for bradycardia ... 42
7.2.2.2 Pace and ablate ... 42
7.2.2.3 Role in cardiac resynchronization therapy ... 42
7.3 Left bundle branch area pacing ... 43
7.4 Leadless pacing ... 43
8 Indications for pacing in specific conditions ... 44
8.1 Pacing in acute myocardial infarction ... 44
8.2 Pacing after cardiac surgery and heart transplantation ... 44
8.2.1 Pacing after coronary artery bypass graft and valve surgery ... 44
8.2.2 Pacing after heart transplantation ... 45
8.2.3 Pacing after tricuspid valve surgery ... 45
8.3 Pacing after transcatheter aortic valve implantation ... 46
8.4 Cardiac pacing and cardiac resynchronization therapy in congenital heart disease ... 48
8.4.1 Sinus node dysfunction and bradycardia—tachycardia syndrome ... 48
8.4.1.1 Indications for pacemaker implantation ... 48
8.4.2 Congenital atrioventricular block ... 48
8.4.2.1 Indications for pacemaker implantation ... 48
8.4.3 Post-operative atrioventricular block ... 49
8.4.3.1 Indications for pacemaker implantation ... 49
8.4.4 Cardiac resynchronization ... 49
8.5 Pacing in hypertrophic cardiomyopathy ... 49
8.5.1 Bradyarrhythmia ... 49
8.5.2 Pacing for the management of left ventricular outflow tract obstruction ... 49
8.5.3 Pacemaker implantation following septal myectomy and alcohol septal ablation ... 50
8.5.4 Cardiac resynchronization therapy in end-stage hypertrophic cardiomyopathy ... 50
8.6 Pacing in rare diseases ... 50
8.6.1 LongQT syndrome ... 50
8.6.2 Neuromuscular diseases ... 50
8.6.3 Dilated cardiomyopathy with lamin A/C mutation ... 51
8.6.4 Mitochondrial cytopathies ... 51
8.6.5 Infiltrative and metabolic diseases ... 51
8.6.6 Inflammatory diseases ... 51
8.6.6.1 Sarcoidosis ... 52
8.7 Cardiac pacing in pregnancy ... 52
9 Special considerations on device implantations and perioperative management ... 52
9.1 General considerations ... 52
9.2 Antibiotic prophylaxis ... 52
9.3 Operative environment and skin antisepsis ... 52

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

9.4 Management of anticoagulation 53
9.5 Venous access 53
9.6 Lead considerations 54
9.7 Lead position 54
9.8 Device pocket 54
10 Complications of cardiac pacing and cardiac resynchronization therapy 55
10.1 General complications 55
10.2 Specific complications 56
10.2.1 Lead complications 56
10.2.2 Haematoma 56
10.2.3 Infection 56
10.2.4 Tricuspid valve interference 56
10.2.5 Other 57
11 Management considerations 57
11.1 Magnetic resonance imaging in patients with implanted cardiac devices 57
11.2 Radiation therapy in pacemaker patients 59
11.3 Temporary pacing 60
11.4 Peri-operative management in patients with cardiovascular implantable electronic devices 61
11.5 Cardiovascular implantable electronic devices and sports activity 61
11.6 When pacing is no longer indicated 62
11.7 Device follow-up 62
12 Patient-centred care and shared decision-making in cardiac pacing and cardiac resynchronization therapy 63
13 Quality indicators 63
14 Key messages 65
15 Gaps in evidence 66
16 'What to do' and 'what not to do' messages from the guidelines 67
17 Supplementary data 70
18 Author Information 70
19 Appendix 70
20 References 71

Tables of Recommendations

Recommendations for non-invasive evaluation 18
Recommendation for ambulatory electrocardiographic monitoring 19
Recommendations for exercise testing 19
Recommendations regarding imaging before implantation 20
Recommendations for laboratory tests 20
Recommendations for genetic testing 21
Recommendation for sleep evaluation 21
Recommendation for tilt testing 21
Recommendation for implantable loop recorders 21
Recommendations for electrophysiology study 23
Recommendations for pacing in sinus node dysfunction 26
Recommendations for pacing for atrioventricular block 27
Recommendations for pacing in patients with bundle branch block 29
Recommendations for pacing for reflex syncope 32
Recommendations for cardiac pacing in patients with suspected (undocumented) syncope and unexplained falls 32
Recommendations for cardiac resynchronization therapy in patients in sinus rhythm 34
Recommendations for cardiac resynchronization therapy in patients with persistent or permanent atrial fibrillation 37
Recommendation for upgrade from right ventricular pacing to cardiac resynchronization therapy 37
Recommendation for patients with heart failure and atrioventricular block 38
Recommendations for adding a defibrillator with cardiac resynchronization therapy 39
Recommendations for using His bundle pacing 43
Recommendations for using leadless pacing (leadless pacemaker) 44
Recommendations for cardiac pacing after acute myocardial infarction 44
Recommendations for cardiac pacing after cardiac surgery and heart transplantation 46
Recommendations for cardiac pacing after transcatheter aortic valve implantation 48
Recommendations for cardiac pacing in patients with congenital heart disease 49
Recommendations for pacing in hypertrophic obstructive cardiomyopathy 50
Recommendations for cardiac pacing in rare diseases 50
Recommendation for patients with LMNA gene mutations 51
Recommendations for pacing in Kearns—Sayre syndrome 51
Recommendations for pacing in cardiac sarcoidosis 52
Recommendations regarding device implantations and peri-operative management 55
Recommendations for performing magnetic resonance imaging in pacemaker patients 59
Recommendations regarding temporary cardiac pacing 61
Recommendation when pacing is no longer indicated 62
Recommendations for pacemaker and cardiac resynchronization therapy-pacemaker follow-up 63
Recommendation regarding patient-centred care in cardiac pacing and cardiac resynchronization therapy 63

List of tables

Table 1 Classes of recommendations 7
Table 2 Levels of evidence 7
Table 3 New concepts and sections in current guidelines 8
Table 4 New recommendations in 2021 9
Table 5 Changes in cardiac pacing and cardiac resynchronization therapy guideline recommendations since 2013 13
Table 6 Drugs that may cause bradycardia or conduction disorders 17
Table 7 Intrinsic and extrinsic causes of bradycardia 18
Table 8 Choice of ambulatory electrocardiographic monitoring depending on symptom frequency 19
Table 9 Advantages and disadvantages of a 'backup' ventricular lead with His bundle pacing 42
Table 10 Predictors for permanent pacing after transcatheter aortic valve implantation 47

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Table 11 Management of anticoagulation in pacemaker procedures 53
Table 12 Complications of pacemaker and cardiac resynchronization therapy implantation 56
Table 13 Frequency of follow-up for routine pacemaker and cardiac resynchronization therapy, either in person alone or combined with remote device management 62
Table 14 Topics and content that may be included in patient education 64
Table 15 A selection of the developed quality indicators for patients undergoing cardiovascular implantable electronic device implantation 65

List of figures

Figure 1 Central Illustration 14
Figure 2 Classification of documented and suspected bradyarrhythmias 15
Figure 3 Initial evaluation of patients with symptoms suggestive of bradycardia 17
Figure 4 Evaluation of bradycardia and conduction disease algorithm 22
Figure 5 Optimal pacing mode and algorithm selection in sinus node dysfunction and atrioventricular block 25
Figure 6 Decision algorithm for patients with unexplained syncope and bundle branch block 28
Figure 7 Decision pathway for cardiac pacing in patients with reflex syncope 30
Figure 8 Summary of indications for pacing in patients >40 years of age with reflex syncope 31
Figure 9 Indication for atrioventricular junction ablation in patients with symptomatic permanent atrial fibrillation or persistent atrial fibrillation unsuitable for atrial fibrillation ablation 36
Figure 10 Patient's clinical characteristics and preference to be considered for the decision-making between cardiac resynchronization therapy pacemaker or defibrillator 40
Figure 11 Three patients with different types of transitions in QRS morphology with His bundle pacing and decrementing pacing output 41
Figure 12 Management of conduction abnormalities after transcatheter aortic valve implantation 47
Figure 13 Integrated management of patients with pacemaker and cardiac resynchronization therapy 58
Figure 14 Flowchart for evaluating magnetic resonance imaging in pacemaker patients 59
Figure 15 Pacemaker management during radiation therapy 60
Figure 16 Example of shared decision-making in patients considered for pacemaker/CRT implantation 64

Abbreviations and acronyms

AF	Atrial fibrillation
APAF	Ablate and Pace in Atrial Fibrillation (trial)
ATP	Antitachycardia pacing
AV	Atrioventricular
AVB	Atrioventricular block
AVJ	Atrioventricular junction
AVN	Atrioventricular node
BBB	Bundle branch block
BLOCK-HF	Biventricular versus RV pacing in patients with AV block (trial)
b.p.m.	Beats per minute
BRUISE CONTROL	Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial
BRUISE CONTROL-2	Randomized Controlled Trial of Continued Versus Interrupted Direct Oral Anti-Coagulant at the Time of Device Surgery
CABG	Coronary artery bypass graft
CARE-HF	CArdiac REsynchronization in Heart Failure (trial)
CHD	Congenital heart disease
CI	Confidence interval
CIED	Cardiovascular implantable electronic device
CMR	Cardiovascular magnetic resonance
COMPANION	COmparison of Medical therapy, PAcing aNd defibrillatION (trial)
CPAP	Continuous positive airway pressure
CRT	Cardiac resynchronization therapy
CRT-D	Defibrillator with cardiac resynchronization therapy
CRT-P	Cardiac resynchronization therapy-pacemaker
CSM	Carotid sinus massage
CSS	Carotid sinus syndrome
CT	Computed tomography
DANPACE	DANish Multicenter Randomized Trial on Single Lead Atrial PACing vs. Dual Chamber Pacing in Sick Sinus Syndrome
DDD	Dual-chamber, atrioventricular pacing
ECG	Electrocardiogram/electrocardiographic
Echo-CRT	Echocardiography Guided Cardiac Resynchronization Therapy (trial)
EF	Ejection fraction
EHRA	European Heart Rhythm Association
EMI	Electromagnetic interference
EORP	EurObservational Research Programme
EPS	Electrophysiology study
ESC	European Society of Cardiology
EuroHeart	European Unified Registries On Heart Care Evaluation and Randomized Trials
HBP	His bundle pacing
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

HFrEF	Heart failure with reduced ejection fraction
HOT-CRT	His-optimized cardiac resynchronization therapy
HR	Hazard ratio
HV	His–ventricular interval (time from the beginning of the H deflection to the earliest onset of ventricular depolarization recorded in any lead, electrophysiology study of the heart)
ICD	Implantable cardioverter-defibrillator
ILR	Implantable loop recorder
LBBB	Left bundle branch block
LGE	Late gadolinium contrast enhanced
LQTS	Long QT syndrome
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MADIT-CRT	Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (trial)
MI	Myocardial infarction
MIRACLE	Multicenter Insync RAndomized Clinical Evaluation (trial)
MOST	MOde Selection Trial in Sinus-Node Dysfunction
MRI	Magnetic resonance imaging
MUSTIC	MUltisite STimulation In Cardiomyopathies (trial)
NOAC	Non-vitamin K antagonist oral anticoagulant
NYHA	New York Heart Association
OAC	Oral anticoagulant
OMT	Optimal medical therapy
OR	Odds ratio
PATH-CHF	PAcing THerapies in Congestive Heart Failure (trial)
PCCD	Progressive cardiac conduction disease
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PM	Pacemaker
RA	Right atrium/atrial
RAFT	Resynchronization–Defibrillation for Ambulatory Heart Failure Trial
RBBB	Right bundle branch block
RCT	Randomized controlled trial
RESET-CRT	Re-evaluation of Optimal Re-synchronisation Therapy in Patients with Chronic Heart Failure (trial)
REVERSE	REsynchronization reVErses Remodelling in Systolic left vEntricular dysfunction (trial)
RV	Right ventricular/right ventricle
RVA	Right ventricular apical
RVOT	Right ventricular outflow tract
RVS	Right ventricular septum
S. aureus	*Staphylococcus aureus*
SAR	Specific absorption rate
SAS	Sleep apnoea syndrome
SCD	Sudden cardiac death
SND	Sinus node dysfunction
SR	Sinus rhythm
TAVI	Transcatheter aortic valve implantation
VKA	Vitamin K antagonist
WRAP-IT	World-wide Randomized Antibiotic Envelope Infection Prevention Trial

1 Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision-making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver, as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organizations. Because of their impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines). The ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

In addition to the publication of Clinical Practice Guidelines, the ESC carries out the EurObservational Research Programme of international registries of cardiovascular diseases and interventions which are essential to assess diagnostic/therapeutic processes, use of resources, and adherence to guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

Furthermore, the ESC has developed and embedded in this document a set of quality indicators (QIs), which are tools to evaluate the level of implementation of the guidelines and may be used by the ESC, hospitals, healthcare providers, and professionals to measure clinical practice as well as in educational programmes, alongside the key messages from the guidelines, to improve quality of care and clinical outcomes.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC subspecialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Clinical Practice Guidelines Committee (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to pre-defined scales, as outlined below.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Table 1 Classes of recommendations

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

©ESC 2021

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

©ESC 2021

real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/guidelines) and have been compiled in a report and published in a supplementary document simultaneously with the guidelines.

This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arose during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions, the guidelines are signed-off by all the experts involved in the Task Force. The finalized document is signed-off by the CPG for publication in the *European Heart Journal*. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, summary cards for non-specialists, and an electronic version

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access to the full text version of the guidelines, which is freely available via the ESC website and hosted on the EHJ website. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate, and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgement, as well as in the determination and the implementation of preventive, diagnostic, or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription.

2 Introduction

Pacing is an important part of electrophysiology and of cardiology in general. Whereas some of the situations requiring pacing are clear and have not changed over the years, many others have evolved and have been the subject of extensive recent research, such as pacing after syncope (section 5), pacing following transcatheter aortic valve implantation (TAVI; *section 8*), cardiac resynchronization therapy (CRT) for heart failure (HF) and for prevention of pacing-induced cardiomyopathy (*section 6*), and pacing in various infiltrative and inflammatory diseases of the heart, as well as in different cardiomyopathies (*section 8*). Other novel topics include new diagnostic tools for decision-making on pacing (*section 4*), as well as a whole new area of pacing the His bundle and the left bundle branch (*section 7*). In addition, attention has increased in other areas, such as how to systematically minimize procedural risk and avoid complications of cardiac pacing (*section 9*), how to manage patients with pacemakers in special situations, such as when magnetic resonance imaging (MRI) or irradiation are needed (*section 11*), how to follow patients with a pacemaker with emphasis on the use of remote monitoring, and how to include shared decision-making in caring for this patient population (*section 12*).

The last pacing guidelines of the European Society of Cardiology (ESC) were published in 2013; therefore, a new set of guidelines was felt to be timely and necessary.

To address these topics, a Task Force was established to create the new guidelines. As well as receiving the input of leading experts in the field of pacing, the Task Force was enhanced by representatives from the Association for Acute CardioVascular Care, the Heart Failure Association, the European Association of Cardiothoracic Surgery, the European Association of Percutaneous Cardiovascular Interventions, the ESC Working Group on Myocardial and Pericardial Diseases, as well as the Association of Cardiovascular Nursing & Allied Professions.

2.1 Evidence review

This document is divided into sections, each with a section coordinator and several authors. They were asked to thoroughly review the recent literature on their topics, and to come up with recommendations and grade them by classification as well as by level of evidence. Where data seemed controversial, a methodologist (Dipak Kotecha) was asked to evaluate the strength of the evidence and to assist in determining the class of recommendation and level of evidence. All recommendations were voted on by all authors of the document and were accepted only if supported by at least 75% of the co-authors.

The leaders (Jens Cosedis Nielsen and Michael Glikson) and the coordinators of this document (Yoav Michowitz and Mads Brix Kronborg) were responsible for alignment of the recommendations between sections, and several members of the writing committee were responsible for overlap with other ESC Guidelines, such as the HF guidelines and the valvular heart disease guidelines.

2.2 Relationships with industry

All work in this document was voluntary and all co-authors were required to declare and prove that they do not have conflicts of interests, as defined recently by the Scientific Guideline Committee of the ESC and the ESC board.

2.3 What is new in these guidelines

2.3.1 New concepts and new sections

Table 3 New concepts and sections in current guidelines

Concept/section	Section
New section on types and modes of pacing, including conduction system pacing and leadless pacing	3.4
New section on sex differences in pacing	3.5
New section on evaluation of patients for pacing	4
Expanded and updated section on CRT	6
New section on alternative pacing strategies and sites	7
Expanded and updated section on pacing in specific conditions, including detailed new sections on post TAVI, postoperative and pacing in the presence of tricuspid valve diseases, and operations	8
A new section on implantation and perioperative management, including perioperative anticoagulation	9
An expanded revised section on CIED complications	10
A new section on various management considerations, including MRI, radiotherapy, temporary pacing, perioperative management, sport activity, and follow up	11
A new section on patient-centred care	12

CIED = cardiovascular implantable electronic device; CRT = cardiac resynchronization therapy; MRI = magnetic resonance imaging; TAVI = transcatheter aortic valve implantation.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

2.3.2 New recommendations in 2021

Table 4 New recommendations in 2021

Recommendations	Class[a]	Level[b]
Evaluation of the patient with suspected or documented bradycardia or conduction system disease		
Monitoring		
In patients with infrequent (less than once a month) unexplained syncope or other symptoms suspected to be caused by bradycardia, in whom a comprehensive evaluation did not demonstrate a cause, long-term ambulatory monitoring with an ILR is recommended.	I	A
Ambulatory electrocardiographic monitoring is recommended in the evaluation of patients with suspected bradycardia to correlate rhythm disturbances with symptoms.	I	C
Carotid massage		
Once carotid stenosis is ruled out[c], carotid sinus massage is recommended in patients with syncope of unknown origin compatible with a reflex mechanism or with symptoms related to pressure/manipulation of the carotid sinus area.	I	B
Tilt test		
Tilt testing should be considered in patients with suspected recurrent reflex syncope.	IIa	B
Exercise test		
Exercise testing is recommended in patients who experience symptoms suspicious of bradycardia during or immediately after exertion.	I	C
In patients with suspected chronotropic incompetence, exercise testing should be considered to confirm the diagnosis.	IIa	B
In patients with intra-ventricular conduction disease or AVB of unknown level, exercise testing may be considered to expose infranodal block.	IIb	C
Imaging		
Cardiac imaging is recommended in patients with suspected or documented symptomatic bradycardia to evaluate the presence of structural heart disease, to determine left ventricular systolic function, and to diagnose potential causes of conduction disturbances.	I	C
Multimodality imaging (CMR, CT, PET) should be considered for myocardial tissue characterization in the diagnosis of specific pathologies associated with conduction abnormalities needing pacemaker implantation, particularly in patients younger than 60 years.	IIa	C
Laboratory tests		
In addition to preimplant laboratory tests,[d] specific laboratory tests are recommended in patients with clinical suspicion for potential causes of bradycardia (e.g. thyroid function tests, Lyme titre, digitalis level, potassium, calcium, and pH) to diagnose and treat these conditions.	I	C
Sleep evaluation		
Screening for SAS is recommended in patients with symptoms of SAS and in the presence of severe bradycardia or advanced AVB during sleep.	I	C
Electrophysiological study		
In patients with syncope and bifascicular block, EPS should be considered when syncope remains unexplained after non-invasive evaluation or when an immediate decision about pacing is needed due to severity, unless empirical pacemaker implantation is preferred (especially in elderly and frail patients).	IIa	B
In patients with syncope and sinus bradycardia, EPS may be considered when non-invasive tests have failed to show a correlation between syncope and bradycardia.	IIb	B
Genetics		
Genetic testing should be considered in patients with early onset (age <50 years) of progressive cardiac conduction disease.	IIa	C
Genetic testing should be considered in family members following the identification of a pathogenic genetic variant that explains the clinical phenotype of cardiac conduction disease in an index case.	IIa	C
Cardiac pacing for bradycardia and conduction system disease		
Pacing is indicated in symptomatic patients with the bradycardia-tachycardia form of SND to correct bradyarrhythmias and enable pharmacological treatment, unless ablation of the tachyarrhythmia is preferred.	I	B
Pacing is indicated in patients with atrial arrhythmia (mainly AF) and permanent or paroxysmal third- or high-degree AVB irrespective of symptoms.	I	C
In patients with SND and DDD PM, minimization of unnecessary ventricular pacing through programming is recommended.	I	A
Dual chamber cardiac pacing is indicated to reduce recurrent syncope in patients aged >40 years with severe, unpredictable, recurrent syncope who have: • spontaneous documented symptomatic asystolic pause/s >3 s or asymptomatic pause/s >6 s due to sinus arrest or AVB; or • cardioinhibitory carotid sinus syndrome; or • asystolic syncope during tilt testing.	I	A

Continued

Continued

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

In patients with recurrent unexplained falls, the same assessment as for unexplained syncope should be considered.	IIa	C
AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pauses, after AF conversion, taking into account the clinical situation.	IIa	C
In patients with the bradycardia-tachycardia variant of SND, programming of atrial ATP may be considered.	IIb	B
Dual-chamber cardiac pacing may be considered to reduce syncope recurrences in patients with the clinical features of adenosine-sensitive syncope.	IIb	B
Cardiac resynchronization therapy		
In patients who are candidates for an ICD and who have CRT indication, implantation of a CRT-D is recommended.	I	A
In patients who are candidates for CRT, implantation of a CRT-D should be considered after individual risk assessment and using shared decision-making.	IIa	B
In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT rather than standard RV pacing should be considered in patients with HFmrEF.	IIa	C
In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), RV pacing should be considered in patients with HFpEF.	IIa	B
In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT may be considered in patients with HFpEF.	IIb	B
Alternate site pacing		
His bundle pacing		
In patients treated with HBP, device programming tailored to specific requirements of His bundle pacing is recommended.	I	C
In CRT candidates in whom coronary sinus lead implantation is unsuccessful, HBP should be considered as a treatment option along with other techniques such as surgical epicardial lead.	IIa	B
In patients treated with HBP, implantation of a right ventricular lead used as "backup" for pacing should be considered in specific situations (e.g. pacemaker-dependency, high-grade AVB, infra-nodal block, high pacing threshold, planned AVJ ablation), or for sensing in case of issues with detection (e.g. risk of ventricular undersensing or oversensing of atrial/His potentials).	IIa	C
HBP with a ventricular backup lead may be considered in patients in whom a "pace-and-ablate" strategy for rapidly conducted supraventricular arrhythmia is indicated, particularly when intrinsic QRS is narrow.	IIb	C
HBP may be considered as an alternative to right ventricular pacing in patients with AVB and LVEF >40%, who are anticipated to have >20% ventricular pacing.	IIb	C
Leadless pacing		
Leadless pacemakers should be considered as an alternative to transvenous pacemakers when no upper extremity venous access exists or when risk of device pocket infection is particularly high, such as previous infection and patients on haemodialysis.	IIa	B
Leadless pacemakers may be considered as an alternative to standard single lead ventricular pacing, taking into consideration life expectancy and using shared decision-making.	IIb	C
Indications for pacing in specific conditions		
Pacing in acute myocardial infarction		
Implantation of a permanent pacemaker is indicated with the same recommendations as in a general population (*section 5.2*) when AVB does not resolve within a waiting period of at least 5 days after MI.	I	C
In selected patients with AVB in context of anterior wall MI and acute HF, early device implantation (CRT-D/CRT-P) may be considered.	IIb	C
Pacing in cardiac surgery		
1) High-degree or complete AVB after cardiac surgery. A period of clinical observation for at least 5 days is indicated in order to assess whether the rhythm disturbance is transient and resolves. However, in the case of complete AVB with low or no escape rhythm when resolution is unlikely, this observation period can be shortened.	I	C
SND after cardiac surgery and heart transplantation. Before permanent pacemaker implantation, a period of observation for up to 6 weeks should be considered.	IIa	C
Chronotropic incompetence after heart transplantation. Cardiac pacing should be considered for chronotropic incompetence persisting more than 6 weeks after heart transplantation to improve quality of life.	IIa	C

Continued

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Surgery for valvular endocarditis and intraoperative complete AVB. Immediate epicardial pacemaker implantation should be considered in patients with surgery for valvular endocarditis and complete AVB if one of the following predictors of persistence is present: preoperative conduction abnormality, *Staphylococcus aureus* infection, intracardiac abscess, tricuspid valve involvement, or previous valvular surgery.	**IIa**	**C**
Patients requiring pacing at the time of tricuspid valve surgery. Transvalvular leads should be avoided and epicardial ventricular leads used. During tricuspid valve surgery, removal of pre-existing transvalvular leads should be considered and preferred over sewing-in the lead between the annulus and a bio-prosthesis or annuloplasty ring. In the case of an isolated tricuspid annuloplasty based on an individual risk-benefit analysis, a pre-existing right ventricular lead may be left in place without jailing it between ring and annulus.	**IIa**	**C**
Patients requiring pacing after biological tricuspid valve replacement/tricuspid valve ring repair. When ventricular pacing is indicated, transvenous implantation of a coronary sinus lead or minimally invasive placement of an epicardial ventricular lead should be considered and preferred over a transvenous transvalvular approach.	**IIa**	**C**
Patients requiring pacing after mechanical tricuspid valve replacement. Implantation of a transvalvular right ventricular lead should be avoided.	**III**	**C**
Pacing in transcatheter aortic valve implantation		
Permanent pacing is recommended in patients with complete or high-degree AVB that persists for 24 - 48 h after TAVI.	**I**	**B**
Permanent pacing is recommended in patients with new onset alternating BBB after TAVI.	**I**	**C**
Early[e] permanent pacing should be considered in patients with pre-existing RBBB who develop any further conduction disturbance during or after TAVI.[f]	**IIa**	**B**
Ambulatory ECG monitoring[g] or an electrophysiology study[h] should be considered for patients with new LBBB with QRS >150 ms or PR >240 ms with no further prolongation during >48 h after TAVI.	**IIa**	**C**
Ambulatory ECG monitoring[g] or electrophysiology study[h] may be considered for TAVI patients with pre-existing conduction abnormality who develop further prolongation of QRS or PR >20 ms.	**IIb**	**C**
Prophylactic permanent pacemaker implantation is not indicated before TAVI in patients with RBBB and no indication for permanent pacing.	**III**	**C**
Various syndromes		
In patients with neuromuscular diseases such as myotonic dystrophy type 1 and any second- or third-degree AVB or HV ≥70 ms, with or without symptoms, permanent pacing is indicated.[i]	**I**	**C**
In patients with LMNA gene mutations, including Emery-Dreifuss and limb girdle muscular dystrophies who fulfil conventional criteria for pacemaker implantation or who have prolonged PR with LBBB, ICD implantation with pacing capabilities should be considered if at least 1-year survival is expected.	**IIa**	**C**
In patients with Kearns-Sayre syndrome who have PR prolongation, any degree of AVB, bundle branch block, or fascicular block, permanent pacing should be considered.	**IIa**	**C**
In patients with neuromuscular disease such as myotonic dystrophy type 1 with PR ≥240 ms or QRS duration ≥120 ms, permanent pacemaker implantation may be considered.[i]	**IIb**	**C**
In patients with Kearns-Sayre Syndrome without cardiac conduction disorder, permanent pacing may be considered prophylactically.	**IIb**	**C**
Sarcoidosis		
In patients with cardiac sarcoidosis who have permanent or transient AVB, implantation of a device capable of cardiac pacing should be considered.[i]	**IIa**	**C**
In patients with sarcoidosis and indication for permanent pacing who have LVEF <50%, implantation of a CRT-D should be considered.	**IIa**	**C**
Special considerations on device implantations and perioperative management		
Administration of preoperative antibiotic prophylaxis within 1 h of skin incision is recommended to reduce risk of CIED infection.	**I**	**A**
Chlorhexidine alcohol instead of povidone-iodine alcohol should be considered for skin antisepsis.	**IIa**	**B**

Continued

Continued

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

For venous access, the cephalic or axillary vein should be considered as first choice.	IIa	C
For implantation of coronary sinus leads, quadripolar leads should be considered as first choice.	IIa	C
To confirm target ventricular lead position, use of multiple fluoroscopic views should be considered.	IIa	C
Rinsing the device pocket with normal saline solution before wound closure should be considered.	IIa	C
In patients undergoing a reintervention CIED procedure, the use of an antibiotic-eluting envelope may be considered.	IIb	B
Pacing of the mid-ventricular septum may be considered in patients with a high risk of perforation (elderly, previous perforation).	IIb	C
In pacemaker implantations in patients with possible pocket issues such as increased risk of erosion due to low body mass index, Twiddler's syndrome or aesthetic reasons, a submuscular device pocket may be considered.	IIb	C
Heparin-bridging of anticoagulated patients is not recommended.	III	A
Permanent pacemaker implantation is not recommended in patients with fever. Pacemaker implantation should be delayed until the patient has been afebrile for at least 24 h.	III	B
Management considerations		
Remote monitoring		
Remote device management is recommended to reduce number of in-office follow-up in patients with pacemakers who have difficulties to attend in-office visits (e.g. due to reduced mobility or other commitments or according to patient preference).	I	A
Remote monitoring is recommended in case of a device component that has been recalled or is on advisory, to enable early detection of actionable events in patients, particularly those who are at increased risk (e.g. in case of pacemaker-dependency).	I	C
In-office routine follow-up of single- and dual-chamber pacemakers may be spaced by up to 24 months in patients on remote device management.	IIa	A
Temporary pacing		
Temporary transvenous pacing is recommended in cases of haemodynamic-compromising bradyarrhythmia refractory to intravenous chronotropic drugs.	I	C
Transcutaneous pacing should be considered in cases of haemodynamic compromising bradyarrhythmia when temporary transvenous pacing is not possible or available.	IIa	C
Temporary transvenous pacing should be considered when immediate pacing is indicated and pacing indications are expected to be reversible, such as in the context of myocardial ischaemia, myocarditis, electrolyte disturbances, toxic exposure, or after cardiac surgery.	IIa	C
Temporary transvenous pacing should be considered as a bridge to permanent pacemaker implantation, when this procedure is not immediately available or possible due to concomitant infection.	IIa	C
For long-term temporary transvenous pacing, an active fixation lead inserted through the skin and connected to an external pacemaker should be considered.	IIa	C
Miscellaneous		
When pacing is no longer indicated, a decision on the management strategy should be based on an individual risk-benefit analysis in a shared decision-making process together with the patient.	I	C
MRI may be considered in pacemaker patients with abandoned transvenous leads if no alternative imaging modality is available.	IIb	C

Continued

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Patient-centred care		
In patients considered for pacemaker or CRT, the decision should be based on the best available evidence with consideration of individual risk-benefits of each option, the patient's preferences, and goals of care, and it is recommended to follow an integrated care approach and use the principles of patient-centred care and shared decision making in the consultation.	I	C

© ESC 2021

AF = atrial fibrillation; ATP = antitachycardia pacing; AV = atrioventricular; AVB = atrioventricular block; AVJ = atrioventricular junction; BBB = bundle branch block; BMI = body mass index; CIED = cardiovascular implantable electronic device; CMR = cardiovascular magnetic resonance; CRT = cardiac resynchronization therapy; CRT-D = defibrillator with cardiac resynchronization therapy; CRT-P = cardiac resynchronization therapy-pacemaker; CSM = carotid sinus massage; CT = computed tomography; DDD = dual-chamber, atrioventricular pacing; ECG = electrocardiogram; EPS = electrophysiology study; HBP = His bundle pacing; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HV = His–ventricular interval; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; OMT = optimal medical therapy; PET = positron emission tomography; PR = PR interval; QRS = Q, R, and S waves; RBBB = right bundle branch block; RV = right ventricular; SAS = sleep apnoea syndrome; SND = sinus node dysfunction; SR = sinus rhythm; TAVI = transcatheter aortic valve implantation.

[a]Class of recommendation.

[b]Level of evidence.

[c]CSM should not be undertaken in patients with previous transient ischaemic attack, stroke, or known carotid stenosis. Carotid auscultation should be performed before carotid sinus massage. If a carotid bruit is present, carotid ultrasound should be performed to exclude carotid disease

[d]Complete blood counts, prothrombin time, partial thromboplastin time, serum creatinine, and electrolytes.

[e]Immediately after procedure or within 24 h.

[f]Transient high-degree AVB, PR prolongation, or QRS axis change.

[g]Ambulatory continuous ECG monitoring (implantable or external) for 7–30 days.

[h]Electrophysiology study with HV ≥70 ms may be considered positive for permanent pacing.

[i]Whenever pacing is indicated in neuromuscular disease, an ICD should be considered according to relevant guidelines.

2.3.3 Changes in cardiac pacing and cardiac resynchronization therapy guideline recommendations since 2013

Table 5 Changes in cardiac pacing and cardiac resynchronization therapy guideline recommendations since 2013

	2013	2021
	Class[a]	
Cardiac pacing for bradycardia and conduction system disease		
In patients with syncope, cardiac pacing may be considered to reduce recurrent syncope when asymptomatic pause(s) >6 s due to sinus arrest are documented.	IIa	IIb
Cardiac resynchronization therapy		
Patients who have received a conventional pacemaker or an ICD and who subsequently develop symptomatic HF with LVEF ≤35% despite OMT and who have a significant[b] proportion of RV pacing should be considered for upgrade to CRT.	I	IIa
CRT rather than RV pacing is recommended for patients with HFrEF (<40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB in order to reduce morbidity. This includes patients with AF.	IIa	I
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, a QRS duration of 130–149 ms, and LBBB QRS morphology despite OMT, to improve symptoms and reduce morbidity and mortality.	I	IIa
In patients with symptomatic AF and uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT is recommended in patients with HFrEF.	IIa	I
Specific indications for pacing		
In patients with congenital heart disease, pacing may be considered for persistent postoperative bifascicular block associated with transient complete AVB.	IIa	IIb
Management considerations		
In patients with MRI-conditional pacemaker systems[c], MRI can be performed safely following manufacturer instructions.	IIa	I
In patients with non-MRI-conditional pacemaker systems, MRI should be considered if no alternative imaging mode is available and if no epicardial leads, abandoned or damaged leads, or lead adaptors/extenders are present.	IIb	IIa

Continued

© ESC 2021

AF = atrial fibrillation; AVB = atrioventricular block; AVJ = atrioventricular junction; CRT = cardiac resynchronization therapy; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; OMT = optimal medical therapy; RV = right ventricular; SR = sinus rhythm.

[a]Class of recommendation.

[b]A limit of 20% RV pacing for considering interventions for pacing-induced HF is supported by observational data. However, there are no data to support that any percentage of RV pacing can be considered as defining a true limit below which RV pacing is safe and beyond which RV pacing is harmful.

[c]Combination of MRI conditional generator and lead(s) from the same manufacturer.

3 Background

3.1 Epidemiology

The prevalence and incidence of pacemaker implantation are unknown in many countries, yet several estimations have been published based on the analysis of large observational studies and databases. There is considerable variability in reported pacemaker implant rates between European countries, ranging from <25

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

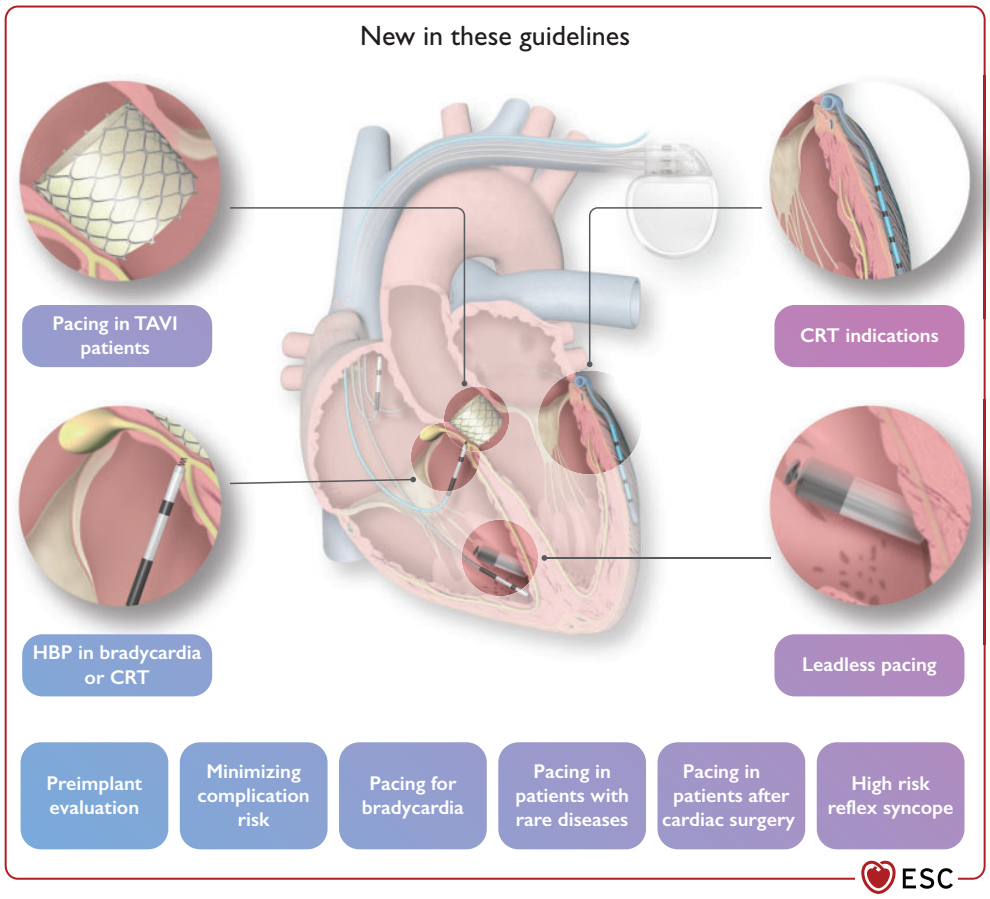

Figure 1 The 2021 ESC Guidelines on cardiac pacing and CRT present new and updated recommendations for these treatments in relevant patient populations.

pacemaker implantations per million people in Azerbaijan, Bosnia and Herzegovina, and Kyrgyzstan, to >1000 implantations per million people in France, Italy, and Sweden.[1] These differences may result from under- or overtreatment with pacemaker therapy in some countries, or from variations in sociodemographic characteristics and pathological conditions. There is a continuous growth in the use of pacemakers due to the increasing life expectancy and ageing of populations.[2–8] The estimated number of patients globally undergoing pacemaker implantation has increased steadily up to an annual implant rate of ~1 million devices.[2] Degeneration of the cardiac conduction system and changes in intercellular conduction can be manifestations of cardiac pathology or non-cardiac disease, and are most prevalent in older patients. Therefore, most bradycardias requiring cardiac pacing are observed in the elderly, with >80% of pacemakers being implanted in patients above the age of 65 years.

3.2 Natural history

High-degree atrioventricular block (AVB) and sinus node dysfunction (SND) are the most common indications for permanent pacemaker therapy. Conservatively treated (i.e. non-paced) patients with high-degree AVB have notably poorer survival compared with pacemaker-treated patients.[9–12] In contrast, SND follows an unpredictable course, and there is no evidence to show that pacemaker therapy results in improved prognosis.[13–15]

Improving life expectancy is not, however, the only objective of pacemaker therapy. Quality of life is an essential metric for measuring a patient's clinical status and outcome, and provides a holistic picture of clinical treatment effectiveness.[16] Studies have been unanimous in finding improved quality of life in patients receiving pacing therapy.[17–22]

3.3 Pathophysiology and classification of bradyarrhythmias considered for permanent cardiac pacing therapy

Definitions of various conduction disturbances are presented in *Supplementary Table 1*.

Sinus bradycardia can be considered physiological in response to specific situations, such as in well-conditioned athletes, young individuals, and during sleep. Pathological bradyarrhythmias are dependent on their underlying cause and can be broadly categorized into intrinsic and extrinsic aetiologies. Advanced age and age-related degenerative changes are important intrinsic causes of modifications in electrical impulse initiation and propagation of the conduction

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

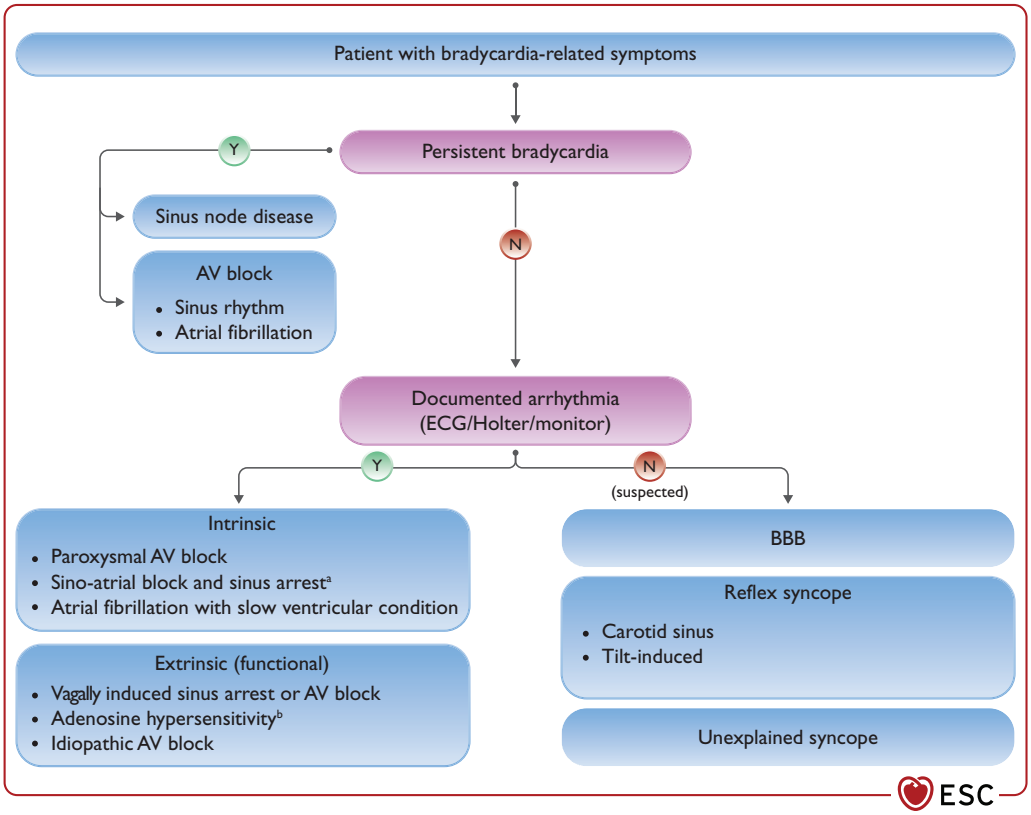

Figure 2 Classification of documented and suspected bradyarrhythmias. AV = atrioventricular; BBB = bundle branch block; ECG = electrocardiogram. [a]Including the bradycardia–tachycardia form of sick sinus syndrome. [b]Deharo *et al.*[32] Figure adapted from Brignole *et al.*[33]

system. In addition, genetic mutations have been linked to conduction disorders (see *section 4.3.5*), and atrial cardiomyopathy[23] may be a specific disease that can result in supraventricular tachyarrhythmia, SND, and atrioventricular node (AVN) disease.[24]

It is essential to differentiate reversible from non-reversible causes of bradycardia. Potential reversible causes of bradycardia include adverse drug effects, myocardial infarction (MI), toxic exposure, infections, surgery, and electrolyte disorders. In a study including 277 patients referred to the emergency department with bradycardia, electrolyte disorders were the underlying cause in 4%, intoxication in 6%, acute MI in 14%, and adverse drug effects in 21%.[25]

In the case of non-reversible pathological causes of slow heart rate, the presence and severity of symptoms play an essential role in the consideration for permanent antibradycardia pacemaker therapy. This may be challenging in patients with competing mechanisms for their symptoms. In general, candidates for pacing therapy can be broadly classified into two groups: patients with persistent bradycardia and patients with intermittent [with or without electrocardiographic (ECG) documentation] bradycardia. Persistent bradycardia usually indicates an intrinsic disease in the sinus node tissue or the atrioventricular (AV) conduction system, whereas intermittent bradycardia can be a result of a wide variety of intrinsic and extrinsic pathological processes, as illustrated in *Figure 2*.[26–31]

3.4 Types and modes of pacing: general description

3.4.1 Endocardial pacing

Endocardial lead-based pacemakers consist of a pulse generator commonly placed in the pectoral region and transvenous lead(s) implanted into the myocardium with the ability to sense cardiac activity and provide therapeutic cardiac stimulation. Since the introduction of transvenous endocardial pacemakers in the 1960s, major technological advances have improved their efficacy and safety. In general, pacemaker implantation is considered a low-risk procedure, yet it is not exempt from device- and procedure-related complications and malfunction. Pacemaker implantation is covered in detail in a recent European Heart Rhythm Association (EHRA) consensus document.[34]

3.4.2 Epicardial pacing

Some clinical scenarios dictate implantation of an epicardial pacemaker system. These include patients with congenital anomalies and no venous access to the heart or with an open shunt between the right and left sides of the circulation, recurrent device infections, occluded veins, and—most commonly today—in conjunction with open cardiac surgery. Epicardial leads are currently implanted using various (minimally invasive) thoracotomy or thoracoscopy and robotic techniques.[35]

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

3.4.3 Cardiac resynchronization therapy (endo- and/or epicardial)

Cardiac dyssynchrony is a difference in the timing of electrical and mechanical activation of the ventricles, which can result in impaired cardiac efficiency. CRT delivers biventricular pacing to correct electromechanical dyssynchrony in order to increase cardiac output.[36] In multiple trials, CRT has shown a significant morbidity and mortality benefit in specific patient groups with reduced left ventricular ejection fraction (LVEF).[37–40]

3.4.4 Alternative methods (conduction system pacing, leadless pacing)

3.4.4.1 Conduction system pacing

Compared with right ventricular (RV) pacing, His bundle pacing (HBP) provides a more physiological simultaneous electrical activation of the ventricles via the His–Purkinje system. HBP can restore conduction in a subset of patients with high-degree AVB, and shorten QRS duration in some patients with left bundle branch block (LBBB) or right bundle branch block (RBBB).[41–44] More studies are ongoing and required to evaluate whether HBP has clinical benefits over CRT or RV pacing. In addition, left bundle branch area pacing is being studied as a pacing modality for patients in whom the conduction disease is too distal for HBP (see *section 7.3*).

3.4.4.2 Leadless pacing

Miniaturized, intracardiac leadless pacemakers have been introduced. These devices are inserted percutaneously through the femoral vein and implanted directly in the RV wall using customized catheter-based delivery systems. The first-generation leadless pacemakers have been proven to provide effective single-chamber pacing therapy.[45–50] Albeit a promising technology, potential difficulty with leadless pacemaker retrieval at the end of service is a limitation. Thus far, there are no randomized controlled data available to compare clinical outcomes between leadless pacing and single-chamber transvenous pacing.

3.4.5 Pacing modes

Technological advances in pacemaker therapy have resulted in a wide variety of pacing modalities. Pacemakers can sense the heart's intrinsic electrical activity and restore the rate and AV sequence of cardiac activation. Abnormal cardiac automaticity and conduction may be treated by single-lead atrial sensing/pacing, single-lead ventricular sensing/pacing, single leads that pace the right ventricle (RV) and sense both the atrium and ventricle, and dual-lead systems that sense and pace the right atrium (RA) and RV. For common pacing modes, refer to *Supplementary Table 2*. The choice of the optimal pacing mode in the presence of conduction disturbances is driven by the underlying morbidity, the impact of pacing therapy on morbidity, and the potential harmful effect of the chosen pacing modality. The choice of pacing modes in specific situations is discussed in *section 5*.

3.4.6 Rate-responsive pacing

The sinus node modulates the heart rate during different types and loads of exercise (i.e. physical exercise, emotions, postural change, and fever) proportional to the metabolic demand. Rate-responsive pacemaker systems strive to produce an appropriate compensatory heart rate during emotional or physical activity by sensing body motion/acceleration, minute ventilation, intracardiac impedance, or other surrogates of physical and mental stress, and are indicated in cases of chronotropic incompetence.[51–57] Dual-sensing rate-responsive pacing (e.g. accelerometer and minute ventilation) may be used in selected patients.[58] A brief overview of the most commonly used rate-responsive pacing sensors is given in *Supplementary Table 3*.

3.5 Sex differences

Pacing indications and complication rates differ between male and female patients. In male patients, primary pacemaker implantation is more often indicated for AVB and less so for SND and atrial fibrillation (AF) with bradycardia.[59,60] In female patients, the rate of procedure-related adverse events is significantly higher, corrected for age and type of device. This higher rate is driven mostly by pneumothorax, pericardial effusion, and pocket haematomas.[59–61] Possible explanations for this are a smaller body size in women and anatomical differences, such as smaller vein diameters and RV diameters.

4 Evaluation of the patient with suspected or documented bradycardia or conduction system disease

4.1 History and physical examination

A careful history and physical examination are essential for the evaluation of patients with suspected or documented bradycardia (*Figure 3*). Current guidelines emphasize the importance of the history and physical examination in the initial evaluation, particularly for identifying patients with structural heart disease.[62,63]

A complete history should include family history, comprehensive cardiovascular risk assessment, and recent/historical diagnoses that may cause bradycardia. The history should be focused on frequency, severity, and duration of symptoms that might suggest bradycardia or conduction system disease. The relationship of symptoms to physical activity, emotional distress, positional changes, medical treatment (*Table 6*), and typical triggers (e.g. urination, defecation, cough, prolonged standing, and shaving) should be explored too, as well as pulse rate if measured during an episode.

Family history may be especially important in young patients with progressive cardiac conduction disease either isolated or in association with cardiomyopathies and/or myopathies.[64,65]

Physical examination should focus on manifestations of bradycardia and signs of underlying structural heart disease or systemic disorders (*Table 7*). Symptomatic slow peripheral pulses should be confirmed with cardiac auscultation or ECG to ensure that other rhythms are not misrepresented as bradycardia (e.g. premature ventricular contractions).

Autonomic regulation disorders are important in the differential diagnosis of syncope or near syncope, and, therefore, orthostatic changes in heart rate and blood pressure may help in the evaluation of the patients.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

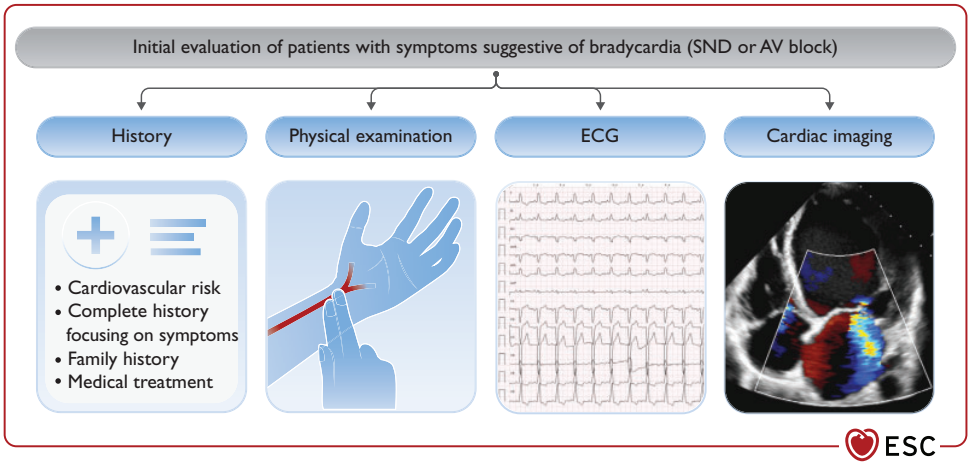

Figure 3 Initial evaluation of patients with symptoms suggestive of bradycardia. AVB = atrioventricular block; ECG = electrocardiogram; SND = sinus node dysfunction.

Table 6 Drugs that may cause bradycardia or conduction disorders

	Sinus node bradycardia	AVB
Beta-blockers	+	+
Antihypertensives		
Non-dihydropyridine calcium channel blockers	+	+
Methyldopa	+	–
Clonidine	+	–
Antiarrhythmics		
Amiodarone	+	+
Dronedarone	+	+
Sotalol	+	+
Flecainide	+	+
Propafenone	+	+
Procainamide	–	+
Disopyramide	+	+
Adenosine	+	+
Digoxin	+	+
Ivabradine	+	–
Psychoactive and neuroactive drugs		
Donepezil	+	+
Lithium	+	+
Opioid analgesics	+	–
Phenothiazine	+	+
Phenytoin	+	+
Selective serotonin reuptake inhibitors	–	+
Tricyclic antidepressants	–	+
Carbamazepine	+	+
Others		
Muscle relaxants	+	–
Cannabis	+	–
Propofol	+	–
Ticagrelor	+	+
High-dose corticosteroids	+	–
Chloroquine	–	+
H_2 antagonists	+	+
Proton pump inhibitors	+	–
Chemotherapy		
Arsenic trioxide	+	+
Bortezomib	+	+
Capecitabine	+	–
Cisplatin	+	–
Cyclophosphamide	+	+
Doxorubicin	+	–
Epirubicin	+	–
5-fluorouracil	+	+
Ifosfamide	+	–
Interleukin-2	+	–
Methotrexate	+	–
Mitroxantrone	+	+
Paclitaxel	+	–
Rituximab	+	+
Thalidomide	+	+
Anthracycline	–	+
Taxane	–	+

AVB = atrioventricular block.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

© ESC 2021

Table 7 Intrinsic and extrinsic causes of bradycardia

	Sinus bradycardia or SND	AVJ disturbances
Intrinsic		
Idiopathic (ageing, degenerative)	+	+
Infarction/ischaemia	+	+
Cardiomyopathies	+	+
Genetic disorders	+	+
Infiltrative diseases		
Sarcoidosis	+	+
Amyloidosis	+	+
Haemochromatosis	+	+
Collagen vascular diseases		
Rheumatoid arthritis	+	+
Scleroderma	+	+
Systemic lupus erythematosus	+	+
Storage diseases	+	+
Neuromuscular diseases	+	+
Infectious diseases		
Endocarditis (perivalvular abscess)	–	+
Chagas disease	+	+
Myocarditis	–	+
Lyme disease	–	+
Diphtheria	–	+
Toxoplasmosis	–	+
Congenital heart diseases	+	+
Cardiac surgery		
Coronary artery bypass grafting	+	+
Valve surgery (including transcatheter aortic valve replacement)	+	+
Maze operation	+	–
Heart transplant	+	+
Radiation therapy	+	+
Intended or iatrogenic AVB	–	+
Sinus tachycardia ablation	+	–
Extrinsic		
Physical training (sports)	+	+
Vagal reflex	+	+
Drug effects	+	+
Idiopathic paroxysmal AVB	–	+
Electrolyte imbalance		
Hypokalaemia	+	+
Hyperkalaemia	+	+
Hypercalcaemia	+	+
Hypermagnesaemia	+	+
Metabolic disorders		
Hypothyroidism	+	+
Anorexia	+	+
Hypoxia	+	+
Acidosis	+	+
Hypothermia	+	+
Neurological disorders		
Increased intracranial pressure	+	+
Central nervous system tumours	+	+
Temporal epilepsy	+	+
Obstructive sleep apnoea	+	+

AV = atrioventricular; AVB = atrioventricular block; AVJ = atrioventricular junction; SND = sinus node dysfunction.
Adapted from Mangrum *et al.*[71] and Da Costa *et al.*[72a]

© ESC 2021

Carotid sinus massage (CSM) can be helpful in any patient ≥40 years old with symptoms suggestive of carotid sinus syndrome (CSS): syncope or near syncope elicited by tight collars, shaving, or turning the head.[66,67] Methodology and response to CSM are described in *section 4.1* in the *Supplementary data*. Diagnosis of CSS requires both the reproduction of spontaneous symptoms during CSM and clinical features of spontaneous syncope compatible with a reflex mechanism.[68–70]

4.2 Electrocardiogram

Together with the history and physical examination, the resting ECG is an essential component of the initial evaluation of patients with documented or suspected bradycardia. A 12-lead ECG or a rhythm strip during the symptomatic episode provides the definitive diagnosis.

For those in whom physical examination suggests a bradycardia, a 12-lead ECG is useful to confirm the rhythm, rate, nature, and extent of conduction disturbance (*Supplementary Table 1*). Furthermore, an ECG may provide information about structural heart or systemic illness (e.g. LV hypertrophy, Q waves, prolonged QT interval, and low voltage) that predict adverse outcomes in symptomatic patients.[62]

4.3 Non-invasive evaluation

Recommendations for non-invasive evaluation

Recommendations	Class[a]	Level[b]
Once carotid stenosis is ruled out,[c] CSM is recommended in patients with syncope of unknown origin compatible with a reflex mechanism or with symptoms related to pressure/manipulation of the carotid sinus area.[68–70]	I	B

© ESC 2021

CSM = carotid sinus massage.
[a]Class of recommendation.
[b]Level of evidence.
[c]CSM should not be undertaken in patients with previous transient ischaemic attack, stroke, or known carotid stenosis. Carotid auscultation should be performed before CSM. If a carotid bruit is present, carotid ultrasound should be performed to exclude the presence of carotid disease.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

4.3.1 Ambulatory electrocardiographic monitoring

The intermittent nature of most symptomatic bradycardia secondary to conduction system disease often requires prolonged ambulatory ECG monitoring to correlate rhythm disturbances with symptoms. This monitoring allows detection of interruption of AV conduction by either primary disease of the conductive system, a vagal or neurocardiogenic mechanism, or reflex AV block.[72,72a]

Ambulatory ECG identifies defects of sinus automaticity, which includes sinus pauses, sinus bradycardia, bradycardia–tachycardia syndrome, asystole post-conversion of atrial flutter or AF, and chronotropic incompetence.

Different versions of ambulatory ECG monitoring have been reviewed recently in a comprehensive expert consensus (*Supplementary Table 4*).[73] Ambulatory ECG selection depends on the frequency and nature of the symptoms (*Table 8*).

Table 8 Choice of ambulatory electrocardiographic monitoring depending on symptom frequency

Frequency of symptom	
Daily	24-h Holter ECG or in-hospital telemetric monitoring
Every 48–72 h	24–48–72 h Holter ECG
Every week	7-day Holter ECG/external loop recorder/external patch recorder
Every month	External loop recorder/external patch recorder/handheld ECG recorder
<1 per month	ILR

© ESC 2021

ECG = electrocardiogram; ILR = implantable loop recorder.
Adapted from Brignole *et al.*[33]

Recommendation for ambulatory electrocardiographic monitoring

Recommendation	Class[a]	Level[b]
Ambulatory ECG monitoring is recommended in the evaluation of patients with suspected bradycardia to correlate rhythm disturbances with symptoms.[73]	I	C

© ESC 2021

ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

4.3.2 Exercise testing

Exercise testing may be useful in selected patients with suspected bradycardia during or shortly after exertion. Symptoms occurring during exercise are likely to be due to cardiac causes, whereas symptoms occurring after exercise are usually caused by a reflex mechanism.

Exercise testing can be used to diagnose symptomatic chronotropic incompetence, defined as an inability to increase the heart rate commensurate with the increased metabolic demands of physical activity.[74,75] The most commonly used definition of chronotropic incompetence has been failure to reach 80% of the expected heart rate reserve. Expected heart rate reserve is defined as the difference between the age-predicted maximal heart rate (220 − age) and the resting heart rate. However, some medical treatments and comorbidities cause exercise intolerance and make the diagnosis of chronotropic incompetence by exercise testing more difficult.

In patients with exercise-related symptoms, the development or progression of AVB may occasionally be the underlying cause. Tachycardia-related exercise-induced second-degree and complete AVB have been shown to be located distal to the AVN and predict progression to permanent AVB.[76–78] Usually, these patients show intraventricular conduction abnormalities on the resting ECG, but a normal resting ECG has also been described in such cases.[77,79] Exercise testing may expose advanced infranodal AVB in the presence of conduction system disease of uncertain location.

In rare cases, conduction disturbances induced by exercise are caused by myocardial ischaemia or coronary vasospasm, and exercise testing may reproduce the symptoms.[80,81]

There are no data supporting an indication for exercise testing in patients without exercise-related symptoms. Exercise testing may be useful in selected patients to distinguish AVN from conduction disturbances in the His–Purkinje system below the AVN in the setting of conduction disturbance at an unclear level.

Recommendations for exercise testing

Recommendations	Class[a]	Level[b]
Exercise testing is recommended in patients who experience symptoms suspicious of bradycardia during or immediately after exertion.[62,74–80]	I	C
In patients with suspected chronotropic incompetence, exercise testing should be considered to confirm the diagnosis.[74,75]	IIa	B
In patients with intraventricular conduction disease or AVB of unknown level, exercise testing may be considered to expose infranodal block.[76,77,79]	IIb	C

© ESC 2021

AVB = atrioventricular block.
[a]Class of recommendation.
[b]Level of evidence.

4.3.3 Imaging

In patients with suspected or documented symptomatic bradycardia, the use of cardiac imaging is recommended to evaluate the presence of structural heart disease, to determine LV systolic function, and to diagnose potential reversible causes of conduction disturbances (*Table 7*).

Echocardiography is the most commonly available imaging technique for evaluation of the above factors. It can also be used in the

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

context of haemodynamic instability. When coronary artery disease is suspected, coronary computed tomography (CT), angiography, or stress imaging is recommended.[82] Cardiovascular magnetic resonance (CMR) and nuclear imaging techniques provide information on tissue characterization (inflammation, fibrosis/scar) and should be considered before pacemaker implantation when specific aetiologies associated with conduction abnormalities are suspected (specially in young patients). Late gadolinium contrast enhanced (LGE) and T2 CMR techniques allow the diagnosis of specific causes of conduction disturbances (i.e. sarcoidosis and myocarditis). Late gadolinium contrast enhancement CMR helps in the decision-making of individuals with arrhythmic events; the presence of large areas of LGE (scar/fibrosis) has been linked to an increased risk of ventricular arrhythmias regardless of LVEF and may indicate the need for an implantable cardioverter-defibrillator (ICD).[83–85] T2 CMR sequences are suited for the detection of myocardial inflammation (i.e. oedema and hyperaemia) as a potential cause of transitory conduction abnormalities that may not need permanent pacemaker implantation.[86] Similarly, positron emission tomography (PET) combined with CMR or CT helps in the diagnosis of inflammatory activity status of infiltrative cardiomyopathies (i.e. sarcoidosis).[87,88]

Recommendations regarding imaging before implantation

Recommendations	Class[a]	Level[b]
Cardiac imaging is recommended in patients with suspected or documented symptomatic bradycardia to evaluate the presence of structural heart disease, to determine LV systolic function, and to diagnose potential causes of conduction disturbances.	I	C
Multimodality imaging (CMR, CT, or PET) should be considered for myocardial tissue characterization in the diagnosis of specific pathologies associated with conduction abnormalities needing pacemaker implantation, particularly in patients younger than 60 years.[83–86,88]	IIa	C

© ESC 2021

CMR = cardiovascular magnetic resonance; CT = computed tomography; LV = left ventricular; PET = positron emission tomography.
[a]Class of recommendation.
[b]Level of evidence.

4.3.4 Laboratory tests

Laboratory tests, including full blood counts, prothrombin time, partial thromboplastin time, renal function, and electrolyte measurements, are warranted as part of pre-procedural planning for pacemaker implantation.

Bradycardia or AVB may be secondary to other conditions (*Table 7*). When suspected, laboratory data are useful for identifying and treating these conditions (e.g. thyroid function, Lyme titre to diagnose myocarditis in a young person with AVB, endocarditis, hyperkalaemia, digitalis levels, and hypercalcaemia).[89–94]

Recommendations for laboratory tests

Recommendations	Class[a]	Level[b]
In addition to pre-implantation laboratory tests,[c] specific laboratory tests are recommended in patients with clinical suspicion for potential underlying causes of reversible bradycardia (e.g. thyroid function tests, Lyme titre, digitalis level, potassium, calcium, and pH) to diagnose and treat these conditions.[90–94]	I	C

© ESC 2021

[a]Class of recommendation.
[b]Level of evidence.
[c]Complete blood counts, prothrombin time, partial thromboplastin time, serum creatinine, and electrolytes.

4.3.5 Genetic testing

Most cardiac conduction disorders are due to either ageing or structural abnormalities of the cardiac conduction system caused by underlying structural heart disease. Genes responsible for inherited cardiac diseases associated with cardiac conduction disorders have been identified.[65,95,96]

Genetic mutations have been linked to a range of abnormalities that may present in isolated forms of cardiac conduction disorder or in association with cardiomyopathy, congenital cardiac anomalies, or extra-cardiac disorders. Most genetically mediated cardiac conduction disorders have an autosomal dominant mode of inheritance[65,95] (*Supplementary Table 5*).

Progressive cardiac conduction disease (PCCD) may be diagnosed in the presence of unexplained progressive conduction abnormalities in young (<50 years) individuals with structurally normal hearts in the absence of skeletal myopathies, especially if there is a family history of PCCD.[97] Common PCCD-associated genes are SCN5A and TRPM4 for isolated forms and LMNA for PCCD associated with HF.

The diagnosis of PCCD in an index patient is based on clinical data including history, family history, and 12-lead ECG. The potential presence of congenital heart disease (CHD) and/or cardiomyopathy must be investigated with cardiac imaging.

Early-onset PCCD, either isolated or with concomitant structural heart disease, should prompt consideration of PCCD genetic testing, particularly in patients with a positive family history of conduction abnormalities, pacemaker implants, or sudden death.[97]

A consensus panel has endorsed mutation-specific genetic testing for family members and appropriate relatives after the identification of a PCCD causative mutation in an index case. Such testing can be deferred in asymptomatic children because of the age-dependent nature of cardiac conduction diseases and incomplete penetrance.[65] However, every case should be individually evaluated depending of the risk of the detected mutation.

Asymptomatic family members who are positive for the family's PCCD-associated mutation should be regularly followed for development of cardiac conduction disease-related symptoms, deterioration of cardiac conduction, and beginning of HF.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Recommendations for genetic testing

Recommendations	Class[a]	Level[b]
Genetic testing should be considered in patients with early onset (age <50 years) of progressive cardiac conduction disease.[c] [65,97]	IIa	C
Genetic testing should be considered in family members following the identification of a pathogenic genetic variant that explains the clinical phenotype of cardiac conduction disease in an index case.[65]	IIa	C

© ESC 2021

[a]Class of recommendation.
[b]Level of evidence.
[c]Progressive cardiac conduction disease: prolonged P wave duration, PR interval, and QRS widening with axis deviation.[96]

4.3.6 Sleep evaluation

Nocturnal bradyarrhythmias are common in the general population. In most circumstances, these are physiological, vagally mediated asymptomatic events, which do not require intervention.[98–100]

Patients with sleep apnoea syndrome (SAS) have a higher prevalence of sleep-related bradycardia (both sinus and conduction system related) during apnoeic episodes.[101,102] SAS-induced hypoxaemia is a key mechanism leading to an increased vagal tone and bradycardic rhythm disorders.[101,102] Another rare mechanism of sleep-related bradycardia (usually in the form of prolonged sinus arrest) is rapid eye movement sleep-related bradycardia, unrelated to apnoea. This mechanism can also be diagnosed by polysomnography.[103] Although most cases quoted in the literature have been treated with pacemakers, the evidence for this is scant, and there is no consensus on how to treat these patients.[103]

Treatment with continuous positive airway pressure (CPAP) alleviates obstructive sleep apnoea-related symptoms and improves cardiovascular outcomes. Appropriate treatment reduces episodes of bradycardia by 72–89%,[104] and patients are unlikely to develop symptomatic bradycardia at long-term follow-up.[104–106] Therefore, patients with asymptomatic nocturnal bradyarrhythmias or cardiac conduction diseases should be evaluated for SAS. If the diagnosis is confirmed, treatment of sleep apnoea with CPAP and weight loss can be effective in improving bradyarrhythmias occurring during sleep, and permanent pacing should be avoided. In patients with known or suspected SAS and symptomatic bradyarrhythmias not associated with sleep, a more complex assessment of the risks associated with bradyarrhythmias vs. the benefit of cardiac pacing is needed.

Recommendation for sleep evaluation

Recommendation	Class[a]	Level[b]
Screening for SAS is recommended in patients with symptoms of SAS and in the presence of severe bradycardia or advanced AVB during sleep.[101–106]	I	C

© ESC 2021

AVB = atrioventricular block; SAS = sleep apnoea syndrome.
[a]Class of recommendation.
[b]Level of evidence.

4.3.7 Tilt testing

Tilt testing should be considered to confirm a diagnosis of reflex syncope in patients in whom this diagnosis was suspected but not confirmed by initial evaluation.[62,107] The endpoint of tilt testing is the reproduction of symptoms along with the characteristic circulatory pattern of the reflex syncope. The methodology and classification of responses are described in *section 4.2* in the *Supplementary data* and in *Supplementary Figure 1*.

A positive cardioinhibitory response to tilt testing predicts, with high probability, asystolic spontaneous syncope; this finding is relevant for therapy when cardiac pacing is considered (see *section 5.4*). Conversely, the presence of a positive vasodepressor, a mixed response, or even a negative response does not exclude asystole during spontaneous syncope.[62]

Recommendation for tilt testing

Recommendation	Class[a]	Level[b]
Tilt testing should be considered in patients with suspected recurrent reflex syncope.[62]	IIa	B

© ESC 2021

[a]Class of recommendation.
[b]Level of evidence.

4.4 Implantable monitors

Patients with infrequent symptoms of bradycardia (less than once per month) need a longer duration of ECG monitoring. For these patients, the implantable loop recorder (ILR) is an ideal diagnostic tool given its capacity for prolonged monitoring (up to 3 years) and without the need for active patient participation (*Table 8*).

In patients with unexplained syncope after the initial evaluation and infrequent symptoms (less than once a month), several studies have demonstrated a higher efficacy of initial ILR implantation compared with a conventional strategy. Many conditions diagnosed by ILR are bradycardia mediated.[108–112] For further discussion on the diagnostic roles of ILR and ambulatory ECG, and indications for their use, refer to the ESC Guidelines for the diagnosis and management of syncope.[62]

Recommendation for implantable loop recorders

Recommendation	Class[a]	Level[b]
In patients with infrequent (less than once a month) unexplained syncope or other symptoms suspected to be caused by bradycardia, in whom a comprehensive evaluation did not demonstrate a cause, long-term ambulatory monitoring with an ILR is recommended.[108–112]	I	A

© ESC 2021

ILR = implantable loop recorder.
[a]Class of recommendation.
[b]Level of evidence.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

4.5 Electrophysiology study

The development of non-invasive ambulatory ECG technologies has reduced the need for the electrophysiology study (EPS) as a diagnostic test. EPS is generally an adjunctive tool in the evaluation of patients with syncope in whom bradycardia is suspected but has not been documented after non-invasive evaluation (*Figure 4*). The goal of an EPS in the context of bradycardia evaluation is to identify abnormal sinus node function or the anatomical location of the cardiac conduction disorders (in the AVN or in the His–Purkinje system distal to the AVN).

In patients with syncope and sinus bradycardia, the pre-test probability of bradycardia-related syncope increases when there is a sinus bradycardia (<50 b.p.m.) or sinoatrial block. Observational studies have shown a relationship between prolonged sinus node recovery time with syncope and the effect of pacing on symptoms.[113,114]

In patients with syncope and bifascicular block, a prolonged His–ventricular interval (HV) ≥70 ms, or HV ≥100 ms after pharmacological stress (ajmaline, procainamide, flecainide, or disopyramide), or induction of second- or third-degree AVB by atrial pacing or by

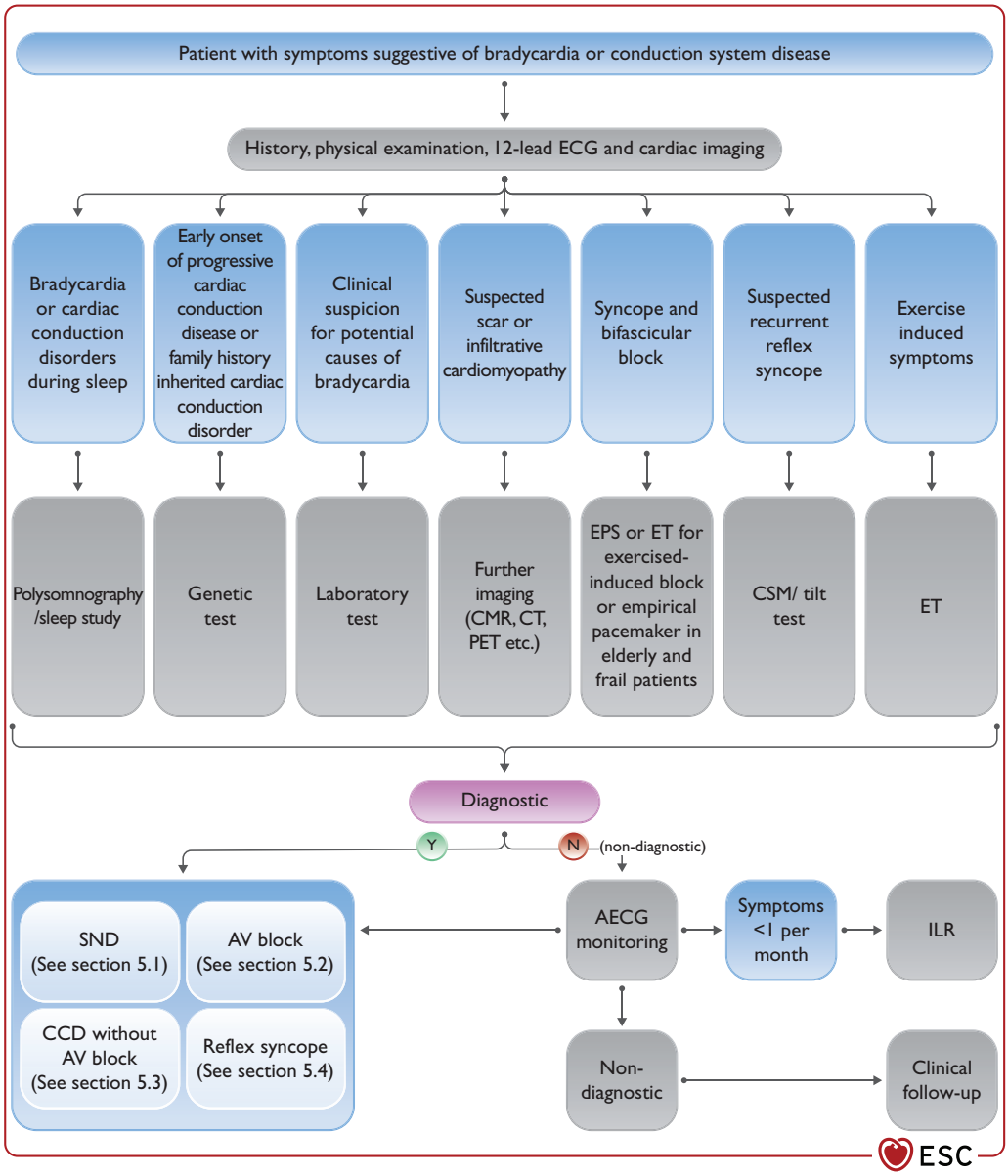

Figure 4 Evaluation of bradycardia and conduction disease algorithm. AECG = ambulatory electrocardiographic monitoring; AV = atrioventricular; CCD = cardiac conduction disease (or disorder); CMR = cardiovascular magnetic resonance; CSM = carotid sinus massage; CT = computed tomography; ECG = electrocardiogram; EPS = electrophysiology study; ET = exercise test; ILR = implantable loop recorder; PET = positron emission tomography; SND = sinus node dysfunction.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

pharmacological stress, identifies a group at higher risk of developing AVB.[115–122]

The efficacy of EPS for the diagnosis of syncope is highest in patients with sinus bradycardia, bifascicular block, and suspected tachycardia,[62] and lowest in patients with syncope, a normal ECG, no structural heart disease, and no palpitations. Therefore, EPS is preferred over ILR in patients with syncope who have a high pre-test probability for significant conduction disease (e.g. abnormal ECG, BBB, ischaemic heart disease, or scar-related cardiomyopathy). For patients with a low pre-test probability (no structural heart disease, normal ECG), ILR is preferred over EPS. EPS is also preferred when there is a high likelihood that another syncopal episode will be dangerous or life-threatening and an immediate diagnosis is likely if EPS is performed.

A negative EPS does not exclude an arrhythmic syncope, and further evaluation is warranted. Approximately one-third of patients with a negative EPS in whom an ILR is implanted develop AVB at follow-up.[123]

Recommendations for electrophysiology study

Recommendations	Class[a]	Level[b]
In patients with syncope and bifascicular block, EPS should be considered when syncope remains unexplained after non-invasive evaluation or when an immediate decision about pacing is needed due to severity, unless empirical pacemaker implantation is preferred (especially in elderly and frail patients).[115–121]	IIa	B
In patients with syncope and sinus bradycardia, EPS may be considered when non-invasive tests have failed to show a correlation between syncope and bradycardia.[113,114]	IIb	B

EPS = electrophysiology study.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

5 Cardiac pacing for bradycardia and conduction system disease

5.1 Pacing for sinus node dysfunction

SND, also known as sick sinus syndrome, comprises a wide spectrum of sinoatrial dysfunctions, ranging from sinus bradycardia, sinoatrial block, and sinus arrest to bradycardia–tachycardia syndrome.[124,125] An additional manifestation of SND is an inadequate chronotropic response to exercise, reported as chronotropic incompetence.

5.1.1 Indications for pacing

5.1.1.1 Sinus node dysfunction

In general, pacing for asymptomatic SND has never been shown to affect prognosis, as opposed to pacing for AVB. Therefore, SND can be considered as an appropriate indication for permanent pacing only when bradycardia due to SND is symptomatic.[126] Patients with SND may manifest symptoms attributable to bradyarrhythmia and/or symptoms of accompanying atrial tachyarrhythmias in the bradycardia–tachycardia form of the disease. Symptoms may be present either at rest or at the end of the tachyarrhythmic episode (conversion pause also named pre-automaticity pause), or develop during exercise, and may range from mild fatigue to light-headedness, dizzy spells, near-syncope, to syncope. Dyspnoea on exertion may be related to chronotropic incompetence. Syncope is a common manifestation of SND and has been reported in 50% of patients who receive a pacemaker for SND.[127]

Establishing a correlation between symptoms and bradyarrhythmia is a crucial step in decision-making. However, age, concomitant heart disease, and other comorbidities may pose difficulties in establishing a clear cause–effect relationship between SND and symptoms.

The effect of cardiac pacing on the natural history of bradyarrhythmias was evaluated in non-randomized studies undertaken at the beginning of the pacemaker era, which suggested a symptomatic improvement with cardiac pacing.[128–131] This was confirmed by one randomized controlled trial (RCT)[14] in which 107 patients (aged 73 ± 11 years) with symptomatic SND were randomized to no treatment, oral theophylline, or dual-chamber (DDD) rate-responsive pacemaker therapy. In this study, the occurrence of syncope and HF was lower in the pacemaker group during a follow-up of 19 ± 14 months.

In patients presenting with exercise intolerance in whom chronotropic incompetence has been identified, the usefulness of cardiac pacing is uncertain, and the decision to implant a pacemaker in such patients should be made on a case by case basis.

In some cases, symptomatic bradyarrhythmias may be related to transient, potentially reversible, or treatable conditions (*section 4*, *Table 7*). In such cases, correction of these factors is required, whereas permanent pacing is not indicated. In clinical practice, it is crucial to distinguish physiological bradycardia (due to autonomic influences or training effects) from inappropriate bradycardia that requires permanent cardiac pacing. For example, sinus bradycardia, even when it is 40–50 b.p.m. while at rest or as slow as 30 b.p.m. while sleeping, particularly in trained athletes, could be accepted as a physiological finding that does not require cardiac pacing. Asymptomatic bradycardia (due to either sinus pauses or AVB episodes) is not uncommon and warrants interpretation in the clinical context of the patient: in healthy subjects, pauses >2.5 s are uncommon, but this *per se* does not necessarily constitute a clinical disorder; asymptomatic bradyarrhythmias are common in athletes.[132] In the absence of published trials, no recommendations for bradycardia detected in asymptomatic patients can be made. On the other hand, in patients investigated for syncope in whom asymptomatic pause(s) >6 s due to sinus arrest are eventually documented, pacing may be indicated. Indeed, such patients constituted a small minority of those included in an observational study and a randomized trial on pacing in reflex syncope.[133,134] In patients presenting with sleep-related asymptomatic intermittent bradycardia (sinus bradycardia or AVB), sleep apnoea and rapid eye movement sleep-related bradycardia should be considered as possible causes.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

5.1.1.2 Bradycardia–tachycardia form of sinus node dysfunction

The bradycardia–tachycardia variant of SND is the most common form, and is characterized by progressive, age-related, degenerative fibrosis of the sinus node tissue and atrial myocardium. Bradyarrhythmias can be associated with various forms of atrial tachyarrhythmias, including AF.[125] In this form of SND, the bradyarrhythmias may correspond to atrial pauses due to sinoatrial blocks or may be due to overdrive suppression after an atrial tachyarrhythmia.[135]

Atrial tachyarrhythmias may be present at the time of diagnosis, typically with sinus arrest and asystolic pauses at the termination of atrial tachyarrhythmias or after device implant. Control of atrial tachyarrhythmias in patients presenting with high ventricular rates may be difficult before implant, as drugs prescribed for rate control may worsen bradyarrhythmias. Ablation of the atrial tachyarrhythmia, mainly AF, has been proposed in lieu of pacing and continuing medications for selected patients,[136–138] but no data are available from RCTs to show whether catheter ablation of AF is non-inferior to cardiac pacing with respect to bradycardia-related symptoms in patients with bradycardia–tachycardia syndrome.[139] If drug treatment is chosen, bradyarrhythmias during drug treatment for rate or rhythm control may be managed by dose reduction or discontinuation as an alternative to cardiac pacing, but in many cases bradyarrhythmias persist.

5.1.2 Pacing mode and algorithm selection

In patients with SND, controlled studies found that DDD was superior to single-chamber ventricular pacing in reducing the incidence of AF. These studies also showed some effect of DDD pacing on the occurrence of stroke.[140,141] Dual-chamber pacing reduces the risk of pacemaker syndrome, which may occur in more than a quarter of patients with SND.[21,142] Pacemaker syndrome is associated with a reduction in quality of life and usually justifies the preference for DDD vs. ventricular rate-modulated pacing in SND, when reasonable.[143] Potential exceptions are very elderly and/or frail patients with infrequent pauses who have limited functional capacity and/or a short expected survival. In these patients, the benefit of DDD(R) vs. VVIR pacing is expected to have limited or no clinical impact, and the incremental risk of complications related to the second atrial lead required in DDD(R) implants should also be considered when choosing the pacing mode. In patients with SND treated with a DDD pacemaker, programming of the AV interval and specific algorithms for minimizing RV pacing may further reduce the risk of AF and particularly of persistent AF.[144] Dual-chamber pacing is safer and more sustainable than atrial-only pacing modes used in the past,[127] even though single-lead atrial pacing was found to be superior to single-lead ventricular pacing.[145,146] The results of studies that evaluated different pacing modes in bradyarrhythmias, including in some cases both SND and AVB, are shown in *Supplementary Table 6*.

With regard to the choice between DDD(R) and atrial pacing atrial sensing inhibited-response rate-adaptive (AAIR) pacing, an RCT with only 177 patients suggested a reduced risk of AF with AAIR.[147] However, the most recent DANish Multicenter Randomized Trial on Single Lead Atrial PACing vs. Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE), which enrolled 1415 patients followed for a mean of 5.4 years, found no difference between DDD(R) and AAIR pacing in all-cause mortality.[127] The DANPACE trial also found a higher incidence of paroxysmal AF [hazard ratio (HR) 1.27] and a two-fold increased risk of pacemaker reoperation with AAIR, with AVB developing in 0.6–1.9% of patients every year.[127] These findings support the routine use of DDD(R) rather than AAIR pacing in patients with SND.

In view of these data, DDD(R) is the pacing mode of first choice in SND (*Figure 5*). Unnecessary RV pacing should be systematically avoided in patients with SND, because it may cause AF and deterioration of HF, particularly if systolic function is impaired or borderline.[144,148] This can be achieved by programming of the AV interval or using specific algorithms for minimizing RV pacing. Programming an excessively long AV interval to avoid RV pacing in patients with prolonged AV conduction may be disadvantageous from a haemodynamic point of view by causing diastolic mitral regurgitation, which may lead to symptoms and/or AF.[144,149,150]

Pacing algorithms for minimizing ventricular pacing are often used in SND.[144,151] A meta-analysis of algorithms for minimizing RV pacing failed to show a significant effect compared with conventional DDD pacing in patients with normal ventricular function with regard to endpoints such as incidence of persistent/permanent AF, all-cause hospitalization, and all-cause mortality.[152] However, the rationale for reducing unnecessary RV pacing remains strong and is coupled with the benefits of extending device longevity.[151,152] Some manufacturer-specific algorithms are more effective in minimizing ventricular pacing, but may confer disadvantages in allowing decoupling between atria and ventricles.[153,154] Rarely, algorithms designed to minimize ventricular pacing can cause life-threatening ventricular arrhythmias that are pause dependent or pause triggered.[155–158] No direct comparison of these algorithms has been performed so far, but pooled data from randomized trials do not show clear-cut superiority of any specific algorithm in improving clinical outcome.[152,159]

In patients with severely reduced LVEF and a SND indication for pacing, in whom a high percentage of ventricular pacing is expected, an indication for CRT or HBP should be evaluated (see *section 6* on CRT and *section 7* on HBP).

The role of pacing algorithms for preventing AF has been the subject of controversy. A series of algorithms for preventing/suppressing AF has been tested, such as dynamic atrial overdrive pacing, atrial pacing in response to atrial premature beats, pacing in response to exercise, and post-mode-switch pacing. The clinical evaluation of these algorithms, also applied at different atrial pacing sites, is not convincing and no clinical benefit with regard to major clinical endpoints has been demonstrated.[160,161]

Atrial antitachycardia pacing [ATP; i.e. delivery of atrial stimuli at high frequencies to convert an atrial tachyarrhythmia to sinus rhythm (SR)] has also been tested for reducing the atrial tachyarrhythmia burden and counteracting the tendency over time towards progression to permanent AF.[162] Conventional delivery of atrial ATP in a way that mirrors the delivery of ventricular ATP (bursts/ramp at arrhythmia onset) has a relatively low success rate, and indeed the trials based on conventional atrial ATP showed no benefit on AF burden or clinical events.[163] A new form of ATP delivery has been

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

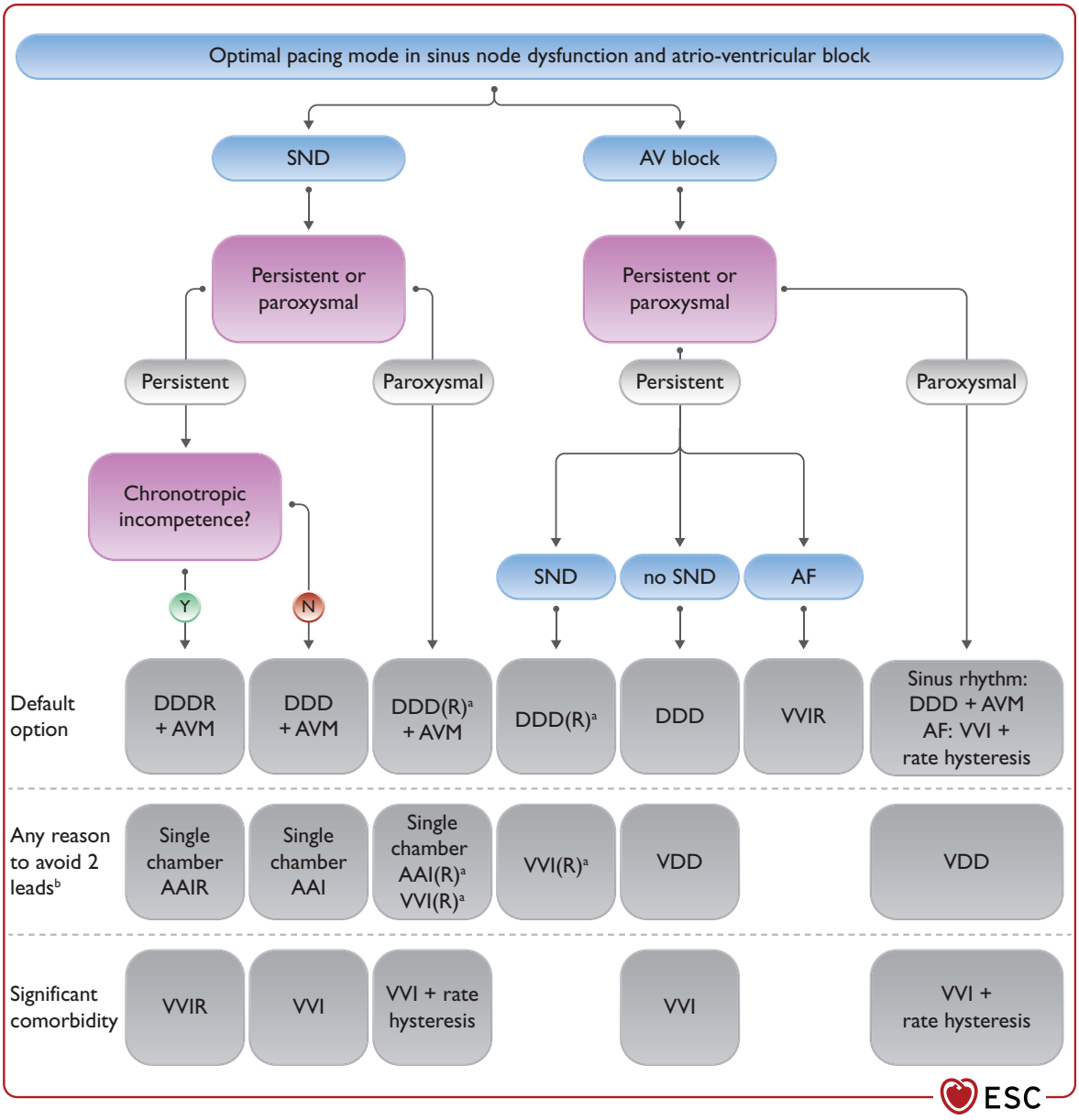

Figure 5 Optimal pacing mode and algorithm selection in sinus node dysfunction and atrioventricular block. AF = atrial fibrillation; AV = atrioventricular; AVM = atrioventricular management [i.e. AV delay programming (avoiding values >230 ms) or specific algorithms to avoid/reduce unnecessary ventricular pacing]; CRT = cardiac resynchronization therapy; SND = sinus node dysfunction. [a](R) indicates that the programming of such a pacing mode is preferred only in the case of chronotropic incompetence. [b]Reasons to avoid two leads include young age and limited venous access. Note: in patients who are candidates for a VVI/VDD pacemaker, a leadless pacemaker may be considered (see *section* 7). For combined CRT indications, see *section 6*. Adapted from Brignole *et al.*[62]

proposed, specifically aimed at reducing atrial tachyarrhythmias, and its efficacy in reducing the progression to permanent AF was validated in an RCT.[162,164]

In this trial,[164] the primary composite outcome at 2 years (death, cardiovascular hospitalizations, or permanent AF) was significantly reduced in patients with a device combining ATP and algorithms for minimizing RV pacing [36% relative risk reduction compared with conventional DDD(R)]. The positive effect on the primary endpoint was due to a lower rate of progression to permanent AF. A post-hoc analysis indicated that this form of atrial ATP was an independent predictor of permanent or persistent AF reduction.[162,164,165] In CHD, where re-entrant atrial arrhythmias are very common, use of DDD(R) pacemakers with atrial ATP may be considered (see *section 8* on pacing in CHD).

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Recommendations for pacing in sinus node dysfunction

Recommendations	Class[a]	Level[b]
In patients with SND and a DDD pacemaker, minimization of unnecessary ventricular pacing through programming is recommended.[144,151,159,164,166–169]	I	A
Pacing is indicated in SND when symptoms can clearly be attributed to bradyarrhythmias.[14,128–131]	I	B
Pacing is indicated in symptomatic patients with the bradycardia–tachycardia form of SND in order to correct bradyarrhythmias and enable pharmacological treatment, unless ablation of the tachyarrhythmia is preferred.[17,20,21,136–138,170,171]	I	B
In patients who present chronotropic incompetence and have clear symptoms during exercise, DDD with rate-responsive pacing should be considered.[172,173]	IIa	B
AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pauses, after AF conversion, taking into account the clinical situation.[136–139,174]	IIa	C
In patients with the bradycardia–tachycardia variant of SND, programming of atrial ATP may be considered.[164,165]	IIb	B
In patients with syncope, cardiac pacing may be considered to reduce recurrent syncope when asymptomatic pause(s) >6 s due to sinus arrest is documented.[133,134]	IIb	C
Pacing may be considered in SND when symptoms are likely to be due to bradyarrhythmias, when the evidence is not conclusive.	IIb	C
Pacing is not recommended in patients with bradyarrhythmias related to SND that are asymptomatic or due to transient causes that can be corrected and prevented.[33]	III	C

© ESC 2021

ATP = antitachycardia pacing; DDD = dual-chamber, atrioventricular pacing; SND = sinus node dysfunction.
[a]Class of recommendation.
[b]Level of evidence.

5.2 Pacing for atrioventricular block

5.2.1 Indications for pacing

Treatment of AVB aims at ameliorating symptoms and preventing syncope and sudden cardiac death (SCD). First-degree AVB is usually asymptomatic. Syncope and dizziness are mainly observed in high-degree and complete AVB, especially in the paroxysmal forms. HF symptoms are more common in chronic AVB with permanent bradycardia, but can also be observed in first-degree AVB with a very prolonged PR interval. Given the commonly advanced age at onset of AVB, manifestations of fatigue, exertional intolerance, and HF are sometimes underestimated. Deterioration of cognitive functions is often only speculative so that the possibilities of improvement after implantation of a pacemaker are unpredictable and unlikely. Death in patients with untreated AVB is due not only to HF secondary to low cardiac output, but also to SCD caused by prolonged asystole or bradycardia-triggered ventricular tachyarrhythmia. Although RCTs of pacing in AVB have not been performed, it is clear from several observational studies that pacing prevents recurrence of syncope and improves survival.[10–12]

5.2.1.1 First-degree atrioventricular block

Usually the prognosis is good in the absence of structural heart disease, and progression to high-degree block is uncommon.[175] The indication for pacing relies on an established correlation between symptoms and AVB. There is weak evidence to show that marked PR prolongation (i.e. ≥300 ms), particularly when it persists or is prolonged during exercise, can lead to symptoms similar to pacemaker syndrome and/or that these can improve with pacing.[176] Symptom correlation is crucial, although it may be difficult if these are non-specific and subtle. In the absence of a clear correlation, a pacemaker is generally not indicated.

5.2.1.2 Second-degree type I atrioventricular block (Mobitz type I or Wenckebach)

In addition to the presence or absence of symptoms, the risk of progression to higher degrees of AVB should be considered. Supranodal block has a benign course, and the risk of progression to type II or a higher degree of AV block is low. Small, retrospective studies have suggested that, over the long term, this type of AVB carries a higher risk of death in patients aged ≥45 years in the absence of pacemaker implantation.[177,178] Infranodal block (rare in this form of block) carries a high risk of progression to complete heart block, syncope, and sudden death, and warrants pacing even in the absence of symptoms.[179,180]

5.2.1.3 Second-degree Mobitz type II, 2:1, and advanced atrioventricular block (also named high-grade atrioventricular block, where the P:QRS ratio is 3:1 or higher), third-degree atrioventricular block

In the absence of a reversible cause, due to the risk of occurrence of severe symptoms and/or possible progression towards a more severe or complete AVB, patients should receive a pacemaker even in the absence of symptoms. In asymptomatic patients in whom a 2:1 AVB is found incidentally, the decision for implantation should be made on a case by case basis including distinction between nodal and infranodal AVB. This distinction may be based on observations such as PR or PP interval prolongation before AVB, the effect of exercise on AV conduction, and an EPS.

5.2.1.4 Paroxysmal atrioventricular block

Because of the risk of syncope and SCD and of the potential progression to permanent AVB, the indications for pacing are the same for paroxysmal as for permanent AVB. It is crucial to rule out a reversible cause and to recognize the reflex forms of AVB, which may not need pacing. Documentation of infranodal block by EPS or the documentation of initiation of the block by atrial or ventricular premature beats, or increased heart rate (tachy-dependent AVB) or decreased heart

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

rate (brady-dependent AVB), support a diagnosis of intrinsic infranodal AVB.[27]

5.2.2 Pacing mode and algorithm selection

5.2.2.1 Dual-chamber vs. ventricular pacing

Large, randomized, parallel trials that included patients with only AVB[181] or with AVB and/or SND[140] failed to show superiority of DDD over ventricular pacing with regard to mortality, and have not consistently shown superiority in terms of quality of life or morbidity (including stroke or transient ischaemic attack and AF).[20,140,181] Dual-chamber pacing is beneficial over ventricular pacing due to the avoidance of pacemaker syndrome, which occurred in up to a quarter of patients with AVB in these trials. In a meta-analysis of 20 crossover trials, DDD was associated with an improved exercise capacity compared with ventricular pacing. However, the effect was driven by non-rate-modulated ventricular pacemakers, and no benefit was observed from the comparison of DDD with VVIR pacing.[182] Pacemaker syndrome is associated with reduction in quality of life and may require a reintervention for upgrading, justifying the preference for DDD when reasonable (i.e. in patients who do not present with significant frailty, very advanced age, significant comorbidities limiting their life expectancy, or a very limited mobility). Another consideration is the diagnosis of AF, which is more reliable from device data in patients with DDD pacemakers. On a case by case basis, in frail elderly patients, and/or when AVB is paroxysmal and pacing anticipated to be infrequent, VVIR pacing may be considered as it carries a lower complication rate.[140]

There is strong evidence to show that chronic conventional RV pacing may be deleterious in some patients and may lead to LV dysfunction and HF,[148] even when AV synchrony is maintained.[183] This effect is only partly explained by the abnormal activation sequence and may involve myocardial perfusion, and humoral, cellular, and molecular changes.[184,185] Compared with a matched control cohort, patients with a pacemaker and an RV lead have an increased risk of HF, which is also associated with older age, previous MI, kidney disease, and male sex.[186] Pacing-induced cardiomyopathy occurs in 10–20% of patients after 2–4 years of RV pacing.[186–188] It is associated with a >20% RV pacing burden.[187–190] However, there are no data to support that any percentage of RV pacing can be considered as defining a true limit below which RV pacing is safe and beyond which RV pacing is harmful. For discussion of potential indications for CRT and/or HBP to prevent pacing-induced cardiomyopathy, please refer to *sections 6* and *7*.

5.2.2.2 Atrioventricular block in the case of permanent atrial fibrillation

In the presence of AF, AVB should be suspected if the ventricular rate is slow and the ventricular rhythm regular. During prolonged monitoring, long ventricular pauses may be detected.[191] In patients with AF and no permanent AVB or symptoms, there is no identifiable, minimum pause duration as an indication for pacing. In the absence of a potentially reversible cause, bradycardia or inappropriate chronotropic response (due to either intermittent or complete AVB) associated or reasonably correlated with symptoms is an indication for cardiac pacing. Any high-degree or infranodal block is also an indication for pacing, even in the absence of symptoms. In the absence of symptoms due to bradycardia and of high-degree or infranodal block, pacing is unlikely to be beneficial and is not indicated.

In patients with AF who undergo atrioventricular junction (AVJ) ablation to control rapid ventricular rates, there is evidence to show that AVJ ablation plus RV pacing improves symptoms and quality of life.[192] In contrast, neutral results were found regarding the progression of HF, hospitalization, and mortality,[193] except in one study.[194] Compared with pharmacological rate control, AVJ ablation and CRT reduced the risks of death due to HF, hospitalization due to HF, or worsening HF by 62%, and improved specific symptoms of AF by 36% in elderly patients with permanent AF and narrow QRS.[195] In other studies, this beneficial effect was limited to patients with HF or reduced ejection fraction (EF).[166,196] For further discussion of the role of CRT following AVJ ablation, refer to *section 6*. There is weak evidence to support a benefit from para-Hisian and Hisian pacing after AVJ ablation for refractory AF.[197–200] For further discussion, refer to *section 7*.

Recommendations for pacing for atrioventricular block

Recommendations	Class[a]	Level[b]
Pacing is indicated in patients in SR with permanent or paroxysmal third- or second-degree type 2, infranodal 2:1, or high-degree AVB, irrespective of symptoms.[c] [9–12]	I	C
Pacing is indicated in patients with atrial arrhythmia (mainly AF) and permanent or paroxysmal third- or high-degree AVB irrespective of symptoms.	I	C
In patients with permanent AF in need of a pacemaker, ventricular pacing with rate response function is recommended.[201–204]	I	C
Pacing should be considered in patients with second-degree type 1 AVB that causes symptoms or is found to be located at intra- or infra-His levels at EPS.[177–180]	IIa	C
In patients with AVB, DDD should be preferred over single-chamber ventricular pacing to avoid pacemaker syndrome and to improve quality of life.[20,140,181,182]	IIa	A
Permanent pacemaker implantation should be considered for patients with persistent symptoms similar to those of pacemaker syndrome and clearly attributable to first-degree AVB (PR >0.3 s).[205–207]	IIa	C
Pacing is not recommended in patients with AVB due to transient causes that can be corrected and prevented.	III	C

AF = atrial fibrillation; AVB = atrioventricular block; DDD = dual-chamber, atrioventricular pacing; EPS = electrophysiology study; SR = sinus rhythm.
[a]Class of recommendation.
[b]Level of evidence.
[c]In asymptomatic narrow QRS complex and 2:1 AVB, pacing may be avoided if supra-Hisian block is clinically suspected (concomitant Wenckebach is observed and block disappears with exercise) or demonstrated at EPS.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

In patients with AF, compared with fixed rate pacing, rate-responsive pacing is associated with better exercise performance, improved daily activities, a decrease in symptoms of shortness of breath, chest pain, and palpitations, and improved quality of life.[201–203] It has also been shown to improve heart rate and blood pressure response to mental stress compared with fixed rate pacing.[204] Therefore, rate-adaptive pacing is the pacing mode of first choice. Fixed-rate VVI pacing should be reserved for older sedentary patients who have very limited activity. Commonly, the minimum rate is programmed higher (e.g. 70 b.p.m.) than for patients in SR in an attempt to compensate for loss of active atrial filling.

5.3 Pacing for conduction disorders without atrioventricular block

This section focuses on patients with 1:1 AV conduction and QRS abnormalities caused by delayed or blocked conduction of the His–Purkinje system: BBB, fascicular block in isolation or in combination with BBB, and non-specific intraventricular delay. Bifascicular block is defined as LBBB or the combination of RBBB and with left anterior or posterior fascicular block.

Isolated fascicular block and BBB are rarely associated with symptoms; however, their presence may be a marker for underlying structural heart disease. The presence or absence of symptoms referable to intermittent bradycardia will guide the evaluation of these patients.

5.3.1 Indications for pacing

5.3.1.1 Bundle branch block and unexplained syncope

Although syncope is not associated with an increased incidence of sudden death in patients with preserved cardiac function, a high incidence of total deaths (about one-third sudden) was observed in patients with BBB and HF, previous MI, or low EF.[208–210] Indeed, in those with low EF, syncope is a risk factor for death.[211] Unfortunately, ventricular-programmed stimulation does not seem to identify these patients correctly; therefore, an ICD or a defibrillator with CRT (CRT-D) is indicated in patients with BBB and LVEF <35% for the prevention of SCD (*Figure 6*).[63]

5.3.1.2 Bundle branch block, unexplained syncope, and abnormal electrophysiological study

Electrophysiological assessment includes measurement of the HV at baseline, with stress by incremental atrial pacing or by

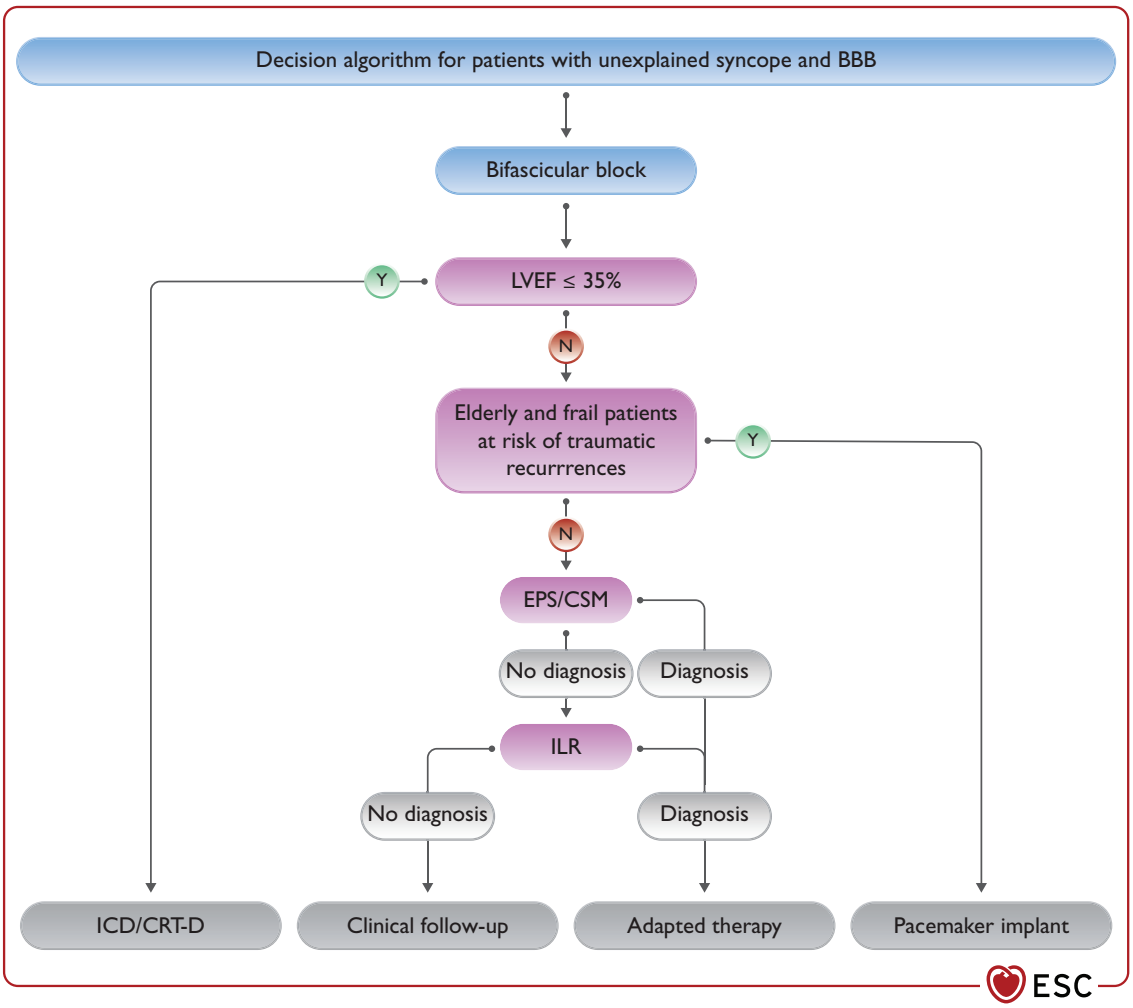

Figure 6 Decision algorithm for patients with unexplained syncope and bundle branch block. BBB = bundle branch block; CRT-D = defibrillator with cardiac resynchronization therapy; CSM = carotid sinus massage; EPS = electrophysiology study; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; LVEF = left ventricular ejection fraction.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

pharmacological provocation (ajmaline, procainamide, or flecainide). Scheinman *et al*. studied the prognostic value of the HV: the progression rate to AVB at 4 years was 4% in patients with HV <70 ms, 12% in patients with HV between 70 and 100 ms, and 24% in patients with HV >100 ms.[121] Development of intra- or infra-His block at incremental atrial pacing or by pharmacological stress test increases the sensitivity and positive predictive value of the EPS to identify patients who will develop AVB.[116–118,120,122,212] A positive EPS yielded a positive predictive value as high as 80% to identify patients who develop AVB. This finding has been indirectly confirmed by a study that showed a significant reduction in syncopal recurrences in patients with positive EPS treated with a pacemaker, compared with a control group of untreated patients with a negative EPS.[119] In patients with unexplained syncope and bifascicular block, EPS is highly sensitive in identifying patients with intermittent or impending high-degree AVB. However, a negative EPS cannot rule out intermittent/paroxysmal AVB as the cause of syncope. Indeed, in patients with a negative EPS, intermittent or stable AVB was documented by ILR in ∼50% of cases. Therefore, elderly patients with bifascicular block and unexplained syncope might benefit from an empirical pacemaker, especially in unpredictable and recurrent syncope that exposes the patient to a high risk of traumatic recurrences. The decision to implant a pacemaker in these patients should be based on individual risk–benefit evaluation.[213]

5.3.1.3 Alternating bundle branch block

This rare condition refers to situations in which there is clear ECG evidence for block in all three fascicles on successive ECGs; examples are LBBB and RBBB morphologies on successive ECGs, or RBBB with associated left anterior fascicular block on one ECG and left posterior fascicular block on another ECG.[214] There is general consensus that this phenomenon is associated with significant infranodal disease and that patients will progress rapidly toward AVB. Therefore, a pacemaker should be implanted as soon as the alternating BBB is detected, even in the absence of symptoms.

5.3.1.4 Bundle branch block without symptoms

Permanent pacemaker implantation is not indicated for BBB without symptoms, with the exception of alternating BBB, because only a minority of these patients will develop AVB (1–2% per year).[115,121,215] The risks of pacemaker implantation and long-term transvenous lead complications are higher than the benefits of pacemaker implantation.[216,217]

5.3.1.5 Patients with neuromuscular diseases

In patients with neuromuscular diseases, cardiac pacing should be considered, as any degree of fascicular block can progress unpredictably, even in the absence of symptoms (see *section* 8.5).

Recommendations for pacing in patients with bundle branch block

Recommendations	Class[a]	Level[b]
In patients with unexplained syncope and bifascicular block, a pacemaker is indicated in the presence of either a baseline HV of ≥70 ms, second- or third-degree intra- or infra-Hisian block during incremental atrial pacing, or an abnormal response to pharmacological challenge.[119,120]	I	B
Pacing is indicated in patients with alternating BBB with or without symptoms.	I	C
Pacing may be considered in selected patients with unexplained syncope and bifascicular block without EPS (elderly, frail patients, high-risk and/or recurrent syncope).[213]	IIb	B
Pacing is not recommended for asymptomatic BBB or bifascicular block.[115,121,215]	III	B

BBB = bundle branch block; EPS = electrophysiology study; HV = His–ventricular interval.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

5.3.2 Pacing mode and algorithm selection

In intermittent bradycardia, pacing may be required only for short periods. In this situation, the benefits of bradycardia and pause prevention must be weighed against the detrimental effects of permanent pacing, particularly pacing-induced HF. Low base-rate programming to achieve backup pacing, and manual adaptation of AV interval, programming AV hysteresis, or other specific algorithms preventing unnecessary RV pacing, play a particularly important role in this patient group.[144,148]

In patients in SR, the optimal pacing mode is DDD. The strong evidence of superiority of DDD vs. VVI pacing is limited to improvement in symptoms and quality of life. Conversely, there is strong evidence of non-superiority with regard to survival and morbidity.[20] Therefore, in elderly or frail patients with intermittent bradycardia, the decision regarding the pacing mode should be made on an individual basis, taking into consideration the increased complication risk and costs of DDD (*Figure* 5).

VDD may be a pacing mode alternative for patients with advanced AV conduction abnormalities and spared sinus node function. In comparison with DDD, VDD system implantation is associated with fewer complications, shorter procedure and fluoroscopy times, and a high incidence of atrial undersensing.[218] Potential atrial undersensing is contributing to the low use of this system as most operators are aiming for AV synchrony.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

5.4 Pacing for reflex syncope

Permanent pacemaker therapy may be effective if asystole is a dominant feature of reflex syncope. Establishing a relationship between symptoms and bradycardia should be the goal of the clinical evaluation of patients with syncope and a normal baseline ECG. The efficacy of pacing depends on the clinical setting. The fact that pacing is effective does not mean it is always necessary. In patients with reflex syncope, cardiac pacing should be the last resort and should only be considered in highly selected patients [i.e. those >40 years of age (mostly >60 years), affected by severe forms of reflex syncope with frequent recurrences associated with a high risk of injury, often without a prodrome]. The 2018 ESC Guidelines on syncope[62] give a detailed description of the diagnostic pathway and indications for pacing, and provide the evidence from trials that support such recommendations. *Figure 7* summarizes the suggested decision pathway.

The algorithm shown in *Figure 7* has been prospectively validated in a multicentre pragmatic study, which showed a low recurrence rate of syncope with pacing of 15% at 2 years, significantly lower than the 37% rate observed in unpaced controls.[219] The 3-year recurrence rate was similar in patients with cardioinhibitory carotid sinus syndrome (16%), asystolic tilt response (23%), and spontaneous asystole documented by ILR (24%), suggesting similar indications and similar results for the three forms of reflex syncope.[220] Whilst some scepticism prevails over the diagnostic accuracy of tilt testing for the diagnosis of syncope, emerging evidence supports the use of tilt testing in the assessment of reflex hypotensive susceptibility.[107,221] Thus, tilt testing may be considered to identify patients with an associated usually antecedent hypotensive response that would be less likely to respond to permanent cardiac pacing. Patients with hypotensive susceptibility need measures directed to counteract hypotensive susceptibility in addition to cardiac pacing (e.g. physical counterpressure manoeuvres, discontinuation/reduction of hypotensive drugs, and administration of fludrocortisone or midodrine).

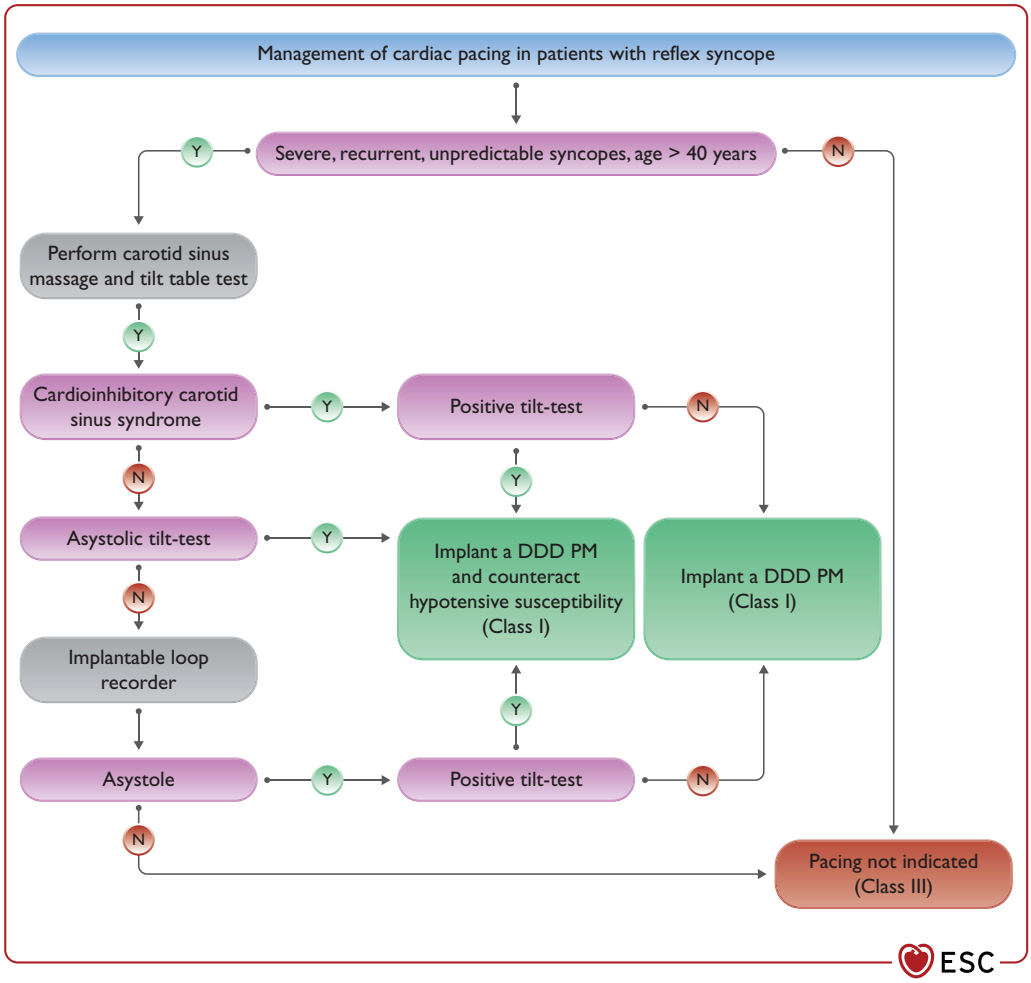

Figure 7 Decision pathway for cardiac pacing in patients with reflex syncope. DDD = dual-chamber, atrioventricular pacing. Note: cardioinhibitory carotid sinus syndrome is defined when the spontaneous syncope is reproduced by the carotid sinus massage in the presence of an asystolic pause >3 s; asystolic tilt positive test is defined when the spontaneous syncope is reproduced in the presence of an asystolic pause >3 s. A symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest, atrioventricular block, or the combination of the two similarly define asystole detected by implantable loop recorder. Figure adapted from Brignole *et al.*[62]

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

5.4.1 Indications for pacing

This Task Force found sufficient evidence in the literature to recommend pacing in highly selected patients with reflex syncope (i.e. those >40 years of age with severe recurrent unpredictable syncopal episodes when asystole has been documented, induced by either CSM or tilt testing, or recorded through a monitoring system)[133,222–228] (see *Supplementary Table 7*). There is sufficient evidence that DDD pacing should be considered in order to reduce recurrence of syncope in patients with dominant cardioinhibitory CSS (asystolic pause >3 s and spontaneous syncope during CSM) and in those in whom there is a correlation between spontaneous symptoms and ECG who are >40 years of age and have severe recurrent unpredictable syncope.[62] Permanent pacemaker therapy may be effective if asystole is a dominant feature of reflex syncope. Establishing a correlation between symptoms and bradycardia should be the goal of the clinical evaluation of patients with syncope and a normal baseline ECG. The efficacy of pacing depends on the clinical setting. A comparison of results in different settings is presented in *Supplementary Table 8*. Since the publication of the 2018 ESC Guidelines on syncope,[62] some trials have added relevant information regarding the subset of patients with tilt-induced asystolic vasovagal syncope. The SPAIN trial was a multicentre, randomized, controlled, crossover study, performed in 46 patients aged >40 years affected by severely recurrent (>5 episodes during life) syncope and cardioinhibitory tilt test response (defined as bradycardia <40 b.p.m. lasting >10 s or asystole >3 s).[226] During the 24-month follow-up, syncope recurred in 4 (9%) patients treated with a DDD pacemaker with closed loop stimulation vs. in 21 (46%) patients who had received a sham pacemaker programmed off (P = 0.0001). In a propensity score-matched comparison study,[229] the 5-year actuarial syncope-free rate was 81% in the pacing group and 53% in propensity-matched patients (P = 0.005; HR = 0.25). Finally, the BioSync CLS trial was a multicentre RCT that investigated the usefulness of the tilt-table test to select candidates for cardiac pacing.[228] Patients aged ≥40 years who had at least two episodes of unpredictable severe reflex syncope during the past year and a tilt-induced syncope with an asystolic pause >3 s were randomized to receive either an active (63 patients) or an inactive (64 patients) dual-chamber pacemaker with close loop stimulation. The study showed that, after a median follow-up of 11.2 months, syncope occurred in significantly fewer patients in the pacing group than in the control group [10 (16%) vs. 34 (53%), respectively; HR 0.23; P = 0.00005). This study supports inclusion of tilt testing as a useful method to select patients with reflex syncope for cardiac pacing.

Based on the results of the above studies, sufficient evidence exists to upgrade from IIb to I the indication for pacing in patients aged >40 years with asystolic tilt response >3 s. *Figure 8* summarizes the recommended indication for pacing. Although there is also a rationale for pacing in patients aged ≤40 years who have the same severity criteria as those >40 years, this Task Force cannot make any recommendation due to the lack of evidence from trials addressing this specific population.

There is weak evidence that DDD may be useful in reducing recurrences of syncope in patients with the clinical features of adenosine-sensitive syncope.[62] In a small multicentre trial performed in 80 highly

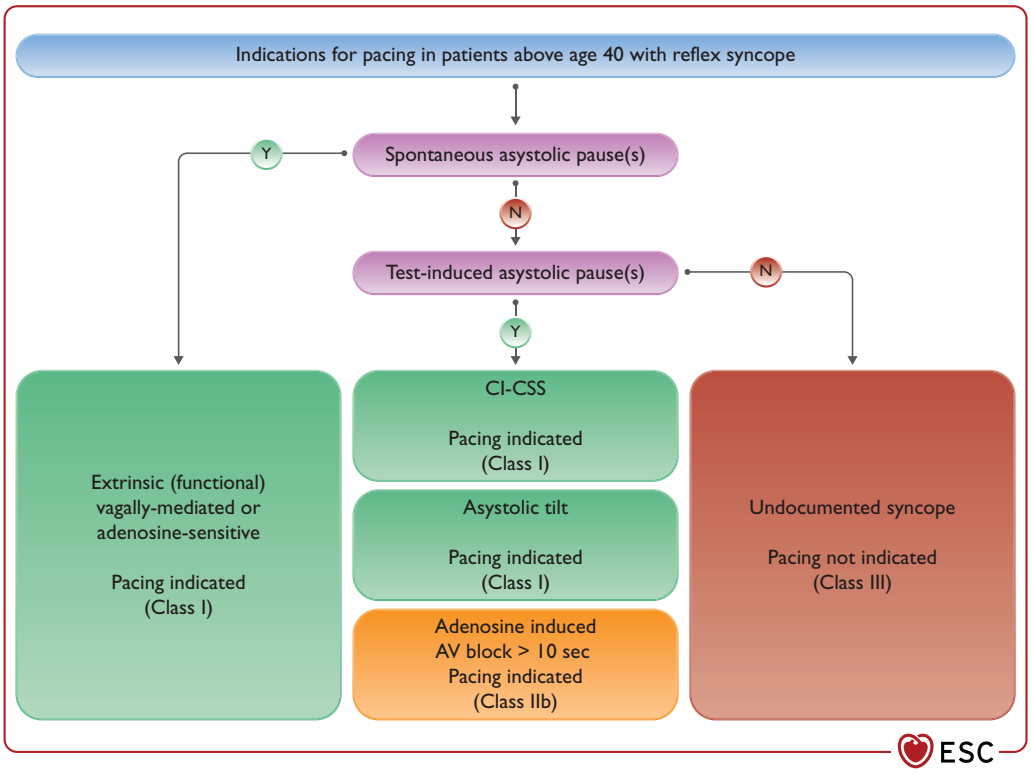

Figure 8 Summary of indications for pacing in patients >40 years of age with reflex syncope. CI-CSS = cardioinhibitory carotid sinus syndrome. Note: spontaneous asystolic pause = 3 s symptomatic or 6 s asymptomatic. Adapted from Brignole *et al.*[62]

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

selected elderly patients with unexplained unpredictable syncope who had induction of third-degree AVB of ≥10 s to intravenous injection of a bolus of 20 mg of adenosine triphosphate, DDD significantly reduced the 2-year syncope recurrence rate from 69% in the control group to 23% in the active group.[230] Finally, cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex.[231,232]

5.4.2 Pacing mode and algorithm selection

Even if the quality of evidence is weak, DDD pacing is widely preferred in clinical practice to single-chamber RV pacing in counteracting blood pressure fall and preventing symptom recurrences. In patients with tilt-induced vasovagal syncope, DDD was used mostly with a rate-drop response feature that provides rapid DDD if the device detects a rapid decrease in heart rate. A comparison between DDD closed-loop stimulation and conventional DDD has been performed by means of a crossover design in two small studies. Both studies showed fewer syncope recurrences with closed-loop stimulation, both in the acute setting during repeated tilt testing[233] and during 18-month clinical follow-up.[227] However, until a formal parallel trial is performed, no recommendation can be given regarding the selection of the pacing mode (i.e. DDD with rate-drop response or DDD with closed-loop stimulation) and its programming.

Recommendations for pacing for reflex syncope

Recommendations	Class[a]	Level[b]
Dual-chamber cardiac pacing is indicated to reduce recurrent syncope in patients aged >40 years, with severe, unpredictable, recurrent syncope who have: • spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest or AVB; or • cardioinhibitory carotid sinus syndrome; or • asystolic syncope during tilt testing.[62,219,220,226,228,229]	I	A
Dual-chamber cardiac pacing may be considered to reduce syncope recurrences in patients with the clinical features of adenosine-sensitive syncope.[230]	IIb	B
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex.[231,232]	III	B

AVB = atrioventricular block.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

5.5 Pacing for suspected (undocumented) bradycardia

In patients with recurrent unexplained syncope or falls at the end of the conventional work-up, ILR monitoring should be considered in an attempt to document a spontaneous relapse instead of embarking on empiric cardiac pacing.[62]

5.5.1 Recurrent undiagnosed syncope

In patients with unexplained syncope at the end of a complete work-up and absence of any conduction disturbance, the lack of a rationale and the negative results of small studies[234,235] give sufficient evidence of inefficacy of cardiac pacing. Thus, cardiac pacing is not recommended until a diagnosis is made (*Figure 8*).

5.5.2 Recurrent falls

Between 15% and 20% of unexplained falls may be syncopal in nature, possibly bradyarrhythmic. Retrograde amnesia, which is frequent in the falling elderly, is responsible for misinterpretation of the event.[62] The management of unexplained falls should be the same as that for unexplained syncope (see *section 5.4.1*). In a randomized double-blind trial,[236] cardiac pacing was ineffective in preventing recurrences in patients with an unexplained fall in whom carotid sinus hypersensitivity was unable to induce syncope.

Recommendations for cardiac pacing in patients with suspected (undocumented) syncope and unexplained falls

Recommendations	Class[a]	Level[b]
In patients with recurrent unexplained falls, the same assessment as for unexplained syncope should be considered.[62]	IIa	C
Pacing is not recommended in patients with unexplained falls in the absence of any other documented indication.[236]	III	B
Pacing is not recommended in patients with unexplained syncope without evidence of SND or conduction disturbance.[234,235]	III	C

SND = sinus node dysfunction.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

6 Cardiac resynchronization therapy

6.1 Epidemiology, prognosis, and pathophysiology of heart failure suitable for cardiac resynchronization therapy by biventricular pacing

The prevalence of HF in the developed world approximates 1–2% of the adult population, rising to ≥10% among people aged >70 years.[237] The prevalence of HF is increasing (by 23% over the past decade according to one estimate) mainly due to the ageing of the population, with the age-specific incidence actually declining.[238–241] There are three distinct phenotypes of HF based on the measurement of LVEF [<40%, HF with reduced EF (HFrEF); 40–49%, HF with mildly reduced EF (HFmrEF); and ≥50%, HF with preserved EF (HFpEF)].[242] CRT is clinically useful mainly for patients with HFrEF and LVEF ≤35%. Patients with HFrEF constitute ~50% of the entire

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

population with HF, and HFrEF is less prevalent among individuals aged 70 years or older. The prognosis of HF varies according to the defined population. In contemporary clinical trials of HFrEF, 1-year mortality rates of ~6% are seen, whereas in large registry-based surveys, 1-year mortality rates exceed 20% in patients recently hospitalized for HF, but are closer to 6% in those recruited with stable outpatient HF.[243] The concept of CRT is based on the fact that in patients with HF and LV systolic dysfunction, high-grade intraventricular conduction delays are frequently observed, with a prevalence of QRS duration >120 ms in 25–50% of patients and of LBBB in 15–27% of cases. Moreover, in such patients, AV dyssynchrony is also often present with prolonged PR on the surface ECG in up to 52% of cases.[244–246] These electrical abnormalities may result in AV, interventricular, and intra-LV mechanical dyssynchrony.[247,248]

Recommendations for CRT are based on the results of the major RCTs of CRT, most of which have been restricted to the ~60% of HFrEF patients who are in SR. CRT is recommended (in addition to guideline-directed medical therapy) in only defined subsets of the HF patient population, the majority being symptomatic HF patients in SR with a reduced LVEF and a QRS duration ≥130 ms. Other smaller groups that may be considered for CRT include New York Heart Association (NYHA) class III or IV HF patients in AF with a reduced LVEF and a QRS duration ≥130 ms, provided a strategy to ensure biventricular capture is in place or the patient is expected to return to SR, and occasionally as an upgrade from a conventional pacemaker or an ICD in HFrEF patients who develop worsening HF with a high rate of ventricular pacing. A recent survey in the USA, which derived a nationally representative estimate of the entire US population of hospitalized patients, found that over a 10-year period (2003–2012), there were an estimated 378 247 CRT-D implantations, representing ~40 000 per year, or roughly 135 per million per year.[249] In Europe, previous estimates have reported that ~400 patients per million population per year might be suitable for CRT. This was based on an estimated prevalence of 35% for LVEF ≤35% in a representative HF population, of which 41% of patients were estimated to have a QRS duration ≥120 ms. The change to a higher threshold of QRS duration of 130 ms will reduce these estimates modestly.[250,251] In Sweden, a recent survey of 12 807 HFrEF patients showed that 7% had received CRT and 69% had no indication for CRT, but 24% had an indication and had not received CRT. These data highlight the underuse of CRT.[252,253] Finally, the Task Force stresses the point that the decision to implant CRT requires a shared decision-making with the patient.

6.2 Indication for cardiac resynchronization therapy: patients in sinus rhythm

CRT improves cardiac function, symptoms, and well-being, and reduces morbidity and mortality in an appropriately selected group of HF patients. CRT also improves quality-adjusted life-years among patients with moderate to severe HF. The beneficial effects of CRT have been extensively proven in patients with NYHA class II, III, and IV.[37,39,40,254–266] In contrast, there is rather limited evidence of CRT benefit in patients with NYHA functional class I and ischaemic cardiomyopathy.[40,265] In the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) study,[265] a total of 265 (7.8%) of 1820 patients were class I and had an ischaemic cardiomyopathy. At 7-year follow-up, the subgroup of patients with LBBB, NYHA functional class I, and ischaemic cardiomyopathy showed a non-significant trend towards lower risk of death from any cause [relative risk 0.66, 95% confidence interval (CI) 0.30–1.42; $P = 0.29$]. Therefore, present CRT recommendations are applicable to all patients in NYHA functional class II–IV of any aetiology.

The MUltisite STimulation In Cardiomyopathies (MUSTIC),[256,257] Multicenter Insync RAndomized Clinical Evaluation (MIRACLE), PACing THerapies in Congestive Heart Failure (PATH-CHF) I and II,[58,254,255,259] COmparison of Medical therapy, PAcing aNd defibrillatION (COMPANION),[260] and CArdiac REsynchronization in Heart Failure (CARE-HF)[39,261] trials compared the effect of CRT vs. guideline-directed medical therapy in NYHA functional class III or IV; in contrast, most recent trials have compared CRT-D with ICD on top of best medical therapy in NYHA functional class II.[37,40,262–266] Few studies have compared CRT-pacemaker (CRT-P) with conventional pacing.[190,267,268] Most studies of CRT have specified that LVEF should be ≤35%, but MADIT-CRT[40] and the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT)[37] considered an LVEF ≤30%, and the REsynchronization reVErses Remodelling in Systolic left vEntricular dysfunction (REVERSE) trial[262] specified ≤40%. Relatively few patients with an LVEF of 35–40% have been randomized, but an individual participant data meta-analysis suggests no diminution of the effect of CRT in this group.[33]

Not all patients respond favourably to CRT. Several characteristics predict reduction in ventricular volume (reverse remodelling) and improvement in morbidity and mortality. QRS width predicts CRT response and was the inclusion criterion in all randomized trials (for ECG criteria for LBBB and RBBB, see *Supplementary Table 1*). QRS morphology has been related to a beneficial response to CRT. Several studies have shown that patients with LBBB morphology are more likely to respond favourably, whereas there is less certainty about patients with non-LBBB morphology. Sipahi *et al.*[269,270] performed a meta-analysis in which they examined 33 clinical trials investigating the effect of QRS morphology on CRT, but only four (COMPANION, CARE-HF, MADIT-CRT, and RAFT) included outcomes according to QRS morphology. When they evaluated the effect of CRT on composite adverse clinical events in 3349 patients with LBBB at baseline, they observed a 36% reduction in risk with the use of CRT (relative risk 0.64, 95% CI 0.52–0.77; $P < 0.00001$). However, such benefit was not observed in patients with non-LBBB conduction abnormalities (relative risk 0.97, 95% CI 0.82–1.15; $P < 0.75$). When the analysis was limited to trials without ICD (CARE-HF and COMPANION), the benefit of CRT was still observed only in patients with LBBB ($P < 0.000001$). In a meta-analysis excluding COMPANION and MADIT-CRT, LBBB was not found to be a predictor of mortality, in contrast to QRS duration.[266] In a recent large meta-analysis of five RCTs (COMPANION, CARE-HF, MADIT-CRT, RAFT, and REVERSE) including 6523 participants (1766 with non-LBBB QRS morphology), CRT was not associated with a reduction in death and/or HF hospitalization in patients with non-LBBB QRS morphology (HR 0.99, 95% CI 0.82 - 1.2).[271] As patients have been aggregated in the non-LBBB category in nearly all studies and post-hoc analyses on the beneficial effect of QRS morphology in CRT, it is not possible to provide a separate recommendation for CRT in patients presenting with diffuse intraventricular conduction disturbance and

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

RBBB.[272–277] Patients with RBBB do not benefit from CRT[278] unless they show a so-called masked LBBB on ECG,[277] characterized by a broad, slurred, sometimes notched R wave on leads I and aVL, together with a leftward axis deviation. Individualized positioning of the LV lead is crucial in these patients.

An important recent notion is the possible role played by a prolonged PR in HF patients with non-LBBB. A few single-centre studies and two post-hoc analyses of large RCTs (COMPANION and MADIT-CRT) indicated a potential benefit of implanting CRT in this patient subgroup.[244,279,280] In MADIT-CRT, the subgroup of non-LBBB patients who had a prolonged PR did benefit from CRT-D, with a 73% reduction in the risk of HF or death and an 81% reduction in the risk of all-cause mortality compared with ICD-only therapy.[279] In non LBBB patients with normal PR, CRT-D was associated with a trend towards an increased risk of HF or death and a >2-fold higher mortality compared with ICD therapy, suggesting a bidirectional significant interaction. However, the data are too limited to give a recommendation.[279]

The results of the MADIT-CRT, REVERSE, and RAFT trials suggest that in patients with LBBB, there is likely to be potential benefit in all patients with LBBB regardless of QRS duration, and that no cut-off point can be identified clearly to exclude patients who will not respond according to the QRS duration.[272,273,275] In contrast, any benefit of CRT in patients with non-LBBB is evident mostly in those with a QRS duration ≥150 ms. Importantly, as shown in the MADIT-CRT long-term study and RAFT, the benefit in patients with QRS <150 ms appeared later during follow-up.[265,273]

The Echocardiography Guided Cardiac Resynchronization Therapy (Echo-CRT) trial suggested possible harm from CRT when baseline echocardiographic mechanical dyssynchrony in patients with QRS duration <130 ms is used.[264,281] Therefore, selection of CRT patients based solely on the use of cardiac imaging data is strongly discouraged in patients with so-called 'narrow' QRS (i.e. <130 ms).

Individual patient data pooled from three CRT-D vs. ICD trials enrolling predominantly patients with NYHA class II HF showed that women are more likely to respond than men.[282] In the US Food and Drug Administration meta-analysis of patient-level data, Zusterzeel *et al.*[283] found that the main difference occurred in patients with LBBB and a QRS of 130–149 ms. In this group, women had a 76% reduction in HF or death [absolute CRT-D to ICD difference, 23% (HR 0.24, 95% CI 0.11–0.53; $P < 0.001$)] and a 76% reduction in death alone [absolute difference 9% (HR 0.24, 95% CI 0.06–0.89; $P = 0.03$)], whereas there was no significant benefit in men for HF or death [absolute difference 4% (HR 0.85, 95% CI 0.60–1.21; $P = 0.38$)] or death alone [absolute difference 2% (HR 0.86, 95% CI 0.49–1.52; $P = 0.60$)]. A possible explanation for the greater benefit of CRT in women has been attributed to sex difference in LV size, as sex-specific differences in response disappear when QRS duration is normalized to LV end-diastolic volume.[284] Recently, computer modelling confirmed that sex differences in the LV size account for a significant proportion of the sex difference in QRS duration, and provided a possible mechanistic explanation for the sex difference in CRT response.[285,286] Simulations accounting for the smaller LV size in female CRT patients predict 9 - 13 ms lower QRS duration thresholds for females. As with other ECG parameters (e.g. duration of QT and corrected QT), it is conceivable that QRS duration also has to reflect sex difference.

ECG criteria of intraventricular conduction disturbance, LBBB, and non-LBBB have not been consistently defined and reported in any of the past CRT studies.[287,288] Similarly, the modality of QRS measurement (automatic or manual, and ECG recording machine) was not reported in CRT studies. However, the selection of ECG criteria appears to influence hard endpoints.[287–290] Similarly, ECG recording modality and ECG manufacturer have been shown to possibly affect the automatically measured QRS duration.

Finally, CRT is considered in patients on optimal medical treatment (OMT), including beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and mineralocorticoid receptor antagonists. However, a study raises the question of the timing of CRT, because the efficacy of the medical treatment can be limited in patients with LBBB, suggesting considering CRT sooner.[291] Moreover, whereas everyday clinical practice supports the use of sacubitril/valsartan, ivabradine, and sodium–glucose co-transporter-2 inhibitors, it must be emphasized that in the landmark trials documenting the efficacy of these drugs, very few patients had an indication for CRT. Thus, there are no strong data to support the mandatory use of these drugs before considering CRT.[292–295]

Recommendations for cardiac resynchronization therapy in patients in sinus rhythm

Recommendations	Class[a]	Level[b]
LBBB QRS morphology		
CRT is recommended for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality.[37,39,40,254–266,283,284]	I	A
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration 130–149 ms, and LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity and mortality.[37,39,40,254–266,283,284]	IIa	B
Non-LBBB QRS morphology		
CRT should be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity.[37,39,40,254–266,283,284]	IIa	B
CRT may be considered for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration 130–149 ms, and non-LBBB QRS morphology despite OMT, in order to improve symptoms and reduce morbidity.[273–278,281]	IIb	B
QRS duration		
CRT is not indicated in patients with HF and QRS duration <130 ms without an indication for RV pacing.[264,282]	III	A

CRT = cardiac resynchronization therapy; HF = heart failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; SR = sinus rhythm.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

6.3 Patients in atrial fibrillation

This section considers indications for CRT in patients with permanent AF or persistent AF unsuitable for AF ablation or after unsuccessful AF ablation. AF ablation has been reported to improve LVEF and reduce the HF hospitalization rate in selected patients. In particular, AF ablation is recommended for reversing LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable, regardless of symptoms.[296] Therefore, CRT should be considered in those patients with persistent AF and HFrEF when AF ablation cannot be performed or is declined by the patient. With regard to indications for rate control therapy and in particular to AVJ ablation, refer to the ESC Guidelines for the management of AF.[296]

6.3.1 Patients with atrial fibrillation and heart failure who are candidates for cardiac resynchronization therapy

A major determinant of the success of CRT is the effective delivery of biventricular pacing. A particular aspect of AF patients is that AF rhythm with fast ventricular rate and irregularity may interfere with adequate biventricular pacing delivery. AF may reduce the rate of effective biventricular capture by creating spontaneous, fusion, or pseudo-fusion beats. A high rate of biventricular pacing is not reached in two-thirds of patients with persistent or permanent AF.[297]

Data from large registries show that AF patients undergoing CRT have an increased risk of mortality even after adjusting for several clinical variables.[297–299] In most AF patients with intact AV conduction, an adequate biventricular pacing delivery can be achieved only by means of AVJ ablation.[300–302] A substudy of the RAFT trial[300] was unable to show benefit of CRT without AVJ ablation with regard to the combined endpoint of death or hospitalization for HF; notably, only 47% of the patients had a biventricular capture >90%. The decision to perform AVJ ablation is still a matter of debate, but most studies have shown improvements in LV function, functional capacity, exercise capacity, and survival (with the same magnitude as in patients with SR).[301] Gasparini *et al.*[302] compared total mortality of 443 AF patients who received AVJ ablation (n = 443) and of 895 AF patients who received rate-slowing drugs with the mortality of 6046 patients who were in SR. The long-term survival after CRT among patients with AF and AVJ ablation was similar to that observed among patients in SR (HR 0.93); the mortality was higher for AF patients treated with rate-slowing drugs (HR 1.52). The most common rate-controlling drugs used in AF are beta-blockers; although safe even in the context of AF and HFrEF, they do not necessarily have the same benefit as in patients with SR[303] and the benefit–risk ratio is influenced by other cardiovascular comorbidities.[304,305] In a systematic review and meta-analysis,[306] AVJ ablation, compared with no AVJ ablation, reduced mortality by 37% and reduced the rate of non-response by 59% in patients with biventricular pacing <90%, but showed no benefit in those with ≥90% biventricular pacing. Similarly, Tolosana *et al.* observed the same rate of responders (defined as ≥10% decrease in end-systolic volume) in AF patients who received AVJ ablation or rate-slowing drugs and patients in SR who had adequate biventricular pacing (97, 94, and 97%, respectively).[307] Importantly, AVJ ablation did not improve survival for patients in AF treated with CRT compared with those treated with rate-slowing drugs when an adequate biventricular pacing was achieved either with ablation (97%) or with drugs (94%).[308]

In conclusion, despite the weak evidence due to lack of large, randomized trials, the prevailing opinion of experts is in favour of the usefulness of CRT in patients with permanent AF and NYHA class III and IV with the same indications as for patients in SR, provided that AVJ ablation is added in those patients with incomplete (<90 - 95%) biventricular capture due to AF (*Figure 9*). However, there are other causes for incomplete biventricular pacing such as frequent premature ventricular beats, which may need to be treated (with drugs or ablation) before considering AVJ ablation. Importantly, evaluation of the biventricular pacing percentage is mainly given by the percentage of biventricular pacing using device memory, which does not reflect exactly the rate of effective biventricular capture. Holter monitoring may help to assess the real biventricular capture percentage.[309,310] A new algorithm has been developed that can continuously assess the effective biventricular pacing.[311]

For patients with permanent AF, there are no data supporting the difference in the magnitude of response to CRT according to the QRS morphology or a QRS duration cut-off of 150 ms.

It is important to remember that limited data are available for patients in NYHA class II.

6.3.2 Patients with uncontrolled heart rate who are candidates for atrioventricular junction ablation (irrespective of QRS duration)

AVJ ablation should be considered to control heart rate in patients unresponsive or intolerant to intensive rate and rhythm control therapy, or who are ineligible for AF ablation, accepting that these patients will become pacemaker dependent.[296] In particular, AVJ ablation combined with CRT may be preferred to AF ablation in severely symptomatic patients with permanent AF and at least one hospitalization for HF.[296]

AVJ ablation and permanent pacing from the RV apex provides highly efficient rate control and regularization of the ventricular response in AF, and improves symptoms in selected patients.[192] A large study with a propensity score-matched control group[194] showed a 53% reduction in total mortality in patients who underwent AVJ ablation compared with those treated with pharmacological rate control therapy. A class IIa indication is provided in the 2020 ESC Guidelines on AF.[296]

The downside of RV pacing, however, is that it induces LV dyssynchrony in ~50% of patients,[312] and that this may lead to worsening of HF symptoms in a minority. In the majority of patients, AVJ ablation improves LVEF even with RV apical (RVA) pacing due to amelioration of tachycardia-induced LV dysfunction, which commonly exists in these patients. CRT may prevent RV pacing-induced LV dyssynchrony. The multicentre, randomized, prospective Ablate and Pace in Atrial Fibrillation (APAF) trial[313] included 186 patients in whom a CRT or RV pacing device was implanted, followed by AVJ ablation. During a median follow-up of 20 months, CRT significantly reduced by 63% the primary composite endpoint of death due to HF, hospitalization due to HF, or worsening of HF. The beneficial effects of CRT were similar in patients with an EF ≤35%, NYHA class ≥III, and QRS width ≥120 ms, and in other patients with EF>35% or NYHA class < III or narrow QRS. Compared with the RV pacing group, responders increased from 63% to 83% (P = 0.003).[314] A meta-analysis of 696 patients from five trials showed a 62% reduction in

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

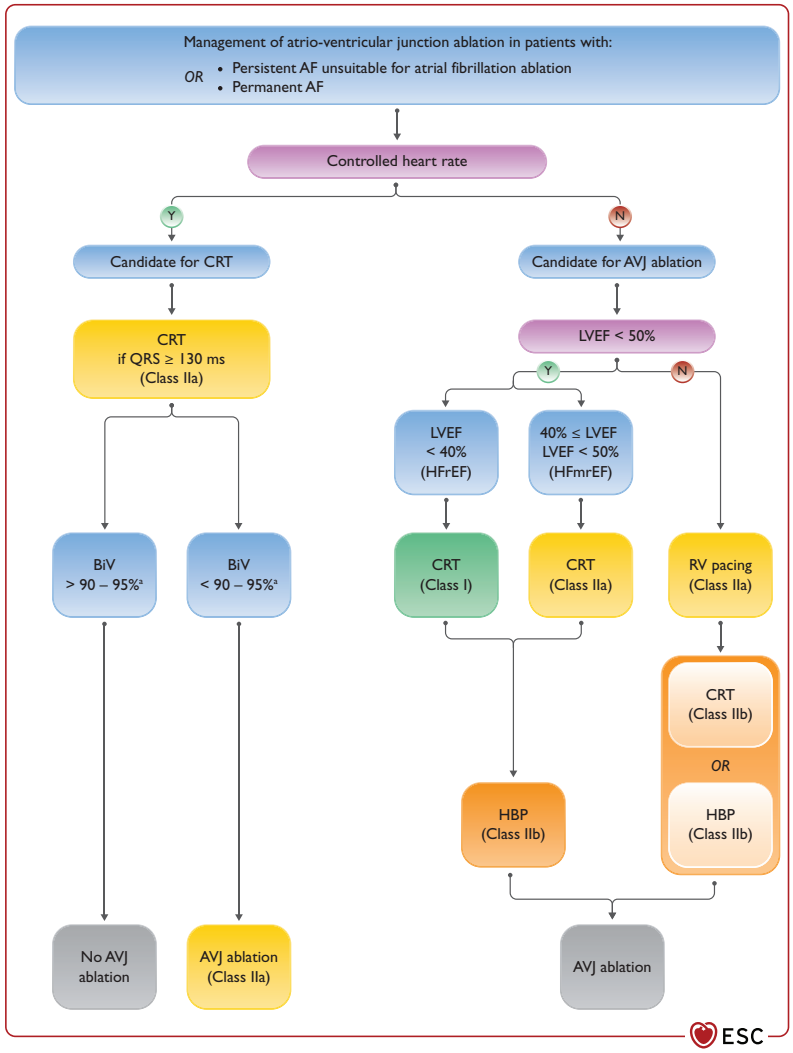

Figure 9 Indication for atrioventricular junction ablation in patients with symptomatic permanent atrial fibrillation or persistent atrial fibrillation unsuitable for atrial fibrillation ablation. AF = atrial fibrillation; AVJ = atrioventricular junction; BiV = biventricular; CRT = cardiac resynchronization therapy; ESC = European Society of Cardiology; HBP = His bundle pacing; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; QRS = Q, R, and S waves; RV = right ventricular/right ventricle. [a]Due to a rapid ventricular response. Note: the figure is based on the recommendations in the ESC Guidelines on AF.[296]

hospitalization for HF and a modest improvement in LVEF compared with RV pacing, but not in 6-min walked distance and quality of life assessed by means of the Minnesota Living with Heart Failure questionnaire.[315] In the APAF-CRT RCT, 102 elderly patients (mean age 72 years) with permanent AF, a narrow QRS (≤110 ms), and at least one hospitalization for HF in the previous year were randomized to AVJ ablation and CRT or to pharmacological rate control therapy.[195] After a median follow-up of 16 months, the primary composite outcome of HF death, hospitalization due to HF, or worsening HF had occurred in 10 patients (20%) in the ablation (AVJ) plus CRT arm and in 20 patients (38%) in the drug control arm (HR 0.38; $P = 0.013$). The results were mostly driven by a reduction in hospitalization for HF. The HR was 0.18 ($P = 0.01$) in patients with LVEF ≤35% and 0.62 ($P = 0.36$) in those with LVEF >35%. Furthermore, patients undergoing AVJ ablation and CRT had a 36% reduction in the specific symptoms and physical limitations of AF at 1-year follow-up ($P = 0.004$). In contrast to the main composite endpoint, the greatest symptomatic improvements were observed in patients with LVEF >35% ($P = 0.0003$).

In conclusion, there is evidence from randomized trials of an additional benefit of performing CRT pacing in patients with reduced EF, who are candidates for AVJ ablation for rate control to reduce hospitalization and improve quality of life. There is evidence that CRT is superior to RV pacing in relieving symptoms, but not mortality and hospitalization in patients with mid-range reduced systolic function (*Figure 9*).

6.3.3 Emerging novel modalities for CRT: role of conduction system pacing

HBP, alone or in conjunction with coronary sinus pacing, is a promising novel technique for delivering CRT, useful in AF patients

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

undergoing AVJ ablation.[198,199,316–318] Non-conventional CRT using HBP coronary sinus pacing (so-called 'His-optimized CRT') or left bundle branch area pacing, in comparison with conventional CRT, can achieve a narrower QRS with a 'quasi-normal' axis morphology, echocardiographic improvement of mechanical resynchronization indexes, and a better short-term clinical outcome.[319–321] In general, the potential benefit of HBP depends on the ability to achieve a narrow QRS complex that is similar to the native QRS complex, rather than on the LVEF. Widespread adoption of this technique relies upon further validation of its efficacy in large RCTs and improvements in lead design, delivery tools, and devices (see *section 7*).

Recommendations for cardiac resynchronization therapy in patients with persistent or permanent atrial fibrillation

Recommendations	Class[a]	Level[b]
1) In patients with HF with permanent AF who are candidates for CRT:		
1A) CRT should be considered for patients with HF and LVEF ≤35% in NYHA class III or IV despite OMT if they are in AF and have intrinsic QRS ≥130 ms, provided a strategy to ensure biventricular capture is in place, in order to improve symptoms and reduce morbidity and mortality.[302,306,307,322]	IIa	C
1B) AVJ ablation should be added in the case of incomplete biventricular pacing (<90–95%) due to conducted AF.[297–302]	IIa	B
2) In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration):		
2A) CRT is recommended in patients with HFrEF.[196,197,306,308]	I	B
2B) CRT rather than standard RV pacing should be considered in patients with HFmrEF.	IIa	C
2C) RV pacing should be considered in patients with HFpEF.[188,196,323]	IIa	B
2D) CRT may be considered in patients with HFpEF.	IIb	C

© ESC 2021

AF = atrial fibrillation; AVJ = atrioventricular junction; CRT = cardiac resynchronization therapy; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced ejection fraction (<40%); HFmrEF = heart failure with mildly reduced ejection fraction (40 - 49%); HFpEF = heart failure with preserved ejection fraction (≥50%) according to the 2021 ESC HF Guidelines;[242] LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.

6.4 Patients with conventional pacemaker or implantable cardioverter defibrillator who need upgrade to cardiac resynchronization therapy

Several studies have demonstrated the deleterious effect of chronic RV pacing with respect to an increased risk of HF symptoms or hospitalizations, which may be reduced by programming to maximize intrinsic conduction or prevented by CRT.[148,183,190,324] Previously, the benefit of CRT upgrade had been investigated only by observational controlled trials and registries,[325–339] mainly comparing upgrade with *de novo* CRT; in early, small, observational pre- vs. post-CRT studies;[340–346] and in crossover trials,[347–350] providing only limited clinical outcome data.

Based on a recent meta-analysis of observational studies, mostly single-centre,[351] echocardiographic and functional response as well as the risk of mortality or HF events was similar in patients after *de novo* vs. upgrade CRT; however, in previous subgroup analyses from large, randomized, prospective trials such as RAFT,[37] morbidity or mortality benefit was not confirmed.

Clinical outcomes are also influenced by the clinical characteristics of patients referred to CRT upgrade. Based on data from the European CRT Survey II,[352] a high-volume registry, and clinical characteristics from previous studies,[351] patients referred for a CRT upgrade differ from patients referred for *de novo* CRT implantation: they are older (even compared with those in RCTs), mainly male patients, and have more comorbidities such as AF, ischaemic heart disease, anaemia, and renal failure.

On average, the number of upgrade procedures reaches 23% of total CRT implantations, 60% from a conventional device and 40% from an ICD[352] in ESC countries, showing significant regional differences regarding the type of implanted device, such as CRT-P or CRT-D.[352,353]

Regarding procedure-related complications, several studies described a higher burden during upgrade procedures, ranging from 6.8% to 20.9% compared with *de novo* implantations.[339,354] This was not confirmed in a recent analysis of registry data, where upgrades had similar complication rates to *de novo* implantations.[352] Notably, 82% of these procedures were performed in high-volume centres. However, data on the long-term infection rates or lead revisions after CRT upgrade are scarce.[354,355]

The first prospective, randomized trial, the BUDAPEST CRT Upgrade study, is still ongoing, but may clarify these questions.[356]

Recommendation for upgrade from right ventricular pacing to cardiac resynchronization therapy

Recommendation	Class[a]	Level[b]
Patients who have received a conventional pacemaker or an ICD and who subsequently develop symptomatic HF with LVEF ≤35% despite OMT, and who have a significant[c] proportion of RV pacing, should be considered for upgrade to CRT.[37,148,185,190,324–352]	IIa	B

© ESC 2021

CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]A limit of 20% RV pacing for considering interventions for pacing-induced HF is supported by observational data. However, there are no data to support that any percentage of RV pacing can be considered as defining a true limit below which RV pacing is safe and beyond which RV pacing is harmful.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

6.5 Pacing in patients with reduced left ventricular ejection fraction and a conventional indication for antibradycardia pacing

Three randomized trials proved the superiority of biventricular pacing over RV pacing in patients with moderate to severe systolic dysfunction who required antibradycardia pacing to improve quality of life, NYHA class, and echocardiographic response.[190,357,358] In the Biventricular versus RV pacing in patients with AV block (BLOCK HF) trial, 691 patients with AVN disease and an indication for pacemaker with a mildly reduced EF (<50% by inclusion criteria, average 42.9% in the pacemaker group) were randomized to biventricular or RV pacing with or without an ICD, and followed for an average of 37 months.[190] The primary endpoint (a composite of ≥15% increase in the LV end-systolic volume, HF events, or mortality) was significantly improved in those assigned to CRT. CRT response is high among patients with systolic dysfunction and expected frequent RV pacing. Based on the MOde Selection Trial in Sinus-Node Dysfunction (MOST),[183] at least 40% RV pacing is associated with an increased risk of HF hospitalization or AF.

For patients with normal or preserved EF, data on benefit of CRT are conflicting with respect to hospitalization, and no mortality benefit was shown.[166,268,323,359] However, adverse remodelling caused by RV pacing was prevented by biventricular pacing, especially during long-term follow up.[323,359,360] A single-centre study showed that >20% RV pacing was associated with deleterious LV remodelling in patients with AVB and preserved LVEF.[188] Frailty should also be taken into account in deciding on CRT implantation, because of the higher costs and high complication rates of this procedure.

Recommendation for patients with heart failure and atrioventricular block

Recommendation	Class[a]	Level[b]
CRT rather than RV pacing is recommended for patients with HFrEF (<40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB in order to reduce morbidity. This includes patients with AF.[183,190,196,268,313,323,357–359,361,362]	I	A

© ESC 2021

AF = atrial fibrillation; AVB = atrioventricular block; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction (<40%) according to the 2021 ESC HF Guidelines;[242] NYHA = New York Heart Association; RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.

6.6 Benefit of adding implantable cardioverter defibrillator in patients with indications for cardiac resynchronization therapy

The mortality benefit of CRT-D over CRT-P is still unclear, mostly because no head to head RCTs have been designed to compare these two treatments. While CRT-D may further improve survival over CRT-P by reducing arrhythmic death, it does also add ICD-specific risks such as lead failure and inappropriate shocks, as well as costs.

COMPANION is the only trial to randomize patients to CRT-P or CRT-D, but was designed to assess the effects of CRT compared with OMT.[260] Crucially, it was not designed to compare CRT-D and CRT-P. CRT-P was associated with a marginally non-significant reduction in the risk of all-cause mortality (HR 0.76, 95% CI 0.58 - 1.01; $P = 0.06$), whereas CRT-D was associated with a significant, 36% risk reduction (HR 0.64, 95% CI 0.48–0.86; $P = 0.004$). Analysis of cause-specific mortality showed that SCD was significantly reduced by CRT-D (HR 0.44, 95% CI 0.23 - 0.86; $P = 0.02$) but not CRT-P (HR 1.21, 95% CI 0.7–2.07; $P = 0.50$).[363]

Nevertheless, the CARE-HF extension study proved that CRT-P alone reduced the risk of dying suddenly by 5.6%.[261] In line with these findings, subgroup analyses from RCTs in mild HF consistently found a reduction in ventricular arrhythmias with CRT.[364–368] These effects were especially observed among CRT responders, suggesting that the reduction in SCD risk is related to the extent of reverse LV remodelling with CRT.

Meta-analyses have drawn different conclusions on the matter. In the study by Al-Majed *et al.*,[369] the survival benefit of CRT was largely driven by a reduction in HF-related mortality, but SCD was not reduced. Lam *et al.*[370] showed that CRT-D significantly reduced mortality compared with medical therapy alone [odds ratio (OR) 0.57, 95% CI 0.40–0.80], but not when compared with ICD without CRT (OR 0.82, 95% CI 0.57–1.18) or CRT-P (OR 0.85, 95% CI 0.60–1.22). However, more recently, a network meta-analysis of 13 randomized trials including >12 000 patients found that CRT-D reduced total mortality by 19% (95% CI 1–33%, unadjusted) compared with CRT-P.[275]

Some recent large observational studies highlighted the importance of HF aetiology in the assessment of potential benefits of CRT-D over CRT-P.[371–373] CRT-D was associated with a significant risk reduction in all-cause mortality compared with CRT-P in patients with ischaemic cardiomyopathy. However, this difference was not found in patients with non-ischaemic cardiomyopathy.

These findings are consistent with the results from the DANISH study, which assigned 1116 patients with HF and non-ischaemic cardiomyopathy to receive either a primary prophylactic ICD or usual clinical care alone.[374] In both groups, 58% of patients also had CRT. Subgroup analysis showed that CRT-D was not superior to CRT-P in reducing the primary outcome of all-cause mortality (HR 0.91, 95% CI 0.64–1.29; $P = 0.59$) after a median follow-up of 67.6 months. However, in a large multicentre registry of >50 000 patients, CRT-D was associated with a significantly lower observed mortality.[375] Similar results were found in a recent propensity-matched cohort, where CRT-D was associated with a significantly lower all-cause mortality than CRT-P in patients with ischaemic aetiology and in patients with non-ischaemic HF under 75 years old.[376] Furthermore, the CeRtiTuDe Cohort study[377] showed better survival in CRT-D vs. CRT-P mainly due to a reduction of non-SCD. In an Italian multicentre CRT registry, the only independent predictor of mortality was the lack of an ICD.[378] Whereas these studies are limited by their observational design, important novel information on the issue of CRT-D vs. CRT-P is expected to come from an ongoing randomized trial, Re-evaluation of Optimal Re-synchronisation Therapy in

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Patients with Chronic Heart Failure (RESET-CRT; ClinicalTrials.gov Identifier NCT03494933).

In conclusion, prospective randomized trials are lacking, and available data are insufficient to firmly prove a superiority of CRT-D over CRT-P. However, it is important to consider that CRT trials in mild HF almost exclusively included patients with an ICD,[37,40,262] and that survival benefit of CRT without an ICD is uncertain in this particular group. Furthermore, observational data point towards significant survival benefits by CRT-D over CRT-P in patients with ischaemic cardiomyopathy, while no clear benefit has been shown in those with non-ischaemic cardiomyopathy.

Further predictive power concerning the risk of ventricular arrhythmia may be derived by contrast-enhanced CMR-guided scar characterization.[379,380] When discussing the choice between CRT-D and CRT-P, it is particularly important to consider general predictors of ICD effectiveness such as age and comorbidities associated with a mortality risk that competes with sudden arrhythmic death. Thus, the addition of ICD to CRT should be considered, especially in younger patients with a good survival prognosis, ischaemic aetiology, and a favourable comorbidity profile or presence of myocardial fibrosis (*Figure 10*). Moreover, the benefit of the ICD is governed by the balance between the risk of SCD and the risk of death from other causes, as well as comorbidities. Generally, the rate of sudden arrhythmic death in primary prevention appears to be declining (1%/year).

Owing to the complexity of the matter and the lack of clear evidence, it is particularly important that the choice between CRT-P and CRT-D is guided by a process of shared decision-making between patients and clinicians, taking into account both medical facts and patient values.

Recommendations for adding a defibrillator with cardiac resynchronization therapy

Recommendations	Class[a]	Level[b]
In patients who are candidates for an ICD and who have CRT indication, implantation of a CRT-D is recommended.[260,369,370,381]	I	A
In patients who are candidates for CRT, implantation of a CRT-D should be considered after individual risk assessment and using shared decision-making.[382,383]	IIa	B

© ESC 2021

CRT = cardiac resynchronization therapy; CRT-D = defibrillator with cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.
[a]Class of recommendation.
[b]Level of evidence.

6.7 Factors influencing the efficacy of cardiac resynchronization therapy: role of imaging techniques

The role of cardiac imaging in selecting HF patients for CRT has been evaluated mostly in observational analyses. Cardiac dyssynchrony,[384–386] myocardial scar,[387,388] and site of latest activation of the LV in relation to the LV lead position[389,390] have been associated with response to CRT. LVEF is the only parameter included in the guidelines for the selection of patients for CRT and is key to define the type of HF (<40%, HFrEF; 40–49%, HFmrEF; and ≥50%, HFpEF).[242] Echocardiography is the imaging technique of first choice for the assessment of LVEF. However, when intravenous contrast is not available and the acoustic window does not allow accurate assessment of LVEF, CMR or nuclear imaging should be considered.[242] Strain imaging (based on echocardiography or CMR) to quantify LV systolic function has shown incremental prognostic value in HF, and allows assessment of LV mechanical dyssynchrony.[384,391–393] CMR with LGE techniques (which show the presence of myocardial scar tissue) provide the best resolution to differentiate ischaemic cardiomyopathy and non-ischaemic cardiomyopathy.[394] The location (posterolateral) and extent (transmural vs. non-transmural and percentage of LV mass) of LGE on CMR or with nuclear techniques has been associated with the benefit from CRT.[380,387,395,396] Severe mitral regurgitation,[397] lack of significant electromechanical LV dyssynchrony,[384,385,392] and RV systolic dysfunction[398] have been associated with less improvement in clinical symptoms and reduced survival after CRT. Several imaging techniques have been tested to assess LV mechanical dyssynchrony, but most measures of LV dyssynchrony have not been tested in randomized trials including patients with HFrEF and wide QRS.[399] The presence of septal flash and apical rocking,[400] time differences based on radial strain and patterns of regional longitudinal strain,[384,392,401–403] non-invasive and invasive ECG mapping,[385,404] and vector-cardiography[405] have been proposed as novel techniques to predict response to CRT. Furthermore, LV myocardial work assessed with speckle-tracking echocardiography has been associated with survival in CRT recipients.[406] Coronary sinus venography is commonly performed to detect a suitable coronary vein in which to deploy an LV lead. Randomized trials have not systematically demonstrated that the guidance of LV lead implantation based on imaging (assessing myocardial scar or site of latest activation) is superior to standard practice.[389,390,407,408] Initial experience on using artificial intelligence to combine clinical, electrical, and imaging parameters to define phenotypes of patients that will benefit from CRT is promising, but more data are needed.[409]

Significant (moderate to severe and severe) secondary mitral regurgitation is frequent among candidates for CRT and has been shown to affect long-term survival as well as response to therapy.[406,410] CRT can improve mitral regurgitation in as many as 40% of patients.[406] However, in 60% of patients, significant mitral regurgitation is not corrected and, at long-term follow-up, progression of the underlying disease may lead to further deterioration of mitral valve function and poor prognosis. Transcatheter edge-to-edge mitral valve repair has been demonstrated to improve the response to CRT in registries.[411–414] However, results from recent RCTs including patients with symptomatic severe secondary mitral regurgitation despite guideline-directed medical therapy (including CRT when indicated) have not consistently shown a benefit from transcatheter edge-to-edge mitral valve repair.[415,416]

Therefore, selection of patients for CRT based on imaging is limited to the measurement of LVEF, whereas the assessment of other factors such as extent of myocardial scar, presence of mitral

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

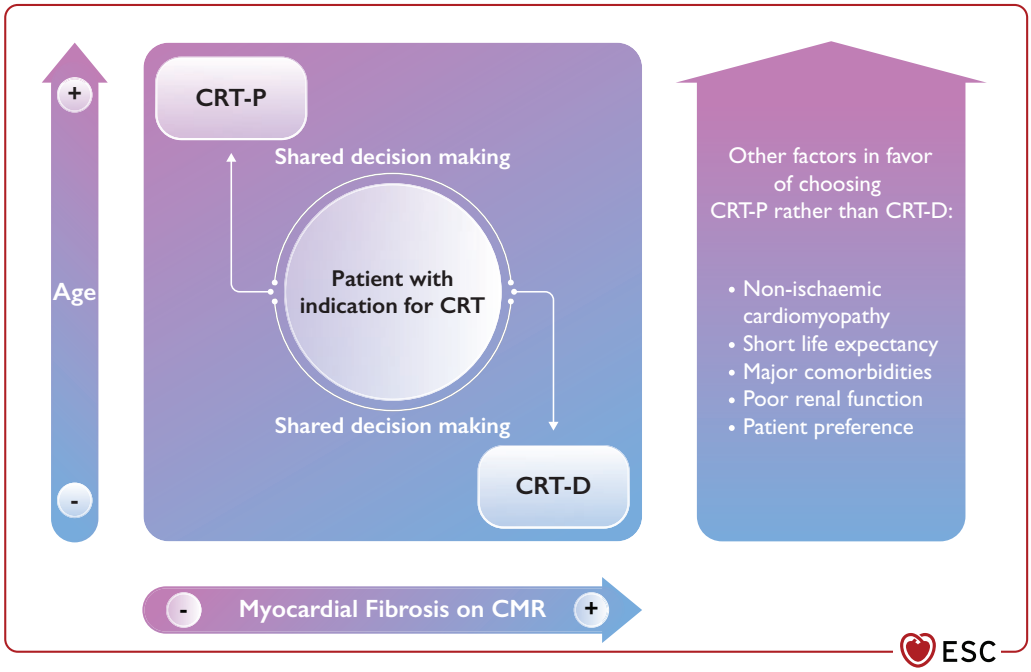

Figure 10 Patient's clinical characteristics and preference to be considered for the decision-making between cardiac resynchronization therapy pacemaker or defibrillator. CRT-P = cardiac resynchronization therapy-pacemaker; CRT-D = defibrillator with cardiac resynchronization therapy; CMR = cardiovascular magnetic resonance.

regurgitation, or RV systolic function is important in identifying potential non-responders that may need additional treatment (mitral valve intervention, for example).

Alternatives to conventional coronary sinus pacing for CRT (epicardial, endocardial) are described in *section 6.1* in the *Supplementary data*.

7 Alternative pacing strategies and sites

Alternative RV pacing sites (as opposed to RVA pacing) include pacing from the RV outflow tract (RVOT), the mid and high RV septum (RVS), HBP, para-Hisian pacing, and left bundle branch area pacing, which includes LV septal pacing and left bundle branch pacing.

7.1 Septal pacing

Since the 2013 ESC Guidelines,[33] two randomized trials found no difference in clinical outcomes between RVS and RVA pacing in the setting of AVB[417] or CRT,[418] respectively. A meta-analysis reported an echocardiographic benefit of RVS pacing in patients with pre-existing reduced LVEF.[419] In an observational study, RVS pacing was associated with a lower risk of perforation.[420] However, true RVS pacing is not easily obtained and ascertained,[421] and neither beneficial nor harmful effects of RVS pacing compared with RVA pacing have been shown on relevant clinical endpoints (*Supplementary Table 9*). Current evidence does not support systematically recommending either RVS or RVA pacing for all patients.

7.2 His bundle pacing

HBP was first reported in humans in 2000,[199] and is steadily gaining interest for providing a more physiological alternative to RV pacing. It may also correct intraventricular conduction delay in a subset of patients, thereby providing an alternative to biventricular pacing for treating HF. The advent of new tools has greatly facilitated implantation, which has become routine in a growing number of centres. HBP is used in lieu of RV pacing, in lieu of biventricular pacing, and as His-optimized CRT (HOT-CRT),[319] which exploits a synergistic effect between HBP and RV pacing, LV pacing, or biventricular pacing to improve synchrony. There is growing evidence, mainly from observational studies, that HBP may be safe and effective in these settings (*Supplementary Table 10*), although large RCTs and long-term follow-up are still lacking.[422] With more data on safety and effectiveness, HBP is likely to play a growing role in pacing therapy in the future.

7.2.1 Implantation and follow-up

The use of guiding catheters to deliver leads has facilitated implantation, with success rates exceeding 80%.[422] In an international registry, implant success was 87% after a learning curve of 40 cases.[423] Selective HBP is easily recognized by an isoelectric interval (corresponding to the HV) between the pacing spike and QRS onset, whereas with non-selective HBP, a 'pseudo-delta' wave is observed due to capture of local myocardium.[424] In addition, correction of BBB may be observed (*Figure 11*). It is important to distinguish non-selective HBP from para-Hisian pacing (where there is no capture of conduction tissue) by evaluating transitions in QRS morphology by reducing pacing output or with pacing manoeuvres.[425]

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

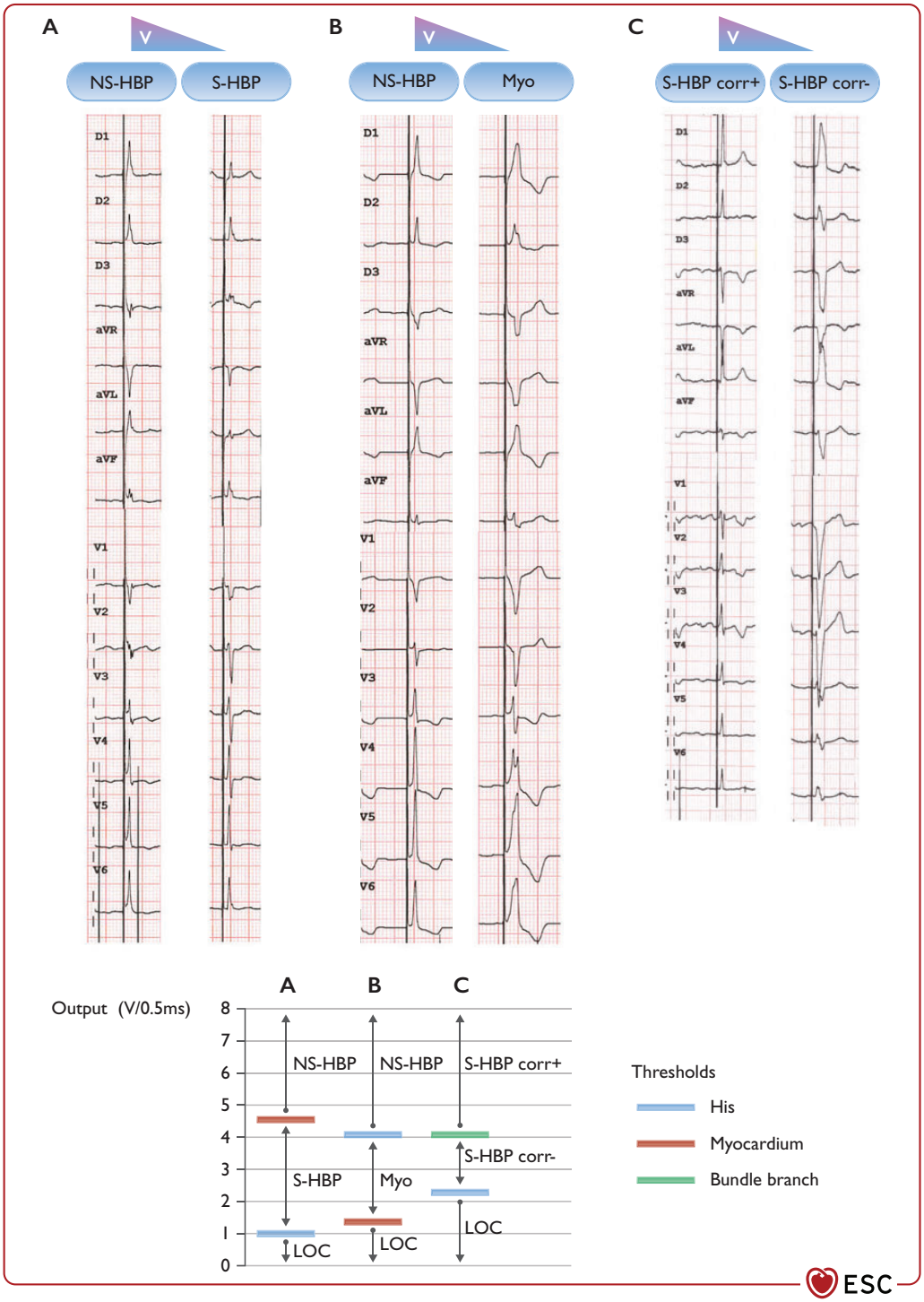

Figure 11 Three patients with different types of transitions in QRS morphology with His bundle pacing and decrementing pacing output. BBB = bundle branch block; Corr± = with/without correction of bundle branch block; LBBB = left bundle branch block; LOC = loss of capture; Myo = myocardium; NSHBP = non-selective His bundle pacing; S-HBP = selective His bundle pacing. (*A*) Non-selective to selective His capture. Note the presence of a 'pseudo-delta' wave with non-selective capture and an isoelectric interval after the pacing spike with selective capture. (*B*) Non-selective His capture to myocardial capture only. (*C*) Selective His capture with correction of BBB to selective His capture with LBBB. Note: the graph on the right of the panel shows a schematic representation of the different thresholds in the three instances.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Table 9 Advantages and disadvantages of a 'backup' ventricular lead with His bundle pacing

Advantages
• Increased safety (in case of loss of capture of the HBP lead)
• Can be used for sensing (lower risk of ventricular undersensing, no risk of His or atrial oversensing)
• Programming of pacing output with lower safety margins
• May serve to narrow the QRS with fusion pacing in the case of selective-HBP with uncorrected RBBB
Disadvantages
• Higher cost
• More transvenous hardware
• Risk associated with the additional lead (e.g. ventricular perforation)
• More complex programming
• "Off-label" use (current regulatory approval and MRI-conditionality for HBP is only granted for His leads connected to the RV port)

HBP = His bundle pacing; MRI = magnetic resonance imaging; RBBB = right bundle branch block.

© ESC 2021

Compared with RV pacing, HBP capture thresholds are on average higher and sensing amplitudes lower. A recent observational study raised concern with regard to increasing HBP pacing thresholds with intermediate follow-up.[426] The higher capture thresholds lead to shorter battery longevity (at 5 years there were 9% generator changes with HBP compared with 1% with RVP).[427] Capture thresholds of HBP at implantation should aim to be <2.0 V/1 ms (or <2.5 V/0.4 ms) and bipolar R-wave sensing amplitude >2.0 mV. With experience, thresholds decrease as implanters gain confidence to reposition leads. Sensing issues include not only ventricular undersensing, but also oversensing of atrial or His potentials (which may be potentially lethal in a pacemaker-dependent patient).

An RV backup lead should be considered if the implanter is inexperienced, or if there are high capture thresholds or sensing issues in pacemaker-dependent patients, in those scheduled for AVN ablation (where there is a risk of compromising HBP), or in patients with high-degree or infranodal block. Pros and cons are listed in *Table 9*.

Several series have shown that the rate of mid-term lead revision is relatively high at ~7%,[318,423,427,428] (and reported to be as high as 11%[426]), and is higher than RV pacing, which is 2–3%.[427,429] Therefore, it is advisable to follow-up these patients at least once every 6 months or place them on remote monitoring (ensuring that automatic threshold measurements correspond to those measured manually, as this may not be the case and depends on device configuration).[430] Device programming should take into account specific requirements for HBP, which are covered in detail elsewhere.[431,432]

7.2.2 Indications

7.2.2.1 Pacing for bradycardia

One study reported that in patients with AVB and normal baseline LVEF, the incidence of RV pacing-induced cardiomyopathy was 12.3% and the risk was increased if the percentage of ventricular pacing was ≥20% (HR 6.76; $P = 0.002$).[188] However, there are no data to support that any percentage of RV pacing can be considered as defining a true limit below which RV pacing is safe and beyond which RV pacing is harmful. Observational data indicate that patients with HBP fare better in terms of HF hospitalizations than patients with RV pacing if the percentage of ventricular pacing is >20% (HR 0.54; $P = 0.01$).[42] Of note, the average baseline LVEF in patients with HBP in that study was 55% and the average QRS duration was 105 ms. HBP may therefore avoid clinical deterioration in these patients, particularly if the intrinsic QRS is narrow or if BBB is corrected by HBP.

In a series of 100 patients with AVB undergoing HBP by experienced operators, implantation was successful in 41/54 (76%) patients with infranodal AVB and higher in the case of nodal block (93%; $P < 0.05$).[433] Over a mean follow-up of 19 ± 12 months, lead revision was necessary in 2/41 (5%) patients with infranodal block and in 3/43 (7%) with nodal block. Notably, the average LVEF in this series was 54%, and there are no data reported specifically on HBP in patients with AVB and reduced LVEF. HBP is an option in patients with a narrow QRS or if HBP corrects BBB, but otherwise biventricular pacing is indicated.

There is a need for RCTs to compare the safety and efficacy of HBP with RV pacing. It is important to balance the potential benefits of HBP with the aforementioned issues of higher capture thresholds and shorter battery longevity, a higher rate of lead revision, and more frequent sensing issues, compared with RV pacing. It is also important to consider the operator's experience and expertise with HBP, and whether a backup ventricular pacing lead is indicated. The patient's safety should be first and foremost in decision-making.

7.2.2.2 Pace and ablate

Seven observational series, totalling >240 patients treated with a 'pace-and-ablate' strategy for rapidly conducted AF, found an improvement in LVEF and NYHA class compared with baseline with HBP.[197–199,434] Long-term results with a median of 3 years of follow-up have been reported, with favourable outcomes.[434] A single-blinded, randomized, crossover study in 16 patients compared HBP with RVA pacing over 6 months and found better NYHA and 6-min walk distance with HBP, without differences in echocardiographic parameters.[200] However, only four patients in this study had confirmed HBP (with para-Hisian pacing in the remaining patients). These studies included patients with reduced as well as preserved LVEF,[197,198] and QRS width was on average <120 ms. HBP is of particular interest in patients with a normal baseline QRS morphology as it preserves intrinsic ventricular synchrony, However, a caveat is that AVJ ablation may result in an increase in HBP capture thresholds or in lead dislodgments in a minority of patients.[197,199,318,426] Owing to these issues and risk of HBP lead failure, a backup RV lead should be considered.

7.2.2.3 Role in cardiac resynchronization therapy

In 1977, Narula showed that pacing of the His bundle can correct LBBB in a subset of patients, implying a proximal site of conduction disturbance with longitudinal dissociation within the His bundle.[435] A recent mapping study reported intra-Hisian block in 46% of patients with LBBB, in whom 94% were corrected by temporary HBP.[436] HBP may therefore be used in lieu of biventricular pacing for HBP-based CRT, as some data have shown that results are comparable (see *Supplementary Table 10*).[437–439] Nevertheless, especially in CRT candidates with LBBB, biventricular pacing has more solid evidence of efficacy and safety, and therefore remains first-line therapy. However, HBP should be considered as a bailout solution in the case of failed

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

LV lead implantation along with other options such as surgical epicardial leads[424,440] (see *section 6.7*). An interesting population is patients with RBBB, who are known to respond less well to biventricular pacing, in whom HBP has shown promising preliminary results in a series of 37 patients.[441] HBP may sometimes incompletely correct BBB, and can be used in conjunction with RV, LV, or biventricular pacing, as in the HOT-CRT study.[319] This is of particular interest in patients with permanent AF, in whom a His lead may be connected to the vacant atrial port, thus offering additional therapeutic options.

7.3 Left bundle branch area pacing

With left bundle branch area pacing, the lead is implanted slightly distal to the His bundle and is screwed deep in the LV septum, ideally to capture the left bundle branch.[442] Advantages of this technique are that electrical parameters are usually excellent, it may be successful in blocks that are too distal to be treated with HBP, and it also facilitates AVJ ablation, which may be challenging with HBP. However, although the technique is very promising, data on this modality are still scarce (*Supplementary Table 11*), and there is concern regarding long-term lead performance and feasibility of lead extraction. Recommendations for using left bundle branch area pacing cannot therefore be formulated at this stage. However, conduction system pacing (which includes HBP and left bundle branch area pacing) is very likely to play a growing role in the future, and the current recommendations will probably need to be revised once more solid evidence of safety and efficacy (from randomized trials) is published. A comparison of RV pacing, HBP, and left bundle branch area pacing is provided in *Supplementary Table 12*.

Recommendations for using His bundle pacing

Recommendations	Class[a]	Level[b]
In patients treated with HBP, device programming tailored to specific requirements of HBP is recommended.[430,431]	I	C
In CRT candidates in whom coronary sinus lead implantation is unsuccessful, HBP should be considered as a treatment option along with other techniques such as surgical epicardial lead.[318,424,440,443]	IIa	B
In patients treated with HBP, implantation of an RV lead used as 'backup' for pacing should be considered in specific situations (e.g. pacemaker dependency, high-grade AVB, infranodal block, high pacing threshold, planned AVJ ablation) or for sensing in the case of issues with detection (e.g. risk of ventricular undersensing or oversensing of atrial/His potentials).[423,426,444]	IIa	C
HBP with a ventricular backup lead may be considered in patients in whom a 'pace-and-ablate' strategy for rapidly conducted supraventricular arrhythmia is indicated, particularly when the intrinsic QRS is narrow.[197,199,200,318]	IIb	C
HBP may be considered as an alternative to RV pacing in patients with AVB and LVEF >40%, who are anticipated to have >20% ventricular pacing.[42,433]	IIb	C

Continued

© ESC 2021

AVB = atrioventricular block; AVJ = atrioventricular junction; CRT = cardiac resynchronization therapy; HBP = His bundle pacing; LVEF = left ventricular ejection fraction; RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.

7.4 Leadless pacing

Leadless pacemakers have been developed to address limitations typically related to pulse generator pocket and transvenous leads of conventional pacemaker systems. Currently, two leadless pacemaker systems have been studied in clinical trials, of which one is currently available for clinical use. Both are inserted into the RV cavity by a femoral venous approach using a specially designed catheter-based delivery system.

A number of prospective registries have reported that implantation success rates are high, with adequate electrical results both at implant and at follow-up (*Supplementary Table 13*). 'Real-world' results of one leadless pacemaker system, including 1817 patients, reported serious adverse events in 2.7% of patients.[50] The prevalence of leadless device infections is low as the principal sources of infection (i.e. the subdermal surgical pocket and pacemaker leads) are absent. However, during the initial operator experience, there was a higher incidence of peri-operative major complications (6.5%), including perforation and tamponade, vascular complications, ventricular arrhythmias, and death.[445] These data highlight the importance of adequate training and supervision in this domain when starting with leadless pacemaker implantation. In addition, implanting physicians should have the same competency and accreditation as those required for standard transvenous pacing to be able to offer the most suitable system for a given patient. Implantation of leadless pacemakers should be performed in an adequate setting (i.e. with high-resolution multiplane fluoroscopy) and with cardiac surgery available on site due to the risk of tamponade, which may be more difficult to manage than with standard pacing.[446,447]

Leadless pacemakers that only function in the VVI(R) mode restrict indications to patients with AF or very infrequent pacing (e.g. paroxysmal AVB). Recently, VDD pacing (by detection of atrial contraction by the accelerometer) has been introduced, which extends indications to patients with AVB with preserved sinus node function. AV synchrony is maintained 70–90% of the time, depending on the patient's position and activity, based on data from two studies including 73 patients in SR and high-degree AV block.[448] There may in future be an alternative to standard DDD pacemakers in selected patients if the potential benefits of leadless pacing outweigh the potential benefits of 100% AV synchrony, atrial pacing, and atrial arrhythmia monitoring.

Indications for leadless pacemakers include obstruction of the venous route used for standard pacemaker implantation (e.g. bilateral venous thoracic outlet syndrome or chronic obstruction of the superior vena cava), pocket issues (e.g. in the case of cachexia or dementia), or particularly increased infection risk [e.g. in the case of dialysis

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

or previous cardiovascular implantable electronic device (CIED) infection]. Observational data showed that a leadless pacemaker was a safe pacing alternative in patients with previous device infection and explant, and in patients on chronic haemodialysis. Whereas observational data indicate high efficacy and low complication rates with leadless pacemakers,[50] there are currently no data from RCTs documenting the long-term safety and efficacy of leadless vs. standard transvenous pacemakers, and therefore the indication for a leadless pacemaker should be carefully considered on a case by case basis. The absence of long-term data on leadless pacemaker performance and limited data on retrievability and end-of-life strategy[449] require careful consideration before selecting leadless pacemaker therapy, especially for younger patients (e.g. with a life expectancy >20 years).

Recommendations for using leadless pacing (leadless pacemaker)

Recommendations	Class[a]	Level[b]
Leadless pacemakers should be considered as an alternative to transvenous pacemakers when no upper extremity venous access exists or when risk of device pocket infection is particularly high, such as previous infection and patients on haemodialysis.[45,47–50,450]	IIa	B
Leadless pacemakers may be considered as an alternative to standard single-lead ventricular pacing, taking into consideration life expectancy and using shared decision-making.[45,47–50]	IIb	C

[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

8 Indications for pacing in specific conditions

8.1 Pacing in acute myocardial infarction

In patients with acute MI, significant bradyarrhythmia may occur due to autonomic influences or damage of the conduction system by ischaemia and/or reperfusion. The right coronary artery supplies the sinus node in 60% and the AVN and His bundle in 90% of patients.[451,452] AVB is located above the His bundle in most patients with inferior infarction, but is usually infra-Hisian and preceded by intraventricular conduction disturbances in anterior infarction.[451,453–457]

The incidence of high-degree AVB in patients with ST-segment elevation MI has declined to 3–4% in the primary percutaneous coronary intervention era.[458–460] High-degree AVB is most frequent in inferior or inferolateral infarctions.[455,458–461]

Patients with high-degree AVB have higher clinical risk and larger infarctions especially when AVB complicates an anterior infarction.[458–460,462,463] New-onset intraventricular conduction disturbance is also associated with larger infarctions.[464–467]

Sinus bradycardia and AVB at presentation can be vagally mediated and may respond to atropine.[455,468] Revascularization is recommended in patients with AVB who have not yet received reperfusion therapy.[469] AVB may require temporary pacing in the presence of refractory symptoms or haemodynamic compromise, but most often resolves spontaneously within a few days and only a minority of patients require permanent pacing.[451,454,456,458,462] In patients with persistent intraventricular conduction abnormalities and transient AVB in whom permanent pacing was recommended in the past, there is no evidence that permanent cardiac pacing improves outcome.[454,470] These patients frequently have HF and poor LV function, and should be evaluated for ICD, CRT-P, or CRT-D rather than conventional pacing if an early device implantation is considered.[471]

If AVB does not resolve within 10 days, a permanent pacemaker should be implanted. In the absence of robust scientific data, the waiting period before pacemaker implantation has to be decided individually. It may last up to 10 days but can be shortened to 5 days depending on the occluded vessel, time delay, and success of revascularization. Conditions favouring consideration of earlier pacemaker implantation include unsuccessful or late revascularization, anterior MI, bifascicular block or AV block before MI, and progression of AV block within the first days after MI. Sick sinus syndrome after occlusion of the right coronary artery resolves in most cases. If revascularization is incomplete, pacemaker implantation can usually still be postponed and implantation only be performed if symptoms due to sinus bradycardia persist.

Recommendations for cardiac pacing after acute myocardial infarction

Recommendations	Class[a]	Level[b]
Implantation of a permanent pacemaker is indicated with the same recommendations as in a general population (*section 5.2*) when AVB does not resolve within a waiting period of at least 5 days after MI.	I	C
In selected patients with AVB in the context of anterior wall MI and acute HF, early device implantation (CRT-D/CRT-P) may be considered.[471]	IIb	C
Pacing is not recommended if AVB resolves after revascularization or spontaneously.[454–456,458]	III	B

AVB = atrioventricular block; CRT-D = defibrillator with cardiac resynchronization therapy; CRT-P = cardiac resynchronization therapy-pacemaker; MI = myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

8.2 Pacing after cardiac surgery and heart transplantation

8.2.1 Pacing after coronary artery bypass graft and valve surgery

AVB may occur in 1–4% of cases after cardiac surgery and in ~8% after repeat valve surgery.[472–476] SND may occur after right lateral atriotomy or transseptal superior approaches to the mitral valve.[473,474]

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Pacemaker implantation is more frequent after valvular than after coronary artery bypass graft (CABG) surgery.[477] In clinical practice, an observation period of 3–7 days is usually applied before implanting a permanent pacemaker[473] to allow regression of transient bradycardias. The ideal timing of pacemaker implantation after cardiac surgery remains a topic of controversy, due to the fact that 60–70% of patients implanted for SND and up to 25% of those implanted for AVB are not pacemaker dependent at follow-up.[473,478] In the case of complete AVB occurring within the first 24 h after valvular surgery and persisting for 48 h, resolution within the next 1–2 weeks is unlikely and earlier implantation of a pacemaker may be considered.[479,480] The same approach appears reasonable for complete AVB with a low rate of escape rhythm.[473] The situation in CHD surgery and in children may be different (see *section 8.4*).

In valvular endocarditis, predictors of AVB after surgery are pre-operative conduction abnormalities, *Staphylococcus aureus* infection, intracardiac abscess, tricuspid valve involvement, and previous valvular surgery.[481] In patients with endocarditis and peri-operative AVB, early pacemaker implantation is reasonable, especially when one or more predicting factors are present. In light of the infected state of the patient, intra-operative implantation of an epicardial pacemaker system during valvular surgery may be reasonable despite the absence of solid data on infection rates of epicardial vs. transvenous pacemaker systems.

8.2.2 Pacing after heart transplantation

SND is common and leads to permanent pacemaker implantation after heart transplantation in 8% of patients.[473] Possible causes of SND include surgical trauma, sinus node artery damage, or ischaemia and prolonged cardiac ischaemic times.[482,483] AVB is less common, and is probably related to inadequate preservation of the donor heart.[473,483,484] Chronotropic incompetence is always present following standard orthotopic heart transplantation, as a result of loss of autonomic control. As sinus node and AVN function improve during the first few weeks after transplantation, an observation period before pacemaker implantation may allow spontaneous improvement of bradycardia.[485] There is general consensus that patients in whom symptomatic bradycardia persists after the third post-operative week may require permanent pacemaker implantation. DDD(R) mode with minimized ventricular pacing in the case of intact AVN conduction is recommended.[483]

8.2.3 Pacing after tricuspid valve surgery

An underestimated aspect of the surgical management of tricuspid valve disease is to address trans-tricuspid pacemaker or ICD leads. Such leads can interfere with the function of a repaired tricuspid valve or tricuspid valve prosthesis.

Placing an epicardial RV lead at the time of tricuspid valve surgery is the most straightforward alternative in cases with type II second- or third-degree AVB. There have been doubts about the long-term performance of epicardial leads, but recent data indicate, at least for epicardial LV leads, performance comparable with transvenous leads.[486]

Ventricular pacing after mechanical tricuspid valve replacement using a coronary sinus lead appears safe and feasible, but only results from small patient cohorts have been published. Procedural success of implantation was 100% in 23 patients; after 5.3 ± 2.8 years, 96% of leads were functional with stable pacing and sensing parameters.[487]

HBP is emerging as a more physiological method of ventricular pacing and may evolve into a possible solution in patients with AV conduction disease after tricuspid valve surgery. One study investigating 30 patients with HBP after cardiac valve operations reported successful permanent HBP in 93% of these patients.[488] This study included 10 patients with tricuspid valve annuloplasty.

After replacement by a mechanical valve, transvalvular lead placement is contraindicated, and implanting either a coronary sinus lead for ventricular pacing or epicardial leads, which may be placed minimally invasively, is recommended. To avoid damaging a repaired tricuspid valve or a tricuspid bioprosthesis, the optimal solution in patients needing ventricular pacing after such surgery should not include transvalvular lead implantation. Implanting a coronary sinus lead for ventricular pacing or minimally invasively placed epicardial leads is judged to be the preferred choice. However, as indicated in observational reports, transvalvular lead implantation was used with acceptable results,[489] and still may be considered in selected patients after tricuspid valve annuloplasty, other types of repair, and replacement of a tricuspid valve by a bioprosthesis.

Performing tricuspid valve replacement in a patient with an existing RV lead, removal of the old RV lead and implantation of an epicardial RV lead should be preferred over sewing in the existing lead between a bioprosthesis and annulus. The reasons are that sewing in the lead may be associated with higher risk of lead failure and, in the case of future need for lead extraction, such a procedure is likely to require open heart surgery, which will be a reintervention with higher operative risk. In cases of tricuspid valve repair with a current annuloplasty ring with an open segment and without concomitant leaflet procedures, an existing RV lead may be left in place without sewing it in between the ring and the annulus. However, even in isolated annuloplasty procedures, an existing RV lead should ideally be removed to avoid future lead-related complications to the repaired tricuspid valve and an epicardial RV lead should be implanted. Particularly in patients not in need of a dual-chamber device, the use of a leadless pacemaker for ventricular pacing may serve as a feasible future alternative after tricuspid valve repair or replacement by a bioprosthesis. However, experience is very limited, and no long-term data are available in this cohort. Crossing a mechanical tricuspid valve with the delivery sheath and a leadless pacemaker is contraindicated.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Recommendations for cardiac pacing after cardiac surgery and heart transplantation

Recommendations	Class[a]	Level[b]
1) High-degree or complete AVB after cardiac surgery A period of clinical observation of at least 5 days is indicated to assess whether the rhythm disturbance is transient and resolves. However, in the case of complete AVB with low or no escape rhythm when resolution is unlikely, this observation period can be shortened.[473,478]	I	C
2) Surgery for valvular endocarditis and intraoperative complete AVB Immediate epicardial pacemaker implantation should be considered in patients with surgery for valvular endocarditis and complete AVB if one of the following predictors of persistence is present: pre-operative conduction abnormality, *Staphylococcus aureus* infection, intracardiac abscess, tricuspid valve involvement, or previous valvular surgery.[481]	IIa	C
3) SND after cardiac surgery and heart transplantation Before permanent pacemaker implantation, a period of observation of up to 6 weeks should be considered.[473]	IIa	C
4) Chronotropic incompetence after heart transplantation Cardiac pacing should be considered for chronotropic incompetence persisting for >6 weeks after heart transplantation to improve quality of life.[485]	IIa	C
5) Patients requiring pacing at the time of tricuspid valve surgery Transvalvular leads should be avoided and epicardial ventricular leads used. During tricuspid valve surgery, removal of pre-existing transvalvular leads should be considered and preferred over sewing in the lead between the annulus and a bioprosthesis or annuloplasty ring. In the case of an isolated tricuspid annuloplasty based on an individual risk–benefit analysis, a pre-existing RV lead may be left in place without jailing it between ring and annulus.	IIa	C
6) Patients requiring pacing after biological tricuspid valve replacement/tricuspid valve ring repair When ventricular pacing is indicated, transvenous implantation of a coronary sinus lead or minimally invasive placement of an epicardial ventricular lead should be considered and preferred over a transvenous transvalvular approach.[487]	IIa	C
7) Patients requiring pacing after mechanical tricuspid valve replacement Implantation of a transvalvular RV lead should be avoided.	III	C

Continued

© ESC 2021

AVB = atrioventricular block; RV = right ventricular; SND = sinus node dysfunction.
[a]Class of recommendation.
[b]Level of evidence.

8.3 Pacing after transcatheter aortic valve implantation

For extended literature on patients with pre-procedural RBBB and post-procedural LBBB see *sections 8.3.1* and *8.3.2* in the *Supplementary data*.

Rates of permanent pacemaker implantation after TAVI range between 3.4% and 25.9% in randomized trials and large registries.[490–502] Whereas the association between pacing after TAVI and outcome is controversial,[503–509] RV pacing may lead to deterioration in LV function.[183,510,511] Thus, efforts to minimize unnecessary permanent pacing are warranted.

Predictors for permanent pacing (*Table 10* and *supplementary table 14*), especially RBBB, which has been identified as the most consistent and powerful predictor for permanent pacemaker implantation, should be incorporated into procedural planning including transcatheter heart valve selection, implantation height, and balloon inflations.

Patients with pre-existing advanced conduction system disease who may have an indication for permanent pacing irrespective of the TAVI procedure need consultation with an electrophysiologist before the procedure. There is currently no evidence to support permanent pacemaker implantation as a 'prophylactic' measure before TAVI in asymptomatic patients or in patients who do not meet the standard indications for pacemaker implantation.

A recommended approach for the management of conduction abnormalities after TAVI is detailed in *Figure 12*. Patients without new conduction disturbances post-TAVI are at very low risk of developing high-degree AVB.[533–535] Conversely, management of patients with persistent complete or high-degree AVB should follow standard guidelines. Permanent pacemaker implantation appears warranted in patients with intraprocedural AVB that persists for 24 - 48 h after TAVI or appears later. Data to guide the management of patients with other conduction abnormalities at baseline or post-procedure are more limited.

Given the close anatomical proximity of the aortic valve and the left bundle branch, the most frequent conduction abnormality after TAVI is new-onset LBBB.[504,536–538] Only a small minority of these patients require pacemaker implantation.[536,537] Thus, EPS[539–541] or long-term monitoring[536] in lieu of pacemaker implantation may be considered[542,543] (see *section 8* in the *Supplementary data*). Several high-risk subgroups of patients with new LBBB have been identified (see *Figure 12*, and *section 8* in the *Supplementary data*). In such patients with dynamic progression of conduction abnormalities after TAVI (new BBB with dynamic prolongation of QRS and/or PR), an extended monitoring period in hospital of up to 5 days should be considered. Conversely, patients with new-onset LBBB but QRS

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Table 10 Predictors for permanent pacing after transcatheter aortic valve implantation

Characteristics	References
ECG	
Right BBB	512–528
PR-interval prolongation	517,521,525,527
Left anterior hemiblock	517,525
Patient	
Older age (per 1-year increase)	529
Male sex	518,519,525,529
Larger body mass index (per 1-unit increase)	529
Anatomical	
Severe mitral annular calcification	512,515
LV outflow tract calcifications	522
Membranous septum length	528,530
Porcelain aorta	531
Higher mean aortic valve gradient	519
Procedural	
Self-expandable valve	512,513,525,529,531
Deeper valve implantation	517,518,520,522,528,532
Larger ratio between prosthesis diameter versus annulus or LV outflow tract diameter	524,529,532
Balloon post-dilatation	519,521,529
TAVI in valve-in-valve vs. native valve procedure	531

AVB = atrioventricular block; BBB = bundle branch block; ECG = electrocardiogram; LV = left ventricular; TAVI = transcatheter aortic valve implantation.
For more detailed data, see *Supplementary Tables 14* and *15*.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

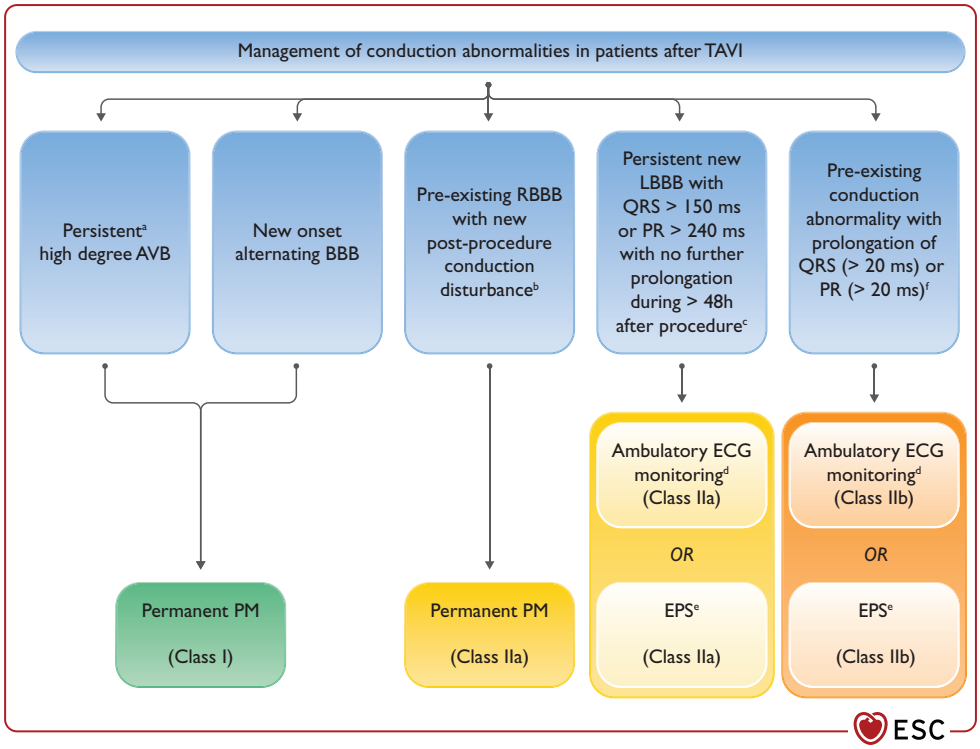

Figure 12 Management of conduction abnormalities after transcatheter aortic valve implantation. AF = atrial fibrillation; AV = atrioventricular; AVB = atrioventricular block; BBB = bundle branch block; ECG = electrocardiogram; EPS = electrophysiology study; HV = His–ventricular interval; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; PM = pacemaker; QRS = Q, R, and S waves; RBBB = right bundle branch block; TAVI = transcatheter aortic valve implantation. [a]24-48 h post-procedure. [b]Transient high-degree AVB, PR prolongation, or axis change. [c]High-risk parameters for high-degree AV block in patients with new-onset LBBB include: AF, prolonged PR interval, and LVEF <40%. [d]Ambulatory continuous ECG monitoring for 7 - 30 days. [e]EPS with HV ≥70 ms may be considered positive for permanent pacing. [f]With no further prolongation of QRS or PR during 48-h observation.

<150 ms may not require further evaluation during hospitalization. When EPS is contemplated, it should be performed ≥3 days post-procedure and after the conduction abnormalities have stabilized.

The type of permanent pacemaker implanted should follow standard guidance (see *sections 5*, *6*, and *7*). Given the low rates of long-term dependency on pacing,[544,545] algorithms promoting spontaneous AV conduction should be used.

Recommendations for cardiac pacing after transcatheter aortic valve implantation

Recommendations	Class[a]	Level[b]
Permanent pacing is recommended in patients with complete or high-degree AVB that persists for 24 - 48 h after TAVI.[546]	I	B
Permanent pacing is recommended in patients with new-onset alternating BBB after TAVI.[533,547]	I	C
Early[c] permanent pacing should be considered in patients with pre-existing RBBB who develop any further conduction disturbance during or after TAVI.[d]	IIa	B
Ambulatory ECG monitoring[e] or EPS[f] should be considered for patients with new LBBB with QRS >150 ms or PR >240 ms with no further prolongation during the >48 h after TAVI.[536,537,548]	IIa	C
Ambulatory ECG monitoring[e] or EPS[f] may be considered for patients with a pre-existing conduction abnormality who develop prolongation of QRS or PR >20 ms.[g]	IIb	C
Prophylactic permanent pacemaker implantation is not indicated before TAVI in patients with RBBB and no indication for permanent pacing.	III	C

© ESC 2021

AF = atrial fibrillation; AVB = atrioventricular block; BBB = bundle branch block; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; EPS = electrophysiology study; HV = His–ventricular interval; LBBB = left bundle branch block; RBBB = right bundle branch block; SR = sinus rhythm; TAVI = transcatheter aortic valve implantation. For the definition of alternating BBB, see *section 5.3.1*.

[a]Class of recommendation.

[b]Level of evidence.

[c]Immediately after procedure or within 24 h.

[d]Transient high-degree AVB, PR prolongation, or QRS axis change.

[e]Ambulatory continuous ECG monitoring (implantable or external) for 7–30 days.[536,549]

[f]EPS should be performed ≥3 days after TAVI. Conduction delay with HV ≥70 ms may be considered positive for permanent pacing.[540,541,550]

[g]With no further prolongation of QRS or PR during 48-h observation.

Note: CRT in patients requiring pacing after TAVI has the same indication as for general patients (see *section 6*).

8.4. Cardiac pacing and cardiac resynchronization therapy in congenital heart disease

Permanent pacing in patients with moderate or complex CHD should be performed in centres with a multidisciplinary team and expertise in CHD-related device therapy. Generally, decision-making for pacemaker therapy in patients with CHD is based on expert consensus and individual evaluation due to lack of evidence from RCTs. In the presence of an intracardiac shunt between the systemic and pulmonary circulation, endovascular lead placement is relatively contraindicated due to the risk of arterial embolism.[551]

The clinical presentation may vary considerably; even severe bradycardia in congenital AVB may remain oligosymptomatic or asymptomatic. Periodic Holter recordings may be useful for patients at specific risk of bradyarrhythmia.

8.4.1 Sinus node dysfunction and bradycardia–tachycardia syndrome

There is no evidence that SND directly leads to increased mortality in CHD. However, it may be associated with a higher rate of postoperative atrial flutter, with 1:1 AV conduction in CHD, and thus lead to morbidity and potentially mortality.[552,553]

8.4.1.1 Indications for pacemaker implantation

In patients with symptomatic chronotropic incompetence, pacemaker implantation is justified when other causes (see *section 4*) have been ruled out.[554,555] Increasing the heart rate through permanent pacing to prevent atrial arrhythmias may be considered.[556] The underlying evidence is weak, as the benefit of atrial-based pacing observed in patients without structural heart disease could not be validated in CHD.[21,557,558] The general consensus is that if permanent pacing is necessary, single-lead atrial-based pacing should be preferred to limit the number of leads, especially in young patients with adequate AV conduction.[559] In patients with congenitally corrected transposition of the great arteries requiring ventricular pacing because of high-degree AVB, CRT should be considered. Current evidence to use devices with atrial antitachycardia pacing to treat intra-atrial re-entrant tachycardias in patients with CHD[560,561] is too limited to make general recommendations.

8.4.2 Congenital atrioventricular block

A number of maternal or fetal factors can cause congenital heart block, particularly autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome (*Supplementary Table 16*).

Patients presenting with congenital AVB may be asymptomatic or may present with reduced exercise capacity, syncopal attacks, congestive HF, ventricular dysfunction, and dilatation. Rarely, in SCD, congenital AVB is diagnosed as the cause.[562,563] SCD may occur through increased propensity to develop bradycardia-related ventricular arrhythmias such as torsades-de-pointes.

8.4.2.1 Indications for pacemaker implantation

There is general consensus that prophylactic pacing is indicated in asymptomatic patients with any of the following risk factors: mean daytime heart rate <50 b.p.m., pauses greater than three times the cycle length of the ventricular escape rhythm, a broad QRS escape rhythm, prolonged QT interval, or complex ventricular ectopy.[564–566] Clinical symptoms, such as syncope, pre-syncope, HF, or chronotropic incompetence, are indications for pacemaker implantation.[564,567,568] If ventricular dysfunction is attributed to haemodynamic compromise caused by bradycardia, permanent pacing may be indicated.[518,567] Despite a modest quality of evidence, there

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

is strong consensus that patients with third- or second-degree AVB (Mobitz type II) must receive permanent cardiac pacing therapy if symptomatic or with risk factors. In asymptomatic patients without risk factors, opinion on the benefit of cardiac pacing diverges, and permanent pacing may be considered.[567,569]

8.4.3 Post-operative atrioventricular block

Post-operative high-degree AVB is estimated to occur in 1–3% of patients undergoing surgery for CHD.[518,569,570] In children, transient early post-operative AVB usually resolves within 7–10 days.[571] In adults with CHD, there are no data to support a different waiting period before deciding for permanent pacing post-operatively than after other cardiac surgery. After recovery from complete AVB, bifascicular block occasionally persists, which is associated with an increased risk of late recurrent AVB and sudden death.[572] The prognosis is poor for patients with untreated post-operative complete AVB.[573]

8.4.3.1 Indications for pacemaker implantation

There is a strong recommendation for permanent pacing in patients with persistent second- or third-degree AVB. In patients with persistent bifascicular block associated with transient AVB or permanent prolonged PR interval, consensus for pacemaker implantation is modest. Post-operative HV interval determination may help to estimate the risk in patients with prolonged PR or bifascicular block.[573] In patients with bifascicular block and long PR after surgery for CHD, the risk of extensive damage to the conduction system is high,[572] therefore pacemaker implantation may be indicated even without HV measurement. Implantation of epicardial leads should be considered during surgery in patients with complex CHD and a high lifetime risk of pacemaker implantation, in order to reduce the rate of reoperation.

Recommendations for cardiac pacing in patients with congenital heart disease

Recommendations	Class[a]	Level[b]
In patients with congenital complete or high-degree AVB, pacing is recommended if one of the following risk factors is present: a. Symptoms b. Pauses >3× the cycle length of the ventricular escape rhythm c. Broad QRS escape rhythm d. Prolonged QT interval e. Complex ventricular ectopy f. Mean daytime heart rate <50 b.p.m.	I	C
In patients with congenital complete or high-degree AVB, permanent pacing may be considered even if no risk factors are present.[566]	IIb	C
In patients with persistent post-operative bifascicular block associated with transient complete AVB, permanent pacing may be considered.[572]	IIb	C
In patients with complex CHD and asymptomatic bradycardia (awake resting heart rate <40 b.p.m. or pauses >3 s), permanent pacing may be considered on an individual basis.	IIb	C

© ESC 2021

AVB = atrioventricular block; BBB = bundle branch block; b.p.m. = beats per minute; CHD = congenital heart disease; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

8.4.4 Cardiac resynchronization

Standard indications for CRT may be considered in CHD, taking into account that the anatomy, morphology of the systemic ventricle, and cause of dyssynchrony, as well as QRS morphology, may be atypical.[574] Multidisciplinary teams in experienced centres should be involved in the decision-making process.

8.5 Pacing in hypertrophic cardiomyopathy

8.5.1 Bradyarrhythmia

AVB in hypertrophic cardiomyopathy (HCM) should generally be treated according to the recommendations in this guideline (see *section 5.2*). Certain genetically inherited subtypes of HCM are more prone to develop AVB, as is the case with transthyretin amyloidosis, Anderson–Fabry and Danon diseases, PRKAG2 syndrome, and mitochondrial cytopathies.[575,576] An ICD/CRT-D rather than a pacemaker should be considered in patients with symptomatic bradycardia who have LVEF ≤35% or otherwise fulfil the criteria for primary prevention of SCD by current guidelines.[576] (For extended literature on conduction disorders in HCM see the *Supplementary data, section 8.5*.)

8.5.2 Pacing for the management of left ventricular outflow tract obstruction

In patients with symptoms caused by LV outflow tract obstruction, treatment options include drugs, surgery, septal alcohol ablation, and AV sequential pacing with a short AV delay. Three small, randomized, placebo-controlled studies and several long-term observational studies reported reductions in LV outflow tract gradients, and variable improvement in symptoms and quality of life with AV sequential pacing.[577–582] Myectomy achieved superior haemodynamic results compared with DDD pacing,[583] but is a more invasive and higher risk intervention. In one trial, a subgroup analysis suggested that older patients (>65 years) are more likely to benefit from DDD AV sequential pacing.[579] A recent meta-analysis—comprising 34 studies and 1135 patients—found that pacing reduced the LV outflow gradient by 35%, with a non-significant trend towards reduction in NYHA class.[584]

Shared decision-making should be employed when considering the treatment of choice for patients with obstructive HCM.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Recommendations for pacing in hypertrophic obstructive cardiomyopathy

Recommendations	Class[a]	Level[b]
AV sequential pacing with short AV delay may be considered in patients in SR who have other pacing or ICD indications if drug-refractory symptoms or baseline or provocable LV outflow tract gradients ≥50 mmHg are present.[576–581,584]	IIb	B
AV sequential pacing with short AV delay may be considered in selected adults with drug-refractory symptoms, ≥50 mmHg baseline or provocable LV outflow tract gradient, in SR, who are unsuitable for or unwilling to consider other invasive septal reduction therapies.[576–581,584]	IIb	B
AV sequential pacing with short AV delay may be considered in selected patients with drug-refractory symptoms, ≥50 mmHg baseline or provocable LV outflow tract gradients, in SR, at high risk of developing AVB during septal ablation.[585,586]	IIb	C

© ESC 2021

AV = atrioventricular; AVB = atrioventricular block; ICD = implantable cardioverter-defibrillator; LV = left ventricular; SR = sinus rhythm.
[a]Class of recommendation.
[b]Level of evidence.
Pacing parameters should be optimized to achieve maximum pre-excitation of the RV apex with minimal compromise of LV filling (typically achieved with a resting sensed AV interval of 100 ± 30 ms).[587]

8.5.3 Pacemaker implantation following septal myectomy and alcohol septal ablation

In a study involving 2482 patients with obstructive HCM, 2.3% developed AVB after septal myectomy[588] (only 0.6% in those with normal baseline conduction vs. 34.8% in patients with pre-existing RBBB). Alcohol septal ablation causes AVB in 7–20% of patients;[576] those with pre-existing conduction defects, mainly LBBB, are at highest risk.[585]

8.5.4 Cardiac resynchronization therapy in end-stage hypertrophic cardiomyopathy

Based on the findings of a small cohort study,[589] CRT was given both a class IIa and a class IIb recommendation in previous guidelines for patients with HCM, HF, LBBB, and LVEF <50%.[576,590] More recent studies did not demonstrate sustained efficacy of this therapy.[591–593] Until further evidence becomes available, standard criteria for CRT are recommended in patients with HCM (*section 6*).

8.6 Pacing in rare diseases

8.6.1 Long QT syndrome

There are multiple inter-relationships between the different forms of long QT syndrome (LQTS) and bradycardia: LQTS can be associated with sinus bradycardia; very long ventricular myocardial refractory periods can cause 2:1 AVB; sudden rate changes can trigger torsades-de-pointes tachycardia; and treatment with beta-blockers to suppress sympathetic triggers of torsades-de-pointes may cause bradycardia.

As current ICDs provide all pacemaker functions, a standalone pacemaker is rarely indicated in LQTS today. However, in individual patients with LQTS and catecholamine-induced torsades-de-pointes, shock therapy may be disadvantageous or even fatal; in these cases, pacing and beta-blocker therapy alone without an ICD may be used. Pacemaker instead of ICD implantation represents a treatment option in neonates and small infants with LQTS,[594] and an alternative in LQTS patients with symptomatic bradycardia (spontaneous or due to beta-blockers) if ventricular tachyarrhythmias are unlikely or if ICD implantation is not desired (e.g. patient preference).

An indication for a pacemaker in LQTS exists in neonates and infants with a 2:1 AVB due to excessive corrected QT prolongation with long myocardial refractory periods.[595]

Temporary pacing at an increased rate (usually 90 - 120 b.p.m.) is an important treatment in LQTS patients with electrical storm, because an increase in the basic heart rate shortens the window of vulnerability for reinduction of torsade de pointes ventricular tachycardia.

8.6.2 Neuromuscular diseases

Neuromuscular diseases are a group of heterogeneous inherited disorders affecting the skeletal muscle and frequently also involve the heart (for extended literature on conduction disorders in neuromuscular disease, see the supplementary literature on pacing in rare disease and *Supplementary Table 17*). The cardiac phenotype variably includes all types of cardiomyopathies, conduction defects with or without cardiomyopathies, and supraventricular and ventricular tachyarrhythmias.[596–598] Duchenne, Becker, and limb-girdle types 2C, 2F, and 2I are muscular dystrophies in which the development of dilated cardiomyopathy is common and usually the predominant feature. Arrhythmias and conduction disease can be associated with the development of cardiomyopathy.[596–598] Such patients are considered for pacemakers or ICDs on the basis of guidelines used for other non-ischaemic cardiomyopathies.[242] Myotonic dystrophy types 1 and 2, Emery–Dreifuss, and limb-girdle type 1B often present with conduction disease and associated arrhythmias, and variably with cardiomyopathy.[596,597] The recommendations present guidance in the instances where the recommendations for cardiac pacing differ from those used for other patients with bradycardia.

Recommendations for cardiac pacing in rare diseases

Recommendations	Class[a]	Level[b]
In patients with neuromuscular diseases such as myotonic dystrophy type 1 and any second- or third-degree AVB or HV ≥70 ms, with or without symptoms, permanent pacing is indicated.[c] [599–602]	I	C
In patients with neuromuscular disease such as myotonic dystrophy type 1 with PR ≥240 ms or QRS duration ≥120 ms, permanent pacemaker implantation may be considered.[c] [600,603,604]	IIb	C

© ESC 2021

AVB = atrioventricular block; CRT = cardiac resynchronization therapy; HV = His–ventricular interval; ICD = implantable cardioverter-defibrillator.
[a]Class of recommendation.
[b]Level of evidence.
[c]Whenever pacing is indicated in neuromuscular disease, CRT or an ICD should be considered according to relevant guidelines.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

8.6.3 Dilated cardiomyopathy with lamin A/C mutation

Mutations in the LMNA gene, which encodes lamin A and C intermediate filaments of the nuclear envelope, cause a variety of inherited diseases defined as 'laminopathies'.[605–607] According to the type of mutation, they can lead to isolated cardiac disorders or additional systemic or musculoskeletal disorders such as the Emery–Dreifuss autosomal dominant variant or limb-girdle dystrophy. Around 5–10% of dilated cardiomyopathies are induced by LMNA gene mutations, manifested as cardiac conduction disease, tachyarrhythmias, or impaired myocardial contractility.[596,606–620] SND and conduction disease are frequently the first manifestation, in many cases with preserved LV size and function.[613,614] LMNA-related cardiomyopathy is more malignant than most other cardiomyopathies, carrying a higher risk of SCD in asymptomatic mutation carriers with preserved or only mildly decreased LV contractility.[610–615] Pacemaker implantation does not reduce the risk of SCD in these patients. A meta-analysis of mode of death in LMNA mutations demonstrated that 46% of patients who died suddenly had an implanted pacemaker. Sudden death rates were similar in those with isolated cardiomyopathy and those with an additional neuromuscular phenotype.[611] Complex ventricular arrhythmias are common in patients with conduction disturbances.[612,613,615] In two studies, patients with LMNA mutations and an indication for permanent pacing underwent ICD implantation, and appropriate ICD therapies occurred in 42% and 52% of patients within 3 and 5 years, respectively.[612,613] These findings led to the clinical practice to consider ICD rather than pacemaker implantation in LMNA-related conduction disease.[614,620] For additional clinical risk factors for ventricular tachyarrhythmias and sudden death found in patients with dilated cardiomyopathy due to LMNA gene mutations, see *Supplementary Table 18*. CRT(D) should be considered if the patient has AVB and LVEF <50%, and a high frequency of ventricular pacing is expected (*section 6* and *Supplementary Table 18*). The risk score of life-threatening ventricular arrhythmia in laminopathies can be predicted by a recently developed and validated module (https://lmna-risk-vta.fr/).[616]

Recommendation for patients with LMNA gene mutations (for references, see *Supplementary Table 18*)

Recommendation	Class[a]	Level[b]
In patients with LMNA gene mutations, including Emery–Dreifuss and limb-girdle muscular dystrophies who fulfil conventional criteria for pacemaker implantation or who have prolonged PR interval with LBBB, ICD implantation with pacing capabilities should be considered if at least 1-year survival is expected.[616]	IIa	C

© ESC 2021

ICD = implantable cardioverter-defibrillator; LBBB, left bundle branch block.
[a]Class of recommendation.
[b]Level of evidence.

8.6.4 Mitochondrial cytopathies

Mitochondrial cytopathies are a heterogeneous group of hereditary disorders, in which cardiomyopathies, conduction defects, and ventricular arrhythmias are the most common cardiac presentations.[621,622] In Kearns–Sayre syndrome, the most common cardiac manifestation is conduction disease, which may progress to complete AVB and cause SCD.[623–625]

Recommendations for pacing in Kearns–Sayre syndrome

Recommendations	Class[a]	Level[b]
In patients with Kearns–Sayre syndrome who have PR prolongation, any degree of AVB, BBB, or fascicular block, permanent pacing should be considered.[c] [621–625]	IIa	C
In patients with Kearns–Sayre syndrome without cardiac conduction disorder, permanent pacing may be considered prophylactically.[c] [621–625]	IIb	C

© ESC 2021

AVB = atrioventricular block; BBB = bundle branch block; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; PR = PR interval.
[a]Class of recommendation.
[b]Level of evidence.
[c]Whenever pacing is indicated, CRT or an ICD should be considered according to the relevant guidelines.

8.6.5 Infiltrative and metabolic diseases

Infiltrative cardiomyopathy is secondary to abnormal deposition and accumulation of pathological products in the myocardial interstitium, while storage diseases lead to their intracellular accumulation. The main cause of infiltrative cardiomyopathy is amyloidosis, while storage diseases include haemochromatosis, Fabry's disease, and glycogen storage diseases. In patients with cardiac amyloid, conduction defects, tachyarrhythmias, and SCD are common. Based upon current knowledge, conventional indications should be used for pacing in this group of patients.

8.6.6 Inflammatory diseases

Infections (viral, bacterial including Borreliosis, protozoa, fungal, parasites), autoimmune (e.g. giant cell myocarditis, sarcoidosis, rheumatic heart disease, connective tissue disease, eosinophilic myocarditis), toxic (alcohol, cocaine, cancer therapies, especially monoclonal antibodies), and physical reactions (radiation therapy) can cause inflammatory heart disease. Involvement of the AVN and the conduction system is more frequent than that of the sinus node. AVB may indicate involvement of the septum in the inflammatory process and is a predictor of adverse outcome. Ventricular arrhythmias may also occur because of myocardial pathology.

When inflammatory heart disease is complicated by bradycardia, especially AVB, specific therapy should be applied if available, eventually backed-up by temporary pacing or intravenous administration of isoprenaline. Otherwise, immunosuppressive therapy or awaiting spontaneous resolution may be sufficient. If bradycardia does not resolve within a clinically reasonable period or cannot be expected to resolve (e.g. after radiation therapy), permanent pacing is indicated. Before choosing a device type, the indication for an ICD and/or CRT rather than a single-chamber or DDD pacemaker should be

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

considered because most causes of inflammatory disease causing bradycardia may also result in reduced myocardial contractility and ventricular fibrosis.

8.6.6.1 Sarcoidosis

Persistent or intermittent AVB can occur in sarcoidosis, which shows a propensity to involve the basal intraventricular septum. In a Finnish registry, 143 of 325 patients (44%) diagnosed with cardiac sarcoidosis had Mobitz II second- or third-degree AVB in the absence of other explanatory cardiac disease.[626] A history of syncope, pre-syncope, or palpitations points towards bradycardia, but also to potential ventricular tachyarrhythmia. AVB is the most common clinical presentation in patients with clinically evident cardiac sarcoidosis.[627,628] Diagnostic steps include ECG monitoring, echocardiography, cardiac MRI, and myocardial or other involved tissue biopsy. Fluorodeoxyglucose-positron emission tomography may be useful.[629] The chances and time course of resolution of AVB with immunosuppressive therapy are not clear,[630] but may be low.[88] Long-term data are available mainly from a Canadian prospective study (32 patients),[627] a Japanese retrospective study (22 patients),[628] and a Finnish registry (325 patients).[626] Reversibility of conduction disorder is unpredictable and, even in patients with transient AVB, permanent pacing should be considered.[631] Immunosuppressive treatment may increase risk of device infection. However, there are no firm data to support device implantation before initiation of immunosuppressive medication. Patients with cardiac sarcoidosis and AVB are at high risk of SCD during long-term follow-up, even if LVEF is >35%.[626] Patients with even a mild or moderate decrease in LVEF (35–49%) are at increased risk of SCD.[632,633] Therefore, in patients with cardiac sarcoidosis who have an indication for cardiac pacing and LVEF <50%, a CRT-D should be considered rather than a pacemaker[634] (*section 6*).

Recommendations for pacing in cardiac sarcoidosis

Recommendations	Class[a]	Level[b]
In patients with cardiac sarcoidosis who have permanent or transient AVB, implantation of a device capable of cardiac pacing should be considered.[c] [88,629,630]	IIa	C
In patients with sarcoidosis and an indication for permanent pacing who have LVEF <50%, implantation of a CRT-D should be considered.[631,634]	IIa	C

© ESC 2021

AVB = atrioventricular block; CRT-D = defibrillator with cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Whenever pacing is indicated in sarcoidosis, an ICD should be considered according to the relevant guidelines.

8.7 Cardiac pacing in pregnancy

Vaginal delivery carries no extra risks in a mother with congenital complete heart block, unless contraindicated for obstetric reasons.[635] For women who have a stable, narrow complex junctional escape rhythm, pacemaker implantation may not be necessary or can be deferred until after delivery if none of the risk factors (syncope, pauses >3× the cycle length of the ventricular escape rhythm, wide QRS escape rhythm, prolonged QT interval, complex ventricular ectopy, mean daytime heart rate <50 b.p.m.) is present. However, women with complete heart block who exhibit a slow, wide QRS complex escape rhythm should undergo pacemaker implantation during pregnancy. The risks of pacemaker implantation are generally low and can be performed safely, especially if the foetus is beyond 8 weeks gestation. A pacemaker for the alleviation of symptomatic bradycardia can be implanted at any stage of pregnancy using echo guidance or electroanatomic navigation minimizing fluoroscopy.[636,637]

9 Special considerations on device implantations and peri-operative management

9.1 General considerations

Patients with clinical signs of active infection and/or fever should not undergo a permanent pacemaker (including leadless pacemaker) implantation until they have been afebrile for at least 24 h. Febrile patients who have been started on antibiotics should ideally receive a complete course of antibiotic treatment and should be afebrile for 24 h after termination of antibiotic treatment before definite pacemaker implantation is performed if acute pacing is not required. If possible, the use of temporary transvenous pacing should be avoided. In patients in need of acute pacing, temporary transvenous pacing should be established, preferably with jugular or axillar/lateral subclavian vein access.[638] In a multicentre, prospective study with 6319 patients, fever within 24 h of implantation (OR 5.83, 95% CI 2.00–16.98) and temporary pacing before implantation (OR 2.46, 95% CI 1.09–5.13) were positively correlated with the occurrence of device infection.[639] In the case of patients with chronic recurrent infection, minimally invasive implantation of an epicardial pacemaker may be considered.

9.2 Antibiotic prophylaxis

The use of pre-operative systemic antibiotic prophylaxis is recommended as the standard of care in pacemaker implantation procedures. The risk of infection is significantly reduced with a single dose of prophylactic antibiotic (cefazolin 1–2 g i.v. or flucloxacillin 1–2 g i.v.) given within 30–60 min [90–120 min for vancomycin (15 mg/kg)] before the procedure.[640–643] The antibiotic prophylaxis should cover *S. aureus* species, but routine coverage of methicillin-resistant *S. aureus* is not recommended. The use of vancomycin should be guided by patient risk for methicillin-resistant *S. aureus* colonization and the prevalence of the bacterium in the corresponding institution.[638]

In contrast, post-operative antibiotic prophylaxis does not reduce the incidence of infection.[644,645]

9.3 Operative environment and skin antisepsis

The pacemaker implantation procedure should be performed in an operating environment that meets the standards of sterility as required for other surgical implant procedures.[638,646]

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Based on data from surgical and intravascular catheter procedures, skin antisepsis should be performed using chlorhexidine–alcohol instead of povidone-iodine–alcohol.[647,648] In a large RCT comprising 2546 patients, chlorhexidine–alcohol was associated with a lower incidence of short-term intravascular catheter-related infections (HR 0.15, 95% CI 0.05 - 0.41; $P = 0.0002$).[647]

9.4 Management of anticoagulation

It is well known that the development of a pocket haematoma after the implantation of a pacemaker system significantly increases the risk for subsequent pocket infection.[641,643,649] The Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL) proved that a clinically significant pocket haematoma is an independent risk factor for subsequent device infection (HR 7.7, 95% CI 2.9–20.5; $P < 0.0001$).[649] Therefore, it is of utmost importance to take all steps to avoid post-operative pocket haematoma.

Heparin bridging for pacemaker implantation in patients anticoagulated with a vitamin K antagonist leads to a significant 4.6-fold increase in post-operative pocket haematoma compared with a continued warfarin strategy.[650] International normalized ratio tapering and temporary shifting of dual antiplatelet to single antiplatelet administration may significantly reduce the haematoma and infection rate by 75% and 74%, respectively, compared with heparin bridging.[651]

Regarding non-vitamin K antagonist oral anticoagulants, the Randomized Controlled Trial of Continued Versus Interrupted Direct Oral Anti-Coagulant at the Time of Device Surgery (BRUISE CONTROL-2) was stopped prematurely due to futility because the event rate was far lower than anticipated; however, it suggested that, depending on the clinical scenario and concomitant antiplatelet therapy, either stopping or continuing non-vitamin K antagonist oral anticoagulants might be reasonable at the time of device implantation.[652]

Patients on dual antiplatelet therapy have a significantly increased risk of post-operative pocket haematoma compared with patients treated with aspirin alone or without antiplatelet therapy. In such cases, $P2Y_{12}$ receptor inhibitors should be discontinued for 3–7 days (according to the specific drug) before the procedure where possible and based on an individualized risk assessment.[638,653,654] For more details on the management of anticoagulation in the pacemaker procedure, refer to *Table 11*.

9.5 Venous access

Transvenous lead implantation for pacemaker implantation is commonly performed by venous access via the cephalic, subclavian, or axillary vein. In the case of clinical signs of venous occlusion of the subclavian vein or the innominate vein, pre-operative imaging (venography or chest CT scan) may be useful in planning venous access or an alternative access ahead of the procedure. In the case of impossible superior venous access, appropriate, alternative approaches may be transfemoral lead implantation, or implantation of a leadless device or epicardial leads.

When using the Seldinger technique, there is a risk of a pneumothorax, haemothorax, inadvertent arterial puncture, and injury to the brachial plexus during venous puncture of the subclavian vein and (less so) the axillary vein. These risks are avoidable by using the cephalic vein approach, which allows venous insertion of leads under direct vision. Subclavian vein access is associated with a 7.8-fold

Table 11 Management of anticoagulation in pacemaker procedures

	Dual antiplatelet therapy[655,656]		NOAC[652]	VKA[650]	OAC + antiplatelet[657]
	Thrombotic risk after PCI				
	Intermediate or low >1 month PCI >6 months acute coronary syndrome at index PCI	**High** <1 month PCI <6 months acute coronary syndrome at index PCI			
Low procedural bleeding risk First implant	Continue aspirin AND Discontinue $P2Y_{12}$ inhibitors: Ticagrelor at least 3 days before surgery Clopidogrel at least 5 days before surgery Prasugrel at least 7 days before surgery	Elective surgery: Consider postponement Otherwise: • Continue aspirin • Continue $P2Y_{12}$ inhibitor	Continue or interrupt as per operator preference. If interruption, then based on CrCl and specific NOAC	Continue[a]	Continue OAC (VKA[a] or NOAC). Discontinue antiplatelet per patient-specific risk/benefit analysis
High procedural bleeding risk Device exchange, upgrade/ revision procedure		Continue aspirin AND Discontinue $P2Y_{12}$ inhibitors: Ticagrelor at least 3 days before surgery, Clopidogrel at least 5 days before surgery, Prasugrel at least 7 days before surgery. Bridging with GP IIb/IIIa inhibitors			

CrCl = creatinine clearance; GP = glycoprotein; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.
[a]Target international normalized ratio within therapeutic range.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

increased risk of pneumothorax.[658] Prospective data on axillary vein puncture suggest a lower risk of access-related complications compared with subclavian puncture.[659] Ultrasound guidance for axillary vein puncture has been described as a helpful technique for achieving a safe and uncomplicated puncture.[660]

With regards to lead failure after implantation, there is evidence that the axillary vein route is associated with a lower rate of lead failures in long-term follow-up. In a retrospective study comprising 409 patients and mean follow-up of 73.6 ± 33.1 months, lead failure occurred in 1.2% of patients with contrast-guided axillary vein puncture, 2.3% of patients with cephalic vein cutdown, and 5.6% of patients with subclavian vein puncture. In multivariable regression analysis, the only predictor of lead failure was subclavian vein puncture instead of axillary vein access (HR 0.26, 95% CI 0.071−0.954; $P = 0.042$). When analysing the success rates of the different venous access approaches, the cephalic vein approach showed the lowest success rate (78.2% vs. axillary vein 97.6% and subclavian vein 96.8%; $P < 0.001$).[661]

9.6 Lead considerations

In choosing between active or passive fixation pacemaker leads in the RA or RV, one should consider the potential for perforation and pericarditis, as well as extractability. Active fixation leads have a higher tendency to create pericardial effusions as well as overt perforations. Passive fixation leads, due to the non-isodiametric design of the lead tip, may be a factor in lower procedural success rates and higher risk for complications with lead extraction, although this point is far from being clear and is still under evaluation.[662] An RCT is required to clarify this issue.

Regarding perforations, an uncontrolled, non-randomized study comprising 3815 patients with implant of an RV lead showed no significant difference with regards to myocardial perforations between active and passive fixation leads (0.5% vs. 0.3%; $P = 0.3$).[663] Active fixation leads also allow selective site pacing in regions of the RV that are smooth walled (e.g. the mid-septum). The RA is, however, thin walled, and perforation of the RA free wall by active fixation leads has been demonstrated. Some implanting physicians prefer to implant passive leads in patients at elevated risk of perforation (e.g. elderly patients). However, based on expert opinion and on the results of a single-centre, retrospective study on ICD leads (637 patients), in young patients, the use of active fixation leads in the RA and RV is recommended in terms of future extractability.[664]

Lead stability and phrenic nerve stimulation are important aspects of coronary sinus lead implantation. With regards to both, quadripolar leads seem to have relevant advantages. The rate of phrenic nerve stimulation requiring lead revision is significantly lower compared with that in bipolar coronary sinus leads.[665,666] Furthermore, lead stability is increased because quadripolar leads can usually be implanted in the wedged position. If implanted in an apical position due to wedging, the use of the proximal poles avoids apical stimulation. Therefore, quadripolar leads are recommended for coronary sinus lead implantation. Active fixation LV leads via a side helix have been developed, and results have proved reliable stability, easy access to the target pacing site, and stable LV pacing threshold in the long term. In comparison with passive fixation quadripolar leads, active fixation bipolar and quadripolar leads achieved similar results. The lead design with an active fixation mechanism via a side helix was developed to allow for full extractability in the long term. However, the ease of extractability at long term has not yet been proven.[667−669]

9.7 Lead position

Ventricular pacing has traditionally been performed from the RV apex. Since the introduction of active fixation leads, alternative pacing sites such as the RVOT septum or the mid-septum have been evaluated in order to provide more physiological pacing. However, despite two decades of research, the clinical benefit of RV non-apical pacing remains uncertain.[670] This may be partly explained by variability in the position of the lead, which is often unintentionally placed on the anterior free wall, where it may be associated with adverse outcome.[671−673] The main advantage of septal pacing probably lies in the avoidance of perforation of the free wall. In a study of 2200 patients implanted with a pacemaker or ICD lead, an apical position was independently associated with cardiac perforation (OR 3.37; $P = 0.024$).[420] A septal position may therefore be preferable in patients at increased risk of perforation, such as elderly patients especially with a body mass index <20 kg/m^2, as well as women.[670,674]

Placing the lead on the mid-septum may be challenging (even more so in the RVOT septum, which is a smaller target area). The use of multiple fluoroscopic views and specially shaped stylets is useful for this purpose and is outlined in a recent EHRA consensus paper.[34] In this context, it is important to mention that the accuracy and reproducibility of fluoroscopic assessment of RV lead positions is often inaccurate.[421]

Multiple fluoroscopic views are also recommended for placing RVA leads, to ensure there is no inadvertent placement of the lead in a coronary sinus tributary or in the LV via an intracardiac shunt or arterial access.

The coronary sinus may be used for LV pacing without the need to cross the tricuspid valve. It may also be used in the case of other difficulties in deploying an RV lead (e.g. in the case of a tricuspid valve prosthesis). In selected patients, the outcome is similar to RV pacing.[675,676]

The RA appendage is usually the preferred site for atrial pacing. The lateral atrium may carry a risk of phrenic nerve capture.[677,678] Alternative pacing sites to avoid AF such as Bachman's bundle and the region of the coronary sinus ostium have not shown benefit and are not to be recommended in routine practice.[679,680]

9.8 Device pocket

In recent years, there has been increasing awareness of the device pocket as a source of complications. Avoidance of pocket infections has become a special focus in device therapy. The role of pocket haematomas in the development of infections has been discussed earlier. It is evident that besides adequate management of anticoagulation, a proper surgical technique with meticulous haemostasis is of utmost importance.

Most pacemakers are implanted with the creation of a subcutaneous pocket.[681] In patients with a low body mass index and therefore little subcutaneous tissue, in the case of Twiddler's syndrome, or for aesthetic reasons, creation of a submuscular pocket may be preferable. However, this may require deeper sedation for implantation and generator replacements due to pain. To date, there are no data from RCTs comparing the two approaches for creating device pockets.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Historical data from 1000 patients with ICD implants showed significantly shorter procedural times for patients with subcutaneous device pockets. No significant differences with regard to pocket haematomas were found. There were no significant differences in the cumulative percentages of patients free from complication during follow-up.[682]

Pocket irrigation at the end of the procedure with normal saline leads to dilution of possible contaminants and eliminates debris from the wound before closure.[683,684] Addition of antibiotics to the rinsing solution does not reduce the risk of device infections.[683]

The World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT study) investigated the effect of an absorbable antibiotic-eluting envelope on the development of post-operative CIED infections. A total of 6983 patients undergoing a CIED pocket revision, generator replacement, or system upgrade, or initial implantation of a CRT-D were randomly assigned, in a 1:1 ratio, to receive the antibiotic envelope or not. The rate of CIED infection in patients who had the antibacterial envelope was 0.7% vs. 1.2% in the control group (HR 0.6, 95% CI 0.36–0.98; $P = 0.04$).[685] No effect on infection rate was observed in the subgroup with pacemakers.[685] Considering cost-effectiveness aspects, the use of an antibiotic envelope may be considered in pacemaker patients at high risk for CIED infections. Risk factors to be considered in this context are end-stage renal disease, chronic obstructive pulmonary disease, diabetes mellitus, and device replacement, revision, or upgrade procedures.[638]

Recommendations regarding device implantations and peri-operative management

Recommendations	Class[a]	Level[b]
Administration of pre-operative antibiotic prophylaxis within 1 h of skin incision is recommended to reduce risk of CIED infection.[641,643,686]	I	A
Chlorhexidine–alcohol instead of povidone-iodine–alcohol should be considered for skin antisepsis.[647,648]	IIa	B
For venous access, the cephalic or axillary vein should be considered as first choice.[658,659]	IIa	B
To confirm target ventricular lead position, use of multiple fluoroscopic views should be considered.	IIa	C
For implantation of coronary sinus leads, quadripolar leads should be considered as first choice.[665,666,687]	IIa	C
Rinsing the device pocket with normal saline solution before wound closure should be considered.[683,684]	IIa	C
In patients undergoing a reintervention CIED procedure, the use of an antibiotic-eluting envelope may be considered.[685,688]	IIb	B
Pacing of the mid-ventricular septum may be considered in patients at high risk of perforation (e.g. elderly, previous perforation, low body mass index, women).[420,674]	IIb	C
In pacemaker implantations in patients with possible pocket issues such as increased risk of erosion due to low body mass index, Twiddler's syndrome, or for aesthetic reasons, a submuscular device pocket may be considered.	IIb	C
Heparin bridging of anticoagulated patients is not recommended.[650,689]	III	A
Permanent pacemaker implantation is not recommended in patients with fever. Pacemaker implantation should be delayed until the patient has been afebrile for at least 24 h.[638,639]	III	B

CIED = cardiovascular implantable electronic device.
[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

10 Complications of cardiac pacing and cardiac resynchronization therapy

10.1 General complications

Cardiac pacing and CRT are associated with a substantial risk of complications (*Table 12*), most of which occur in the perioperative phase,[429,690] but a sizable risk remains during long-term follow-up.[691] Complication rates after dual-chamber pacemaker implantation in the MOST trial were 4.8% at 30 days, 5.5% at 90 days, and 7.5% at 3 years.[692] However, 'real-life' data indicate a higher risk.[690,693] In a recent study of >81 000 patients receiving *de novo* CIED implantations, major complications occurred in 8.2% within 90 days of hospital discharge.[694] Mortality in hospital (0.5%) and within 30 days (0.8%) was low.

Complication risks generally increase with the complexity of the device and are more common in the context of a device upgrade or lead revisions compared with *de novo* implantation. In a Danish population-based cohort study, complications were observed in 9.9% of patients at first device implantation and in 14.8% upon upgrade or lead revision.[354] Procedures limited to replacement of the generator had a lower complication risk (5.9%). In the prospective REPLACE registry, a similar proportion (4%) of complication risks in the setting of generator replacement was reported, but much higher risks were found in those with one or more additional lead insertions (up to 15.3%).[695] Accordingly, major complications were particularly more common with CRT upgrade procedures, a finding that was corroborated in a large US inpatient cohort[339] and a prospective Italian observational study.[696] The rate of procedural complications also increases with comorbidity burden.[697]

Thus, careful shared decision-making is warranted when considering upgrades to more complex systems. This also applies to prophylactic replacement of recalled CIED generators and leads, a scenario in which procedural risks should be carefully weighed against the risks associated with device or lead failure.[698]

Overall, complication rates are closely linked to individual and centre implantation volumes.[429,658,693] Complications were increased by 60% in inexperienced operators who had performed fewer than

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

25 implantations.[429] Data from a large national quality assurance programme for pacemakers and CRT-P showed that the annual hospital implantation volume was inversely related to complication rates, with the greatest difference observed between the lowest (1 - 50 implantations/year) and the second lowest quintile (51 – 90 implantations/year).[699] Furthermore, emergency and out-of-hours procedures are associated with increased complication rates.[354] These data clearly suggest that CIED procedures should be performed by operators and centres with a sufficient procedural volume.

10.2 Specific complications

10.2.1 Lead complications

Pacemaker leads are a frequent source of complications due to dislodgement, insulation defects, lead fractures, and sensing or threshold problems. In a Danish cohort, lead-related interventions (2.4%) were the most common major complication.[354] LV leads have a particular propensity for complications such as dislodgement and coronary vein dissection or perforation.[700] In a nationwide registry, LV leads (4.3%) were more commonly associated with complications compared with RA leads (2.3%) and RV leads (2.2%).[429] A CRT device (OR 3.3) and passive fixation RA lead (OR 2.2) were the most important risk predictors.

A meta-analysis of 25 CRT trials noted mechanical complications in 3.2% (including coronary sinus dissection or perforation, pericardial effusion or tamponade, pneumothorax, and haemothorax), other lead problems in 6.2%, and infections in 1.4%. Peri-implantation deaths occurred in 0.3%.[369]

Table 12 Complications of pacemaker and cardiac resynchronization therapy implantation

Incidence of complications after CIED therapy	%
Lead-related reintervention[354,639,690,692,695,700,701] (including dislodgement, malposition, subclavian crush syndrome, etc.)	1.0 – 5.9
CIED-related infections, <12 months[354,639,641,645,685,695,702]	0.7 – 1.7
Superficial infection[354]	1.2
Pocket infections[354]	0.4
Systemic infections[354]	0.5
CIED-related infections, >12 months[702 – 709]	1.1 – 4.6
Pocket infections[702]	1.3
Systemic infections[702,705]	0.5 – 1.2
Pneumothorax[354,658,690,692,700,701,707]	0.5 – 2.2
Haemothorax[695]	0.1
Brachial plexus injury[695]	<0.1
Cardiac perforation[354,663,690,692,695]	0.3 – 0.7
Coronary sinus dissection/perforation[710,288]	0.7 – 2.1
Revision due to pain/discomfort[354,690]	0.1 – 0.4
Diaphragmatic stimulation requiring reintervention[711,712,665,713]	0.5 – 5
Haematoma[354,639,650,652,654,690,700,714,715]	2.1 – 5.3
Tricuspid regurgitation[716 – 718]	5 – 15
Pacemaker syndrome[146,701,719]	1 – 20
Generator/lead problem[354,639,690]	0.1 – 1.5
Deep venous thrombosis (acute or chronic)[354,720,721]	0.1 – 2.6
Any complication[354,639,690,692,695,707,722,723]	5 – 15
Mortality (<30 days)[354,694]	0.8 – 1.4

CIED = cardiovascular implantable electronic device.

© ESC 2021

10.2.2 Haematoma

Pocket haematoma is a frequent complication (2.1 – 9.5%), which can usually be managed conservatively. Evacuation, required in 0.3 – 2% of cases, is associated with an ~15 times increased risk of infection.[639] Moreover, patients developing pocket haematoma stay in hospital longer and have a higher in-hospital mortality rate (2.0% vs. 0.7%).[724] Hence, appropriate precautions are critical, and reoperation should be limited to patients with severe pain, persistent bleeding, distension of the suture line, and imminent skin necrosis. Many haematomas can be avoided by careful haemostasis and optimal management of antiplatelet and anticoagulant drugs.

10.2.3 Infection

Infection is one of the most worrying CIED complications, causing significant morbidity, mortality, and healthcare costs.[725,726] Infection rates are higher with device replacement or upgrade procedures,[695] as well as CRT or ICD implants compared with simple pacemaker implantation.[727] Olsen *et al.*[702] reported the lifetime risk of system infection in patients with: a pacemaker (1.19%), ICD (1.91%), CRT-P (2.18%), and CRT-D (3.35%). Specifically, patients undergoing reoperations, those with a previous device-related infection, men, and younger patients had a significantly higher risk of infection.

Similar findings have been reported in a large cohort of patients receiving an ICD, with infection rates of 1.4% for single, 1.5% for dual, and 2.0% for biventricular ICDs.[728] In addition, early reintervention (OR 2.70), previous valvular surgery (OR 1.53), reimplantation (OR 1.35), renal failure on dialysis (OR 1.34), chronic lung disease (OR 1.22), cerebrovascular disease (OR 1.17), and warfarin use (OR 1.16) were associated with an increased risk of infection.[702] Infections also occur more frequently with use of temporary pacing or other procedures before implantation (OR 2.5 and 5.8, respectively), early reinterventions (OR 15), and lack of antibiotic prophylaxis (OR 2.5).[639,729]

Further comprehensive information on how to prevent, diagnose, and treat CIED infections has been provided in a recent EHRA consensus document.[642]

10.2.4 Tricuspid valve interference

CIED leads may interfere with tricuspid valve function intraoperatively by causing damage to the tricuspid valve leaflets or the subvalvular apparatus, or chronically after operation or lead extraction. This damage has been linked to haemodynamic deterioration and an adverse clinical outcome.[730] In fact, moderate to severe tricuspid regurgitation is generally associated with excess mortality[731,732] and occurs at a significantly higher rate in CIED patients.[733] The prevalence of significant tricuspid regurgitation (defined as grade 2 or above) following CIED implantation varies between 10% and 39%. Most studies attribute a greater harm with ICD leads and in the

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

presence of multiple RV leads.[45,46,49,445,642,685,697,709,728,730–732] The issue of lead interference with bioprosthetic tricuspid valves or after annuloplasty or repair is debated. Furthermore, there is no firm evidence supporting that pacing-induced RV dyssynchrony significantly contributes to tricuspid regurgitation. A recent study randomizing 63 patients to pacing lead positions in the RV apex, RVS, or LV pacing via the coronary sinus did not affect the development of tricuspid regurgitation.[734] The diagnostic work-up of CIED lead-related tricuspid regurgitation based on clinical, haemodynamic, and in particular echocardiographic (2D, 3D, and Doppler) evaluation is often challenging.[735] While clear guidance for the management of tricuspid regurgitation in the presence of CIED leads is still lacking, a high level of clinical suspicion is required, not discounting the possibility that worsening HF may be a consequence of the mechanical effect on tricuspid leaflet mobility or coaptation.[730] General treatment options include medical therapy aiming to relieve congestion and lead extraction with careful replacement, or use of alternative pacing strategies, such as LV pacing via the coronary sinus or epicardial leads. However, transvenous lead extraction itself carries a risk of damage to the tricuspid valve and, hence, worsening tricuspid regurgitation. While leadless pacing eliminates the need for transvalvular leads, it may still negatively affect tricuspid valve function, potentially due to mechanical interference and abnormal electrical and mechanical ventricular activation.[736] Indications for surgical valve repair or replacement in the context of CIED-induced tricuspid regurgitation follow current recommendations based on the presence of symptoms, severity of tricuspid regurgitation, and RV function. When considering tricuspid valve surgery, management of the RV lead should follow the recommendations outlined in *section 8.2.3*.[737] Methods for percutaneous tricuspid repair have recently gained major attention, but evidence in favour of such interventions in the context of lead-related tricuspid regurgitation is still limited.[738]

10.2.5 Other

Increased complication risks have been observed in women (mainly pneumothorax and cardiac perforation) and in those with a low body mass index.[354,739] Patients older than 80 years were also found to have a lower risk of lead-related reinterventions compared with patients aged 60–79 years (1.0% vs. 3.1%).[354]

Finally, suboptimal atrioventricular synchrony may lead to the pacemaker syndrome, giving rise to cannon waves caused by simultaneous atrial and ventricular contractions and symptoms of fatigue, dizziness, and hypotension (see *section 5*). Long-term RV pacing induces a dyssynchronous ventricular activation pattern that may promote progressive LV dysfunction and clinical HF. Strategies to avoid and resolve the adverse effect of RV pacing have been discussed above (*section 6*).

11 Management considerations

Integrated management of pacemaker and CRT patients, delivered by an interdisciplinary team in partnership with the patient and family, should be adopted in order to deliver comprehensive treatment across the continuum of healthcare (see *section 12*). The integrated-care approach is indicated in pacemaker and CRT patients to ensure a patient-centred approach and patient involvement in shared decision-making. The integrated-care approach has its origins in the chronic care model developed by Wagner *et al.*,[740] and has the potential to improve clinical and patient outcomes in arrhythmia management[741–743] (see *section 12*). Relevant specialists to be included in the interdisciplinary team are included according to the patient's needs and local service availability (*Figure 13*).

11.1 Magnetic resonance imaging in patients with implanted cardiac devices

MRI is a frequent requirement in patients with implanted pacemakers. It may cause adverse effects such as inappropriate device function due to device reset or sensing problems, interaction with the magnetic reed switch, induction of currents resulting in myocardial capture, heating at the lead tip with changes in sensing or capture thresholds, or lead perforation. Risk factors for adverse events with MRIs are listed in *Supplementary Table 19*.

Currently, most manufacturers propose devices that are MRI conditional. It is the entire CIED system (i.e. combination of generator and leads, which need to be from the same manufacturer) that determines MRI conditionality, and not the individual elements. MRI scans may be limited to 1.5 T and a whole-body specific absorption rate (SAR) <2 W/kg (head SAR <3.2 W/kg), but some models allow 3 T and up to 4 W/kg whole-body SAR. The manufacturer may specify an exemption period (usually 6 weeks) after implantation, but it may be reasonable to perform an MRI scan earlier if clinically warranted.

There is ample evidence that MRIs can be performed safely in non-conditional pacemakers, as long as a number of precautions are taken.[744–746] In 2017, the Heart Rhythm Society published an expert consensus statement on MRIs in patients with CIEDs, which was developed with and endorsed by a number of associations including the EHRA and several radiological associations.[745] For detailed recommendations on appropriate workflow and programming, see *Supplementary Tables 20, 21, and 22* and *Supplementary Figure 2*.

When leads are connected to a generator, the latter component absorbs part of the energy and dissipates heat via the large surface area. Abandoned transvenous leads are prone to heating of the lead tip by ~10°C as shown by an *in vitro* study.[747] It is, however, difficult to extrapolate results from experimental models to the *in vivo* setting. No adverse events were reported from four series totalling 125 patients with abandoned transvenous leads.[748–751] The largest study reported 80 patients[749] who underwent 97 scans (including the thoracic region), limited to an SAR <1.5 W/kg. Half of the cohort had measurement of troponin levels before and after the scan, without any significant changes. Therefore, 1.5 T MRI scans (limited to SAR <1.5 W/kg) may be considered in selected patients, taking into account the risk–benefit ratio, particularly if the scans are extrathoracic and patients are not pacemaker dependent.

Epicardial leads connected to a generator result in a 10°C increase in temperature during *in vitro* testing, and by as much as 77°C with abandoned epicardial leads.[747] Data from 23 patients with epicardial leads have been reported,[749–752] including 14 patients with abandoned epicardial leads,[749–751] without any adverse effect of MRI scans. Given the paucity of data related to safety in patients with epicardial leads, lead adaptors/extenders, or damaged leads, recommendations cannot be made at this stage regarding MRIs in these patients.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

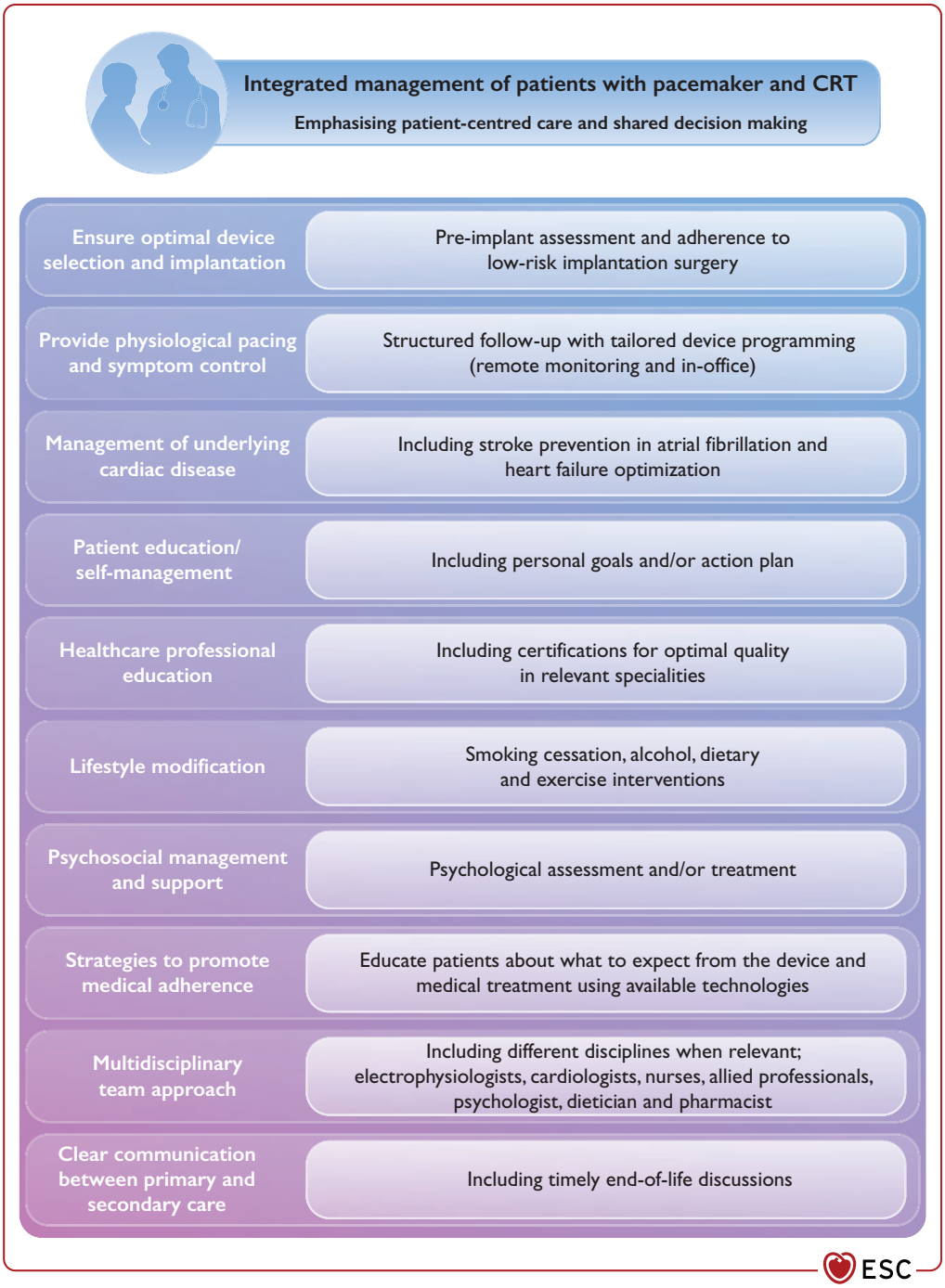

Figure 13 Integrated management of patients with pacemaker and cardiac resynchronization therapy. CRT = cardiac resynchronization therapy.

Evaluation must be made on a case by case basis by balancing the advantages of MRI with the potential risks and availability of alternative imaging methods and using shared decision-making.

In general, MRIs should always be performed in the context of a rigorously applied standardized institutional workflow, following the appropriate conditions of use (including programming).[744,746,753–755]

A flowchart summarizing the management of patients with a pacemaker undergoing MRI is shown in *Figure 14*.

There is evidence indicating that 1.5 T MRIs may be performed in patients with temporary epicardial wires[756] as well as with transvenous pacemaker active fixation leads implanted to externalized pacemakers used for temporary pacing.[751]

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

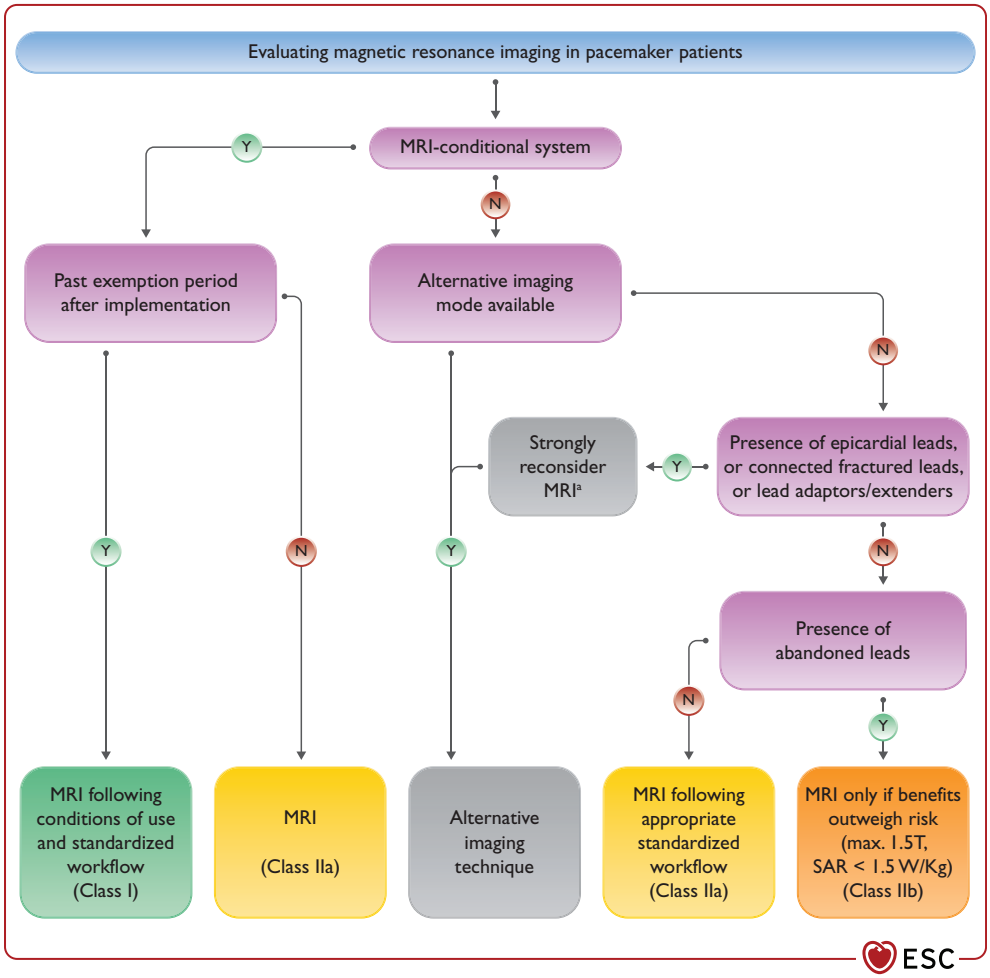

Figure 14 Flowchart for evaluating magnetic resonance imaging in pacemaker patients. MRI = magnetic resonance imaging; SAR = specific absorption rate. [a]Consider only if there is no imaging alternative and the result of the test is crucial for applying life-saving therapies for the patient.

Recommendations for performing magnetic resonance imaging in pacemaker patients

Recommendations	Class[a]	Level[b]
In patients with MRI-conditional pacemaker systems,[c] MRIs can be performed safely following the manufacturer's instructions.[745,753–755]	I	A
In patients with non-MRI-conditional pacemaker systems, MRI should be considered if no alternative imaging mode is available and if no epicardial leads, abandoned or damaged leads, or lead adaptors/extenders are present.[744,746]	IIa	B
MRI may be considered in pacemaker patients with abandoned transvenous leads if no alternative imaging modality is available.[748–751]	IIb	C

MRI = magnetic resonance imaging.
[a]Class of recommendation.
[b]Level of evidence.
[c]Combination of MRI-conditional generator and lead(s) from the same manufacturer.

© ESC 2021

11.2 Radiation therapy in pacemaker patients

An increasing number of patients with CIEDs are referred for radiotherapy,[757] with a reported annual rate of 4.33 treatments per 100 000 person-years. Radiotherapy uses high-energy ionizing radiation including X-rays, gamma rays, and charged particles, which might cause software and hardware errors in CIEDs, especially when photon radiation beam energy exceeds 6–10 MV, and the radiation dose to the device is high (>2–10 Gy).[758,759] Hard errors are rare, and are most often due to direct irradiation to the device. This can cause irreversible hardware damage, requiring device replacement. Soft errors are more common, and are associated with secondary neutron production by irradiation.[760] Such errors typically include resets of the device without causing structural damage, and can be solved without replacement.[757,759]

Electromagnetic interference during radiotherapy can cause oversensing, although this very rarely occurs in clinical practice.[760] Device relocation before radiotherapy is very rarely recommended, and only if the current location of the device interferes

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

with adequate tumour treatment or in very selected high-risk cases.[757,761]

According to published recommendations for CIED patients,[745,759,762] the risk of malfunction (or adverse events) is higher in the following situations for pacemaker patients:

- *With photon radiation applying energy >6–10 MV*: the risk of malfunctions (usually soft errors) is due to secondary neutron production, is not associated with the target zone, and cannot be shielded.
- *With a cumulative dose reaching the device >2 Gy (moderate risk) or >10 Gy (high-risk)*: the dose reaching the pacemaker can be estimated before and measured during treatment, is correlated with the target zone, and can be shielded.
- If the patient is pacemaker dependent.

Appropriate decision-making is suggested in *Figure 15*.

Experience with proton radiation therapy in CIED patients is limited. However, compared with photon irradiation, this radiation modality produces more secondary neutrons, which may affect the risk of device errors or failure.[763] Currently, no specific guidance can be given regarding proton radiation therapy in CIED patients.

The specific recommendations of CIED manufacturers are reported in *Supplementary Table 23*.

11.3 Temporary pacing

Temporary pacing can provide electronic cardiac stimulation in patients with acute life-threatening bradycardia or can be placed prophylactically when the need for pacing is anticipated (e.g. after cardiac surgery).[764,765] Modalities for emergency temporary pacing include transvenous, epicardial, and transcutaneous approaches. The transvenous approach often requires fluoroscopic guidance, although echo-guided placement is also feasible.[766] Balloon-tipped floating catheters are easier to insert, more stable, and safer than semi-rigid catheters.[767,768] Patients who undergo transvenous temporary cardiac pacing have a high risk for procedure-related complications (e.g. cardiac perforation, bleeding, malfunction, arrhythmias, and accidental electrode displacement) and complications related to immobilization (e.g. infection, delirium, and thrombotic events).[764,765,769–775] In addition, previous temporary pacing is associated with an increased risk of permanent pacemaker infection.[639,641] A percutaneous transvenous active fixation lead connected to an external device is safer and more comfortable for patients requiring prolonged temporary pacing.[776–779] There are no good data that support either a jugular or axillar/subclavian access; however, intrathoracic subclavian puncture should be avoided to reduce the risk of pneumothorax. A jugular access should be preferred if implantation of a permanent ipsilateral device is planned. In selected cases where fast and efficient pacing is needed, a femoral access may be used. Owing to instability of passive leads placed through the femoral vein and immobilization of the patient, the duration of this approach should be as short as possible until bradycardia has resolved or a more permanent solution has been established. The epicardial approach is mostly used following cardiac surgery. Removal of these leads is associated with complications such as bleeding and tamponade.[780–782] Transcutaneous temporary pacing is a fast and effective non-invasive method, but is not as

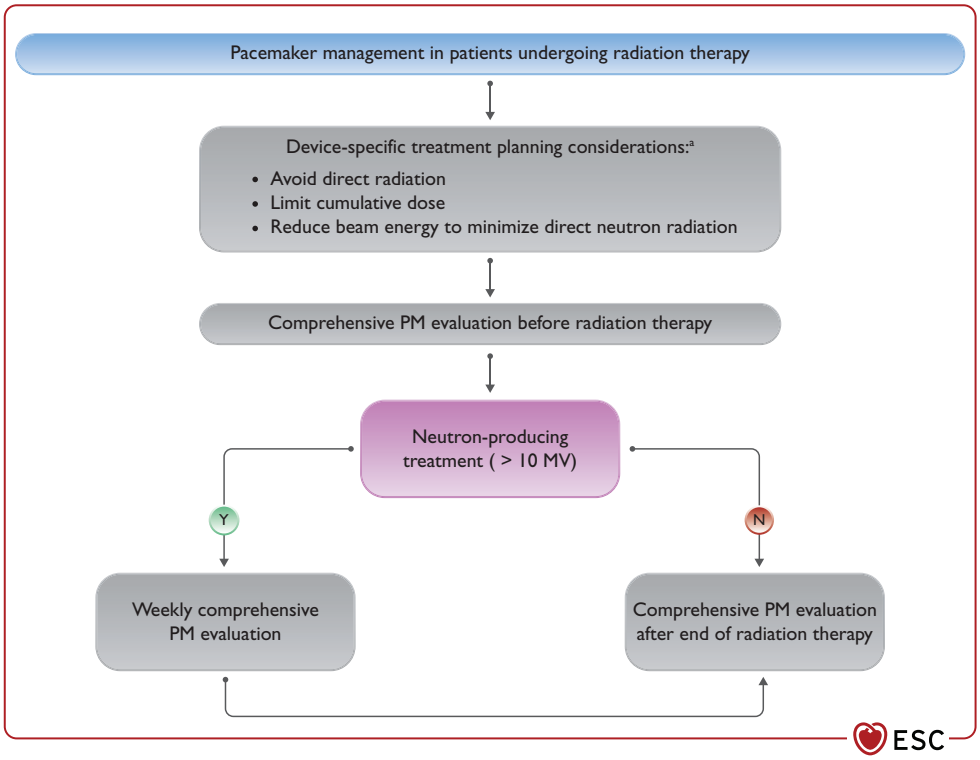

Figure 15 Pacemaker management during radiation therapy ECG = electrocardiographic; PM = pacemaker. [a]Relocation of the device, continuous ECG monitoring, reprogramming, or magnet application are very rarely indicated.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

stable as the transvenous approach, and is limited by the need for continuous sedation.[783] This modality should only be used in emergency settings or when no other option is available, and under close haemodynamic monitoring.[784] Before starting temporary pacing, chronotropic medication should be considered, taking into account side effects, contraindications, and interactions with other medication.

This Task Force concludes that temporary transvenous pacing should be avoided if possible; when it is required, the lead should remain *in situ* for as short a time as possible. The use of temporary pacing should be limited to the emergency treatment of patients with severe bradyarrhythmia causing syncope and/or haemodynamic compromise, and to cases in whom those bradyarrhythmias are anticipated. Temporary transvenous pacing is recommended when pacing indications are reversible, such as in the context of antiarrhythmic drug use, myocardial ischaemia, myocarditis, electrolyte disturbances, toxic exposure, after cardiac surgery, or as a bridge to permanent pacemaker implantation when this procedure is not immediately available or possible due to concomitant infection. Lastly, if a patient meets the permanent pacemaker implantation criteria, this procedure should be performed promptly.

Recommendations regarding temporary cardiac pacing

Recommendations	Class[a]	Level[b]
Temporary transvenous pacing is recommended in cases of haemodynamic-compromising bradyarrhythmia refractory to intravenous chronotropic drugs.[764,765]	I	C
Transcutaneous pacing should be considered in cases of haemodynamic-compromising bradyarrhythmia when temporary transvenous pacing is not possible or available.[783–785]	IIa	C
Temporary transvenous pacing should be considered when immediate pacing is indicated and pacing indications are expected to be reversible, such as in the context of myocardial ischaemia, myocarditis, electrolyte disturbances, toxic exposure, or after cardiac surgery.[771–773]	IIa	C
Temporary transvenous pacing should be considered as a bridge to permanent pacemaker implantation when this procedure is not immediately available or possible due to concomitant infection.[771–773]	IIa	C
For long-term temporary transvenous pacing, an active fixation lead inserted through the skin and connected to an external pacemaker should be considered.[641,776,777,779]	IIa	C

[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

11.4 Peri-operative management in patients with cardiovascular implantable electronic devices

Advisory documents to help manage patients with CIEDs in the peri-operative period have been issued by several professional societies.[786–789] *Supplementary Table 24* summarizes general recommendations on the management of these patients.

- Electromagnetic interference (EMI) may induce oversensing (more likely with unipolar leads), activation of rate-responsive sensors, device resetting, or other damage. The most common source of EMI is electrocautery, although it is rare during bipolar electrocautery >5 cm from the CIED and monopolar electrocautery below the umbilicus.[790] To reduce the risk of EMI, monopolar electrocautery should be applied in short (<5 s) pulses, with the skin patches away from the area of the device. Other sources of EMI include radiofrequency procedures, nerve stimulators, and other electronic devices.
- The peri-operative strategy should be tailored based on the individual needs and values of patients, procedure, and device.[786–789] Most procedures will not require any intervention.[791] In pacemaker-dependent patients, a magnet should be applied during delivery of diathermy pulses, or, if EMI is likely to occur or magnet stability cannot be guaranteed, the device should be reprogrammed to an asynchronous mode (VOO/DOO). The response to magnet application may differ between device manufactures. CIEDs with a rate-responsive function using an active sensor may also require magnet application or disabling of this function to prevent inappropriate rapid pacing. Post-operative CIED interrogation is recommended if malfunction is suspected or if the device has been exposed to strong EMI.

11.5 Cardiovascular implantable electronic devices and sports activity

Regular exercise is strongly recommended for prevention of cardiovascular disease.[792–795] Restrictions to patients with a pacemaker, where appropriate, are motivated by underlying cardiovascular disease. Therefore, it is important to address issues of exercise and sports participation with all pacemaker patients as part of a shared decision-making process. Comprehensive recommendations for physical activity in patients with cardiovascular disease have been published.[792,796]

There is consensus that contact sports (e.g. rugby or martial arts) should be avoided so as not to risk damage of device components or haematoma at the implantation site. For participation in sports such as football, basketball, or baseball, special protective shields are recommended to reduce the risk of trauma to the device. Sport interests and right or left arm dominance should be considered when selecting the implantation site, and submuscular placement can be considered to reduce the risk of impact. A lateral vascular access is

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

preferable to prevent the risk of subclavian crush of the lead associated with arm exercises above shoulder level. It is recommended to abstain from vigorous exercise and ipsilateral arm exercise for 4–6 weeks post-device implantation.

Of note, recommendations regarding sports activity in patients with an ICD differ from those in pacemaker patients.[797,798]

11.6 When pacing is no longer indicated

Different management options are available in patients with implanted pacemaker systems in whom pacing is no longer indicated:

Leave pacemaker generator and pacemaker leads *in situ*.
Explant pacemaker generator and abandon leads.
Explant pacemaker generator and leads.

The feasibility of option 1 depends on the end-of-life behaviour of the implanted generator, which is manufacturer dependent, and may be erratic and lead to complications in rare cases.[799] Option 1 is the preferred approach to selected frail and elderly patients.

Option 2 comes with a low procedural risk but may be associated with the disadvantages of lead abandonment, including future MRI. Especially in young patients, the potential necessary future requirement for lead extraction of abandoned leads due to infection and the associated elevated procedural risk due to longer duration of implantation procedure need to be taken into account. Several studies have shown increased complexity, lower procedural success, and higher complication rates of lead extraction procedures of abandoned leads.[800–803]

Option 3 comes with the highest initial procedural risk, but eliminates all possibilities of future device-related complications. When performed in specialized high-volume centres with current extraction tools, lead extraction procedures can be carried out with high complete procedural success rates and low complication rates.[802] This approach may be appropriate for the combination of a young patient, low risk for extraction, and an experienced extractor.

As part of a patient-centred approach, the decision in such situations has to be based on an individual risk–benefit analysis in a shared decision-making process together with the patient and his/her carers. This includes providing sufficient information to achieve an informed decision-making. Important factors to take into consideration are patient age, patient condition, comorbidities, pacemaker system, lead implant duration, and the patient's life expectancy.

Recommendation when pacing is no longer indicated

Recommendation	Class[a]	Level[b]
When pacing is no longer indicated, the decision on management strategy should be based on an individual risk–benefit analysis in a shared decision-making process together with the patient.	I	C

[a]Class of recommendation.
[b]Level of evidence.

© ESC 2021

11.7 Device follow-up

General principles of follow-up are covered here, as in-depth recommendations are beyond the scope of this document. The patient and the device should be treated as a single entity, with programming tailored to meet the patient's needs. The goals are to (i) ensure patient safety; (ii) provide physiological pacing; (iii) improve patient quality of life; (iv) improve patient clinical management; and (v) maximize device longevity. Requirement for follow-up of the underlying cardiac disease should not be overlooked. In addition to the technical check and optimization of programming, proper counselling of the patient and his/her family are necessary to meet these goals. The frequency of follow-up depends on the type of device (CRT and HBP are associated with more clinical or technical issues and need closer surveillance) and whether they are on remote device management (*Table 13*).

- Remote device management includes *remote follow-up* with full remote device interrogation at scheduled intervals (to replace in-office visits), *remote monitoring* with unscheduled transmission of pre-defined alert events, and *patient-initiated follow-up* with unscheduled interrogations as a result of a patient experiencing a real or perceived clinical event. Most studies have focused on patients with ICDs and CRT-Ds, and have shown a significant reduction in delay between event detection/clinical decision, and fewer inappropriate shocks.[804] Two randomized non-inferiority trials with single-chamber[805] or DDD[805,806] pacemakers (no CRT-P) showed that in-office visits can be safely spaced to 18–24 month intervals if patients are on remote monitoring with devices having automatic threshold algorithms. Spacing of scheduled in-office visits is particularly convenient for elderly patients with limited mobility, but also for young or midlle-aged patients with full-time jobs, family commitments, etc., and in specific situations (e.g. to avoid exposure during a pandemic).
- It is important to conduct remote device management with an appropriate set-up that delivers a structured approach to remote follow-up and a timely response to alerts. Third-party providers can be useful to triage alerts and assist with this task.[807] Importantly, compliance with the General Data Protection Regulation should be respected, as outlined in a recent ESC regulatory affairs/EHRA document.[808]

Table 13 Frequency of follow-up for routine pacemaker and cardiac resynchronization therapy, either in person alone or combined with remote device management

	In-office only	In-office + remote
All devices	Within 72 h and 2–12 weeks after implantation	In-office within 72 h and 2–12 weeks after implantation
CRT-P or HBP	Every 6 months	Remote every 6 months and in-office every 12 months[a]
Single/dual-chamber	Every 12 months then every 3 - 6 months at signs of battery depletion	Remote every 6 months and in-office every 18 - 24 months[a]

CRT-P = cardiac resynchronization therapy-pacemaker; HBP = His bundle pacing.
[a]Remote follow-up can only replace in-office visits if automatic capture threshold algorithms perform accurately (and are previously verified in-office).
Note: additional in-office follow-up may be required (e.g. to verify the clinical effect of modification of programming, or for follow-up a technical issue).
Remote monitoring (i.e. of pre-defined alerts) should be implemented in all instances along with remote follow-ups.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Recommendations for pacemaker and cardiac resynchronization therapy-pacemaker follow-up

Recommendations	Class[a]	Level[b]
Remote device management is recommended to reduce the number of in-office follow-ups in patients with pacemakers who have difficulties to attend in-office visits (e.g. due to reduced mobility or other commitments, or according to patient preference).[805,806,809]	I	A
Remote monitoring is recommended in the case of a device component that has been recalled or is on advisory, to enable early detection of actionable events in patients, particularly those who are at increased risk (e.g. in the case of pacemaker dependency).	I	C
In-office routine follow-up of single- and dual-chamber pacemakers may be spaced by up to 24 months in patients on remote device management.[805,806]	IIa	A
Remote device management of pacemakers should be considered in order to provide earlier detection of clinical problems (e.g. arrhythmias) or technical issues (e.g. lead failure or battery depletion).[806,810]	IIa	B

© ESC 2021

[a]Class of recommendation.
[b]Level of evidence.

12 Patient-centred care and shared decision-making in cardiac pacing and cardiac resynchronization therapy

Providing patient-centred care is a holistic process that emphasizes partnerships in health between patient and clinician, acknowledging the patient's needs, beliefs, expectations, healthcare preferences, goals, and values.[811–813] In patient-centred care, the focus is on shared decision-making, accepting that patients generally prefer to take an active role in decisions about their health.[814,815] This approach has been shown to improve health outcomes and healthcare experiences.[814,816] Clinicians have a duty to define and explain the healthcare problem and make recommendations about the best available evidence across all available options at the time, including no treatment, while ensuring that the patient's values and preferences are considered (*Figure 16*).[817–820]

Decision aids, such as written information and/or the use of interactive websites or web-based applications, can complement the clinicians' counselling and thus facilitate shared decision-making.[822] When decision aids are used, patients feel more knowledgeable, have more accurate risk perceptions, and take a more active part in the decision.[823] In patients with poor language or literacy skills, as well as in those with cognitive impairment, communication strategies, including the help of a qualified interpreter, is recommended, as this helps the patient to make a balanced decision.[824–826] Choosing the appropriate educational material is an important component of promoting the learning process of patients.[827–830] Based on the patient's needs and preferences, the education should be performed before implantation, at discharge, and during follow-up using a person-centred approach (*Table 14*). All patients should receive a brochure provided by the manufacturer as well as a device identification card before discharge.

This Task Force emphasizes the importance of patient-centred care and shared decision-making between patients and clinicians. The decision to implant a pacemaker/CRT should be based on the best available evidence with consideration of the individual risk–benefits of each option, the patient's preferences, and goals of care. The consultation should include whether the patient is a good candidate for pacemaker/CRT treatment, and possible alternative treatment options should be discussed in a way that can be understood by everyone involved in the discussion. Using the principles of shared decision-making and informed consent/refusal, patients with decision-making capacity have the right to refuse pacemaker therapy, even if they are pacemaker dependent.

Recommendation regarding patient-centred care and shared decision-making in cardiac pacing and cardiac resynchronization therapy

Recommendation	Class[a]	Level[b]
In patients considered for pacemaker or CRT, the decision should be based on the best available evidence with consideration of individual risk–benefits of each option, the patient's preferences, and goals of care, and it is recommended to follow an integrated care approach and use the principles of patient-centred care and shared decision-making in the consultation.[831–836]	I	C

© ESC 2021

CRT = cardiac resynchronization therapy.
[a]Class of recommendation.
[b]Level of evidence.

13 Quality indicators

Quality indicators are tools that may be used to evaluate care quality, including that of processes of care and clinical outcomes.[837] They may also serve as a mechanism for enhancing adherence to guideline recommendations through quality assurance endeavours and benchmarking of care providers.[838] As such, the role of quality indicators in driving quality improvement is increasingly recognized and attracts interest from healthcare authorities, professional organizations, payers, and the public.[839]

The ESC recognizes the need for measuring and reporting quality and outcomes of cardiovascular care. One aspect of this is the development and implementation of quality indicators for cardiovascular disease. The methodology by which the ESC quality indicators are

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Figure 16 Example of shared decision-making in patients considered for pacemaker/CRT implantation. Modified from the principles of the SHARE Approach.[821] CRT = Cardiac resynchronization therapy; PM = pacemaker; SDM = Shared Decision Making.

Table 14 Topics and content that may be included in patient education

Topics	Content that may be included in patient education
Biophysiological	Disease/condition, pacemaker indication, implantation process, possible periprocedural or late complications and malfunction, pacemaker/CRT function and technical aspects, patient notifier (if applicable), battery replacement Demonstration of pacemaker dummies
Functional	Daily activities: mobility, physical activities and sports, possible physical restrictions (arm movements), sexual activities, driving restrictions, travelling, wound care, medication use Normal postoperative signs and symptoms and self-care; pain, stiffness in the shoulder, swelling or tenderness around the pacemaker pocket
Financial	Costs of treatment and rights in the social security system, insurance issues, sick leave
Emotional	Possible emotions and reactions to pacemaker treatment: anxiety, worries, body image
Social	Available support: telephone-based support, face-to-face group sessions, patient forums, and peer-support groups Possible employment restrictions and electromagnetic interference
Ethical	Rights and duties of patients and healthcare providers: consent/refusal of pacemaker or CRT therapy, or withdrawal of therapy Information about registration in the national pacemaker registry
Practical	Pacemaker identification card contact information to the pacemaker clinic Follow-up routines: remotely or/and hospital based Where to get more information: reliable web-based information/sources, which organizations provide reliable health information

CRT = cardiac resynchronization therapy.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Table 15 A selection of the developed quality indicators for patients undergoing cardiovascular implantable electronic device implantation

Quality indicator	Domain
Centres providing CIED services should participate in at least one CIED registry	Structural quality indicator[a]
Numerator: Number of centres participating in at least one registry for CIED	
Centres providing CIED services should monitor and report the volume of procedures performed by individual operators on an annual basis	Structural quality indicator
Numerator: Number of centres monitoring and reporting the volume of procedures performed by individual operators	
Centres providing CIED services should have available resources (ambulatory ECG monitoring, echocardiogram) to stratify patients according to their risk for ventricular arrhythmias	Structural quality indicator
Numerator: Number of centres with an available ambulatory ECG and echocardiogram service	
Centres providing CIED services should have a preprocedural checklist to ensure discussion with the patient regarding risks, benefits, and alternative treatment options	Structural quality indicator
Numerator: Number of centres that have a checklist to ensure discussion with patient regarding risks, benefits, and alternative treatment options before CIED implantation	
Centres providing CIED services should have established protocols to follow-up patients within 2 - 12 weeks following implantation	Structural quality indicator
Numerator: Number of centres that have an established protocol to follow up patients within 2 - 12 weeks following CIED implantation	
Proportion of patients considered for CIED implantation who receive prophylactic antibiotics 1 h before their procedure	Patient assessment
Numerator: Number of patients who receive antibiotics 1 h before their CIED implantation procedure ***Denominator:*** Number of patients undergoing CIED implantation procedure	
Annual rate of procedural complications[b] 30 days following CIED implantation	Outcomes
Numerator: Number of patients who develop one or more procedural complications[b] within 30 days of CIED implantation ***Denominator:*** Number of patients undergoing CIED implantation procedure	

CIED = cardiovascular implantable electronic device; ECG = electrocardiogram.
[a]Structural quality indicators are binary measurements (yes/no), and thus only the numerator is defined.
[b]CIED-related bleeding, pneumothorax, cardiac perforation, tamponade, pocket haematoma, lead displacement (all requiring intervention), or infection.

developed has been published.[839] To date, a suite of quality indicators for an initial tranche of cardiovascular conditions has been produced.[839,840] To facilitate quality improvement initiatives, the disease-specific ESC quality indicators are included in corresponding ESC Clinical Practice Guidelines.[296,841] This is further enhanced by way of their integration in the ESC registries, such as the EurObservational Research Programme (EORP) and the European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) project.[842]

A number of registries exist for patients undergoing CIED implantation,[843] providing 'real-world' data about the quality and outcomes of CIED care.[702] However, there is a lack of a widely agreed set of quality indicators that encompasses the multifaceted nature of CIED care, and that serves as a bridge between clinical registries and guideline recommendations. Thus, and in parallel with the writing of these guidelines, a suite of quality indicators for patients undergoing CIED implantation was developed. The full list of these quality indicators, as well as their specifications and development methodology, has been published elsewhere,[844] with a selection presented in *Table 15*.

14 Key messages

- In the evaluation of candidates for permanent pacemaker implantation, a thorough and detailed pre-operative evaluation is recommended. This should always include careful history taking and physical examination, laboratory testing, documentation of the type of bradyarrhythmia requiring treatment, and cardiac imaging. In selected cases, additional tests, EPS, and/or genetic testing are indicated.
- Ambulatory ECG monitoring is useful in the evaluation of patients with suspected bradycardia or cardiac conduction disorder, to correlate rhythm disturbances with symptoms. Choice of type of monitoring should be based on frequency and nature of symptoms and patient preferences.
- In patients with SND including those with bradycardia–tachycardia type of SND, when symptoms can clearly be attributed to bradyarrhythmia, cardiac pacing is indicated.
- In patients with SR and permanent or paroxysmal third- or second-degree type 2 or high-degree AVB, cardiac pacing is indicated irrespective of symptoms.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

- In patients with permanent AF and permanent or paroxysmal AVB, single-lead ventricular pacing is indicated.
- In patients with syncope and unexplained falls, the diagnosis should be ascertained using the available diagnostic methods before pacemaker treatment is considered.
- In patients with symptomatic HF and LVEF ≤35% despite OMT who are in SR and have LBBB QRS morphology, CRT is recommended when QRS duration is ≥150 ms, and should be considered when QRS duration is 130–149 ms. For patients with non-LBBB QRS morphology, evidence for benefit of CRT is less convincing, especially with normal PR and QRS duration <150 ms. CRT should not be used in patients with HF and QRS duration <130 ms, unless there is need for ventricular pacing.
- Selection of patients for CRT based on imaging is limited to the measurement of LVEF, whereas the assessment of other factors, such as extent of myocardial scar, presence of mitral regurgitation, or RV systolic function, is important to anticipate potential non-responders who may need additional treatments (e.g. mitral valve intervention).
- In patients with permanent AF, symptomatic HF, LVEF ≤35%, and QRS ≥130 ms who remain in NYHA class III or ambulatory IV despite OMT, CRT should be considered.
- For patients with AF and CRT, AVJ ablation should be considered when at least 90–95% effective biventricular pacing cannot be achieved.
- For patients with high-degree AVB and an indication for cardiac pacing who have HFrEF (LVEF <40%), CRT rather than RV pacing is recommended.
- HBP may result in normal or near-normal ventricular activation, and is an attractive alternative to RV pacing. To date, no data from randomized trials support that HBP is non-inferior to RV pacing with respect to safety and efficacy. Therefore, HBP may be considered for selected patients with AVB and LVEF >40%, who are anticipated to have >20% ventricular pacing.
- In patients offered HBP, implantation of an RV lead used as 'backup' for pacing should be considered individually.
- HBP may correct ventricular conduction in a subset of patients with LBBB and may therefore be used in lieu of biventricular pacing for HBP-based CRT in selected patients.
- In patients treated with HBP, device programming tailored to specific requirements of HBP must be ensured.
- Implanting a leadless pacemaker should be considered when no upper extremity venous access exists, when risk of device pocket infection is particularly increased, and in patients on haemodialysis.
- Patients undergoing TAVI are at increased risk of developing AVB. Decisions regarding cardiac pacing after TAVI should be taken based upon pre-existing and new conduction disturbances. Ambulatory ECG monitoring for 7–30 days or EPS may be considered in patients post-TAVI with new LBBB or progression of pre-existing conduction anomaly, but not yet any indication for a pacemaker.
- In patients undergoing surgery for endocarditis or tricuspid valve surgery who have or develop AVB under surgery, placement of epicardial pacing leads during surgery should be considered.
- To reduce the risk of complications, pre-operative antibiotics must be administered before CIED procedures, chlorhexidine–alcohol should be preferred for skin antisepsis, and cephalic or axillary vein access should be attempted as first choice.
- Heparin bridging should be avoided in CIED procedures to minimize the risk of haematoma and pocket infection.
- In patients undergoing a CIED reintervention procedure, using an antibiotic-eluting envelope may be considered to reduce the risk of infection.
- In the majority of patients with a pacemaker or CRT, a well-indicated MRI can be performed if no epicardial leads, abandoned or damaged leads, or lead adaptors/extenders are present, and certain precautions are taken.
- Radiation therapy can be offered to patients with a pacemaker or CRT if an individualized treatment planning and risk stratification is done beforehand and the device is interrogated as recommended around the period of radiation therapy.
- Remote device management is valuable for earlier detection of clinical problems and technical issues, and may allow longer spacing between in-office follow-ups.
- The principles of patient-centred care and shared decision-making should be used in the consultation both pre-operatively and during follow-up for patients considered for or living with a pacemaker or CRT.

15 Gaps in evidence

Clinicians responsible for managing pacemaker and CRT candidates, and patients, must frequently make treatment decisions without adequate evidence or consensus of expert opinion. The following is a short list of selected, common issues that deserve to be addressed in future clinical research.

- Best pre-implant evaluation programme, including when to apply advanced imaging methods to ensure optimal choice of CIED for each patient.
- Benefit of implementing genetic testing of CIED patients and their relatives when conduction tissue disease is diagnosed.
- Whether use of rate-adaptive pacing in general is beneficial in patients with SND.
- Whether catheter ablation of AF without pacemaker implantation is non-inferior to pacemaker implantation with respect to freedom from bradycardia-related symptoms in patients with symptomatic conversion pauses after AF.
- In patients with reflex syncope, studies of which pacing mode is superior are needed.
- In patients with an indication for VVI pacing, the long-term efficacy and safety of choosing leadless pacing need to be documented in RCTs.
- In patients with HF, it remains to be shown that CRT improves outcome in patients without LBBB.
- In patients with permanent/persistent AF, HF, and BBB, any beneficial effects of CRT remain to be proven in RCTs.
- There is a lack of RCTs documenting the effect of CRT in patients with HF treated with novel HF drugs including sacubitril/valsartan, ivabradine, and sodium–glucose co-transporter-2 inhibitors.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

- The beneficial effects of upgrading to CRT from a standard pacemaker or ICD in patients with HF and a high frequency of RV pacing need to be documented.
- When implanting the LV electrode, it is unknown whether targeting the latest local activation mechanically or electrically causes an improved effect of CRT and a better patient outcome.
- It is unknown whether employing any type of pre-implant imaging to decide about LV and RV lead placement in CRT may cause better a patient outcome.
- In patients with an indication for permanent pacing and need for a high frequency of RV pacing because of AVB, it is not known which patient and treatment characteristics predict development of pacing-induced cardiomyopathy or HF.
- In patients with AVB and an indication for cardiac pacing, the long-term efficacy and safety of HBP as an alternative to RV pacing need to be proven in RCTs. In addition, the selection of patients most likely to benefit from HBP is not yet defined.
- In patients with HF and an indication for CRT, the long-term efficacy and safety of implementing HBP as an alternative to or element of CRT with biventricular pacing need to be proven in RCTs. In addition, the selection of CRT candidates who are most likely to benefit from HBP is not yet defined.
- Further studies are needed to determine whether HBP could be used to improve response in CRT non-responders.
- The efficacy and safety of left bundle branch area pacing remain to be documented.
- Superiority of a specific location for the RV lead (i.e. septal, outflow tract, or apical) has not been documented for standard pacing indicated for bradycardia or for CRT.
- Better prediction of who will develop AVB after TAVI is needed.
- In symptomatic patients with end-stage HCM and LBBB, there is a need to better define the criteria for CRT implantation and document the clinical features associated with sustained benefit from the procedure.
- Optimal treatment including cardiac pacing for patients with congenital AVB should be investigated.
- In pacemaker candidates with cardiomyopathies with >1 year expected survival who do not fulfil standard criteria for ICD implantation, criteria for ICD instead of pacemaker implantation should be better defined.
- The optimal pre-operative handling in CIED implantations and potential use of pre-operative skin disinfection and/or pre-hospitalization decolonization in *S. aureus* carriers remains to be determined.
- The optimal approach for the different operational procedure elements in CIED implantations, especially for choice of venous access, active or passive fixation leads in right-sided chambers, specific pacing sites, use of haemostatic agents in the pocket, choice of suture types, and application of pressure dressing at the end of the procedure remains to be determined.
- Patients with a need for immediate cardiac pacing occasionally present with fever and infection; typically, treatment includes temporary transvenous pacing and antibiotics, followed by implantation of a permanent pacemaker after the infection has resolved. It is unknown whether immediate implantation of a permanent pacemaker after initiation of antibiotics would be inferior.
- The role of patient education, patient-centred care, and shared decision-making should be studied in CIED populations.

16 'What to do' and 'what not to do' messages from the Guidelines

Recommendations	Class[a]	Level[b]
Evaluation of the patient with suspected or documented bradycardia or conduction system disease		
Monitoring		
Ambulatory ECG monitoring is recommended in the evaluation of patients with suspected bradycardia to correlate rhythm disturbances with symptoms.	I	C
Carotid massage		
Once carotid stenosis is ruled out,[c] CSM is recommended in patients with syncope of unknown origin compatible with a reflex mechanism or with symptoms related to pressure/manipulation of the carotid sinus area.	I	B
Exercise test		
Exercise testing is recommended in patients who experience symptoms suspicious of bradycardia during or immediately after exertion.	I	C
Imaging		
Cardiac imaging is recommended in patients with suspected or documented symptomatic bradycardia to evaluate the presence of structural heart disease, to determine LV systolic function, and to diagnose potential causes of conduction disturbances.	I	C
Laboratory tests		
In addition to pre-implant laboratory tests,[d] specific laboratory tests are recommended in patients with clinical suspicion for potential causes of bradycardia (e.g. thyroid function tests, Lyme titre, digitalis level, potassium, calcium, and pH) to diagnose and treat these conditions.	I	C

Continued

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Sleep evaluation		
Screening for SAS is recommended in patients with symptoms of SAS and in the presence of severe bradycardia or advanced AVB during sleep.	I	C
Recommendation for implantable loop recorder		
In patients with infrequent (less than once a month) unexplained syncope or other symptoms suspected to be caused by bradycardia in whom a comprehensive evaluation did not demonstrate a cause, long-term ambulatory monitoring with an ILR is recommended.	I	A
Cardiac pacing for bradycardia and conduction system disease		
In patients with SND and a DDD pacemaker, minimization of unnecessary ventricular pacing through programming is recommended.	I	A
Pacing is indicated in SND when symptoms can clearly be attributed to bradyarrhythmias.	I	B
Pacing is indicated in symptomatic patients with the bradycardia–tachycardia form of SND to correct bradyarrhythmias and enable pharmacological treatment, unless ablation of the tachyarrhythmia is preferred.	I	B
Pacing is not recommended in patients with bradyarrhythmias related to SND which are asymptomatic or due to transient causes that can be corrected and prevented.	III	C
Pacing is indicated in patients in SR with permanent or paroxysmal third- or second-degree type 2, infranodal 2:1, or high-degree AVB, irrespective of symptoms.[e]	I	C
Pacing is indicated in patients with atrial arrhythmia (mainly AF) and permanent or paroxysmal third- or high-degree AVB, irrespective of symptoms.	I	C
In patients with permanent AF in need of a pacemaker, ventricular pacing with rate response function is recommended.	I	C
Pacing is not recommended in patients with AVB due to transient causes that can be corrected and prevented.	III	C
In patients with unexplained syncope and bifascicular block, a pacemaker is indicated in the presence of either a baseline HV interval of ≥70 ms, second- or third-degree intra- or infra-Hisian block during incremental atrial pacing, or abnormal response to pharmacological challenge.	I	B
Pacing is indicated in patients with alternating BBB with or without symptoms.	I	C
Pacing is not recommended for asymptomatic BBB or bifascicular block.	III	B
Recommendations for pacing for reflex syncope		
Dual-chamber cardiac pacing is indicated to reduce recurrent syncope in patients aged >40 years, with severe, unpredictable, recurrent syncope who have: • spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest or AVB; or • cardioinhibitory carotid sinus syndrome; or • asystolic syncope during tilt testing.	I	A
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex.	III	B
Pacing is not recommended in patients with unexplained falls in the absence of any other documented indication.	III	B
Pacing is not recommended in patients with unexplained syncope without evidence of SND or conduction disturbance.	III	C
CRT		
CRT is recommended for symptomatic patients with HF in SR with LVEF ≤35%, QRS duration ≥150 ms, and LBBB QRS morphology despite OMT, to improve symptoms and reduce morbidity and mortality.	I	A
CRT is not indicated in patients with HF and a QRS duration <130 ms without indication for RV pacing.	III	A
In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT is recommended in patients with HFrEF.	I	B
CRT rather than RV pacing is recommended for patients with HFrEF (<40%) regardless of NYHA class who have an indication for ventricular pacing and high-degree AVB in order to reduce morbidity. This includes patients with AF.	I	A
In patients who are candidates for an ICD, and who have CRT indication, implantation of a CRT-D is recommended.	I	A
Recommendations for using His bundle pacing		
In patients treated with His bundle pacing, device programming tailored to specific requirements of His bundle pacing is recommended.	I	C
Pacing in acute myocardial infarction		
Implantation of a permanent pacemaker is indicated with the same recommendations as in a general population (*section 5.2*) when AVB does not resolve within a waiting period of at least 5 days after MI.	I	C
Pacing is not recommended if AVB resolves after revascularization or spontaneously.	III	B

Continued

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Recommendations for cardiac pacing after cardiac surgery and heart transplantation		
High-degree or complete AVB after cardiac surgery: a period of clinical observation of at least 5 days is indicated to assess whether the rhythm disturbance is transient and resolves. However, this observation period can be shortened in the case of complete AVB with low or no escape rhythm when resolution is unlikely.	I	C
Patients requiring pacing after mechanical tricuspid valve replacement: implantation of a transvalvular RV lead should be avoided.	III	C
Recommendations for cardiac pacing after TAVI		
Permanent pacing is recommended in patients with complete or high-degree AVB that persists for 24 - 48 h after TAVI.	I	B
Permanent pacing is recommended in patients with new-onset alternating BBB after TAVI.	I	C
Prophylactic permanent pacemaker implantation is not indicated before TAVI in patients with RBBB and no indication for permanent pacing.	III	C
Recommendations for cardiac pacing in patients with congenital heart disease		
In patients with congenital complete or high-degree AVB, pacing is recommended if one of the following risk factors is present: i. Symptoms ii. Pauses >3× the cycle length of the ventricular escape rhythm iii. Broad QRS escape rhythm iv. Prolonged QT interval v. Complex ventricular ectopy vi. Mean daytime heart rate <50 b.p.m.	I	C
Recommendations for cardiac pacing in rare diseases		
In patients with neuromuscular diseases such as myotonic dystrophy type 1 and any second- or third-degree AVB or HV ≥70 ms, with or without symptoms, permanent pacing is indicated.[f]	I	C
Recommendations regarding device implantations and peri-operative management		
Administration of pre-operative antibiotic prophylaxis within 1 h of skin incision is recommended to reduce the risk of CIED infection.	I	A
Heparin bridging of anticoagulated patients is not recommended.	III	A
Permanent pacemaker implantation is not recommended in patients with fever. Pacemaker implantation should be delayed until the patient has been afebrile for at least 24 h.	III	B
Recommendations for performing magnetic resonance imaging in pacemaker patients		
In patients with MRI-conditional pacemaker systems,[g] MRI can be performed safely following the manufacturer's instructions.	I	A
Recommendations regarding temporary cardiac pacing		
Temporary transvenous pacing is recommended in cases of haemodynamic-compromising bradyarrhythmia refractory to intravenous chronotropic drugs.	I	C
Recommendation when pacing is no longer indicated		
When pacing is no longer indicated, the decision on management strategy should be based on an individual risk–benefit analysis in a shared decision-making process together with the patient.	I	C
Recommendations for pacemaker and cardiac resynchronization therapy-pacemaker follow-up		
Remote device management is recommended to reduce the number of in-office follow-up visits in patients with pacemakers who have difficulties in attending in-office visits (e.g. due to reduced mobility or other commitments, or according to patient preference).	I	A
Remote monitoring is recommended in the case of a device component that has been recalled or is on advisory, to enable early detection of actionable events in patients, particularly those who are at increased risk (e.g. in case of pacemaker dependency).	I	C
Recommendation regarding patient-centred care in cardiac pacing and cardiac resynchronization therapy		
In patients considered for a pacemaker or CRT, the decision should be based on the best available evidence with consideration of individual risk–benefits of each option, the patient's preferences, and goals of care, and it is recommended to follow an integrated care approach and use the principles of patient-centred care and shared decision-making in the consultation.	I	C

AF = atrial fibrillation; AVB = atrioventricular block; AVJ = atrioventricular junction; BBB = bundle branch block; b.p.m. = beats per minute; CIED = cardiovascular implantable electronic device; CRT = cardiac resynchronization therapy; CRT-D = defibrillator with cardiac resynchronization therapy; CSM = carotid sinus massage; DDD = dual-chamber, atrioventricular pacing; ECG = electrocardiogram; EPS = electrophysiology study; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HV = His–ventricular interval; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; OMT = optimal medical therapy; RBBB = right bundle branch block; RV = right ventricular; SAS = sleep apnoea syndrome; SND = sinus node dysfunction; SR = sinus rhythm; TAVI = transcatheter aortic valve implantation.

[a]Class of recommendation.

[b]Level of evidence.

[c]CSM should not be undertaken in patients with previous transient ischaemic attack, stroke, or known carotid stenosis. Carotid auscultation should be performed before CSM. If a carotid bruit is present, carotid ultrasound should be performed to exclude carotid disease.

[d]Complete blood counts, prothrombin time, partial thromboplastin time, serum creatinine, and electrolytes.

[e]In asymptomatic narrow QRS complex and 2:1 AVB, pacing may be avoided if supra-Hisian block is clinically suspected (concomitant Wenckebach is observed and block disappears with exercise) or demonstrated at EPS.

[f]Whenever pacing is indicated in neuromuscular disease, CRT or an implantable cardioverter-defibrillator should be considered according to relevant guidelines.

[g]Combination of MRI conditional generator and lead(s) from the same manufacturer.

© ESC 2021

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

17 Supplementary data

Supplementary data with additional Supplementary Figures, Tables, and text complementing the full text are available on the *European Heart Journal* website and via the ESC website at https://www.escardio.org/guidelines.

18 Author Information

Author/Task Force Member Affiliations: Mads Brix Kronborg, Department of Cardiology, Aarhus University Hospital, Aarhus N, Denmark; **Yoav Michowitz**, Jesselson Integrated Heart Center, Faculty of Medicine, Hebrew University, Shaare Zedek Medical Center, Jerusalem, Israel; **Angelo Auricchio**, Department of Cardiology, Istituto Cardiocentro Ticino, Lugano, Switzerland; **Israel Moshe Barbash,** Leviev Heart Center, Sheba Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Ramat Gan, Israel; **José A. Barrabés**, Department of Cardiology, Vall d'Hebron Hospital Universitari, Universitat Autonoma de Barcelona, CIBERCV, Barcelona, Spain; **Giuseppe Boriani**, Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; **Frieder Braunschweig**, Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; **Michele Brignole**, Cardiology, IRCCS Istituto Auxologico Italiano, Milan, Italy; **Haran Burri**, Cardiology, University Hospital of Geneva, Geneva, Switzerland; **Andrew J. S. Coats**, Faculty of Medicine, University of Warwick, Coventry, United Kingdom; **Jean-Claude Deharo**, Cardiology La Timone, Aix Marseille Université, Marseille, France; **Victoria Delgado**, Cardiology, Leiden University Medical Center, Leiden, Netherlands; **Gerhard-Paul Diller**, Department of Cardiology III, Adult Congenital and Valvular Heart Disease, University Hospital Muenster, Muenster, Germany; **Carsten W. Israel**, Department of Medicine-Cardiology, Diabetology and Nephrology, Bethel-Clinic, Bielefeld, Germany; **Andre Keren**, Cardiology, Hadassah-Hebrew University Hospital, Jerusalem, Israel; **Reinoud E. Knops**, Cardiology and Electrophysiology, Amsterdam University Medical Center, Amsterdam, Netherlands; **Dipak Kotecha**, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom; **Christophe Leclercq**, Department of Cadiology, Rennes University Hospital, Rennes, France; **Béla Merkely**, Heart and Vascular Center, Semmelweis University, Budapest, Hungary; **Christoph Starck**, Department of Cardiothoracic & Vascular Surgery, German Heart Center Berlin, Berlin, Germany; **Ingela Thylén**, Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; **José Maria Tolosana**, Arrhythmia Section, Cardiovascular Institute, Hospital Clinic, University of Barcelona, Barcelona, Catalonia, Spain.

19 Appendix

ESC Scientific Document Group

Includes Document Reviewers and ESC National Cardiac Societies.

Document Reviewers: Francisco Leyva (CPG Review Coordinator) (United Kingdom), Cecilia Linde (CPG Review Coordinator) (Sweden), Magdy Abdelhamid (Egypt), Victor Aboyans (France), Elena Arbelo (Spain), Riccardo Asteggiano (Italy), Gonzalo Barón-Esquivias (Spain), Johann Bauersachs (Germany), Mauro Biffi (Italy), Ulrika Birgersdotter-Green (United States of America), Maria Grazia Bongiorni (Italy), Michael A. Borger (Germany), Jelena Čelutkienė (Lithuania), Maja Cikes (Croatia), Jean-Claude Daubert (France), Inga Drossart (Belgium), Kenneth Ellenbogen (United States of America), Perry M. Elliott (United Kingdom), Larissa Fabritz (United Kingdom), Volkmar Falk (Germany), Laurent Fauchier (France), Francisco Fernández-Avilés (Spain), Dan Foldager (Denmark), Fredrik Gadler (Sweden), Pastora Gallego Garcia De Vinuesa (Spain), Bulent Gorenek (Turkey), Jose M. Guerra (Spain), Kristina Hermann Haugaa (Norway), Jeroen Hendriks (Netherlands), Thomas Kahan (Sweden), Hugo A. Katus (Germany), Aleksandra Konradi (Russia), Konstantinos C. Koskinas (Switzerland), Hannah Law (United Kingdom), Basil S. Lewis (Israel), Nicholas John Linker (United Kingdom), Maja-Lisa Løchen (Norway), Joost Lumens (Netherlands), Julia Mascherbauer (Austria), Wilfried Mullens (Belgium), KlaudiaVivien Nagy (Hungary), Eva Prescott (Denmark), Pekka Raatikainen (Finland), Amina Rakisheva (Kazakhstan), Tobias Reichlin (Switzerland), Renato Pietro Ricci (Italy), Evgeny Shlyakhto (Russia), Marta Sitges (Spain), Miguel Sousa-Uva (Portugal), Richard Sutton (Monaco), Piotr Suwalski (Poland), Jesper Hastrup Svendsen (Denmark), Rhian M. Touyz (United Kingdom), Isabelle C. Van Gelder (Netherlands), Kevin Vernooy (Netherlands), Johannes Waltenberger (Germany), Zachary Whinnett (United Kingdom), Klaus K. Witte (United Kingdom).

ESC National Cardiac Societies actively involved in the review process of the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: **Algeria:** Algerian Society of Cardiology, Brahim Kichou; **Armenia:** Armenian Cardiologists Association, Armen Khachatryan; **Austria:** Austrian Society of Cardiology, Daniel Scherr; **Belarus:** Belorussian Scientific Society of Cardiologists, Alexandr Chasnoits; **Belgium:** Belgian Society of Cardiology, Georges H. Mairesse; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Mugdim Bajric; **Bulgaria:** Bulgarian Society of Cardiology, Vasil Velchev; **Croatia:** Croatian Cardiac Society, Vedran Velagic; **Cyprus:** Cyprus Society of Cardiology, Elias Papasavvas; **Czech Republic:** Czech Society of Cardiology, Milos Taborsky; **Denmark:** Danish Society of Cardiology, Michael Vinther; **Egypt:** Egyptian Society of Cardiology, John Kamel Zarif Tawadros; **Estonia:** Estonian Society of Cardiology, Jüri Voitk; **Finland:** Finnish Cardiac Society, Jarkko Karvonen; **France:** French Society of Cardiology, Paul Milliez; **Georgia:** Georgian Society of Cardiology, Kakhaber Etsadashvili; **Germany:** German Cardiac Society, Christian Veltmann; **Greece:** Hellenic Society of Cardiology, Nikolaos Fragakis; **Hungary:** Hungarian Society of Cardiology, Laszlo Alajos Gellér; **Ireland:** Irish Cardiac Society, Richard Sheahan; **Israel:** Israel Heart Society, Avishag Laish-Farkash; **Italy:** Italian Federation of Cardiology, Massimo Zecchin; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Ayan Abdrakhmanov; **Kosovo (Republic of):** Kosovo Society of Cardiology, Ibadete Bytyçi; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Kurbanbek Kalysov; **Latvia:** Latvian Society of Cardiology, Oskars Kalejs; **Lebanon:** Lebanese Society of Cardiology, Bernard Abi-Saleh; **Lithuania:** Lithuanian Society of

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Cardiology, Germanas Marinskis; **Luxembourg:** Luxembourg Society of Cardiology, Laurent Groben; **Malta:** Maltese Cardiac Society, Mark Adrian Sammut; **Moldova (Republic of):** Moldavian Society of Cardiology, Mihail Rizov; **Montenegro:** Montenegro Society of Cardiology, Mihailo Vukmirovic; **Morocco:** Moroccan Society of Cardiology, Rachida Bouhouch; **Netherlands**: Netherlands Society of Cardiology, Mathias Meine; **North Macedonia**: North Macedonian Society of Cardiology, Lidija Poposka; **Norway:** Norwegian Society of Cardiology, Ole Christian Mjølstad; **Poland:** Polish Cardiac Society, Maciej Sterlinski; **Portugal:** Portuguese Society of Cardiology, Natália António; **Romania:** Romanian Society of Cardiology, Calin Siliste; **Russian Federation:** Russian Society of Cardiology, Sergey Valentinovich Popov; **San Marino:** San Marino Society of Cardiology, Roberto Bini; **Serbia:** Cardiology Society of Serbia, Goran Milasinovic; **Slovakia:** Slovak Society of Cardiology, Peter Margitfalvi; **Slovenia:** Slovenian Society of Cardiology, Igor Zupan; **Spain:** Spanish Society of Cardiology, Óscar Cano; **Sweden:** Swedish Society of Cardiology, Rasmus Borgquist; **Switzerland:** Swiss Society of Cardiology, Tobias Reichlin; **Syrian Arab Republic:** Syrian Cardiovascular Association, Ahmad Rasheed Al Saadi; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Abdeddayem Haggui; **Turkey:** Turkish Society of Cardiology, Ilyas Atar; **United Kingdom of Great Britain and Northern Ireland:** British Cardiovascular Society, Anthony W. C. Chow.

ESC Clinical Practice Guidelines Committee (CPG): Colin Baigent (Chairperson) (United Kingdom), Magdy Abdelhamid (Egypt), Victor Aboyans (France), Sotiris Antoniou (United Kingdom), Elena Arbelo (Spain), Riccardo Asteggiano (Italy), Andreas Baumbach (United Kingdom), Michael A. Borger (Germany), Jelena Čelutkienė (Lithuania), Maja Cikes (Croatia), Jean-Philippe Collet (France), Volkmar Falk (Germany), Laurent Fauchier (France), Chris P. Gale (United Kingdom), Sigrun Halvorsen (Norway), Bernard Iung (France), Tiny Jaarsma (Sweden), Aleksandra Konradi (Russia), Konstantinos C. Koskinas (Switzerland), Dipak Kotecha (United Kingdom), Ulf Landmesser (Germany), Basil S. Lewis (Israel), Ales Linhart (Czech Republic), Maja-Lisa Løchen (Norway), Lis Neubeck (United Kingdom), Jens Cosedis Nielsen (Denmark); Steffen E. Petersen (United Kingdom), Eva Prescott (Denmark), Amina Rakisheva (Kazakhstan), Marta Sitges (Spain), Rhian M. Touyz (United Kingdom).

19 References

1. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, Wilkins E, Wright L, Vos R, Bax J, Blum M, Pinto F, Vardas P, ESC Scientific Document Group. European Society of Cardiology: cardiovascular disease statistics 2017. *Eur Heart J* 2018;**39**:508–579.
2. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009—a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol* 2011;**34**:1013–1027.
3. Gregoratos G. Permanent pacemakers in older persons. *J Am Geriatr Soc* 1999;**47**:1125–1135.
4. Mond HG. The World Survey of Cardiac Pacing and Cardioverter Defibrillators: calendar year 1997. *Pacing Clin Electrophysiol* 2001;**24**:869–870.
5. Mond HG. The World Survey of Cardiac Pacing and Cardioverter Defibrillators: calendar year 1997—Asian Pacific, Middle East, South America, and Canada. *Pacing Clin Electrophysiol* 2001;**24**:856–862.
6. Ector H, Rickards AF, Kappenberger L, Linde C, Vardas P, Oto A, Santini M, Sutton R, Working Group on Cardiac Pacing. The World Survey of Cardiac Pacing and Implantable Cardioverter Defibrillators: calendar year 1997—Europe. *Pacing Clin Electrophysiol* 2001;**24**:863–868.
7. Mond HG, Irwin M, Ector H, Proclemer A. The world survey of cardiac pacing and cardioverter-defibrillators: calendar year 2005 an International Cardiac Pacing and Electrophysiology Society (ICPES) project. *Pacing Clin Electrophysiol* 2008;**31**:1202–1212.
8. Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG, Hobbs MS. Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. *Open Heart* 2014;**1**:e000177.
9. Johansson BW. Complete heart block. A clinical, hemodynamic and pharmacological study in patients with and without an artificial pacemaker. *Acta Med Scand Suppl* 1966;**451**:1–127.
10. Edhag O. Long-term cardiac pacing. Experience of fixed-rate pacing with an endocardial electrode in 260 patients. *Acta Med Scand Suppl* 1969;**502**:9–110.
11. Edhag O, Swahn A. Prognosis of patients with complete heart block or arrhythmic syncope who were not treated with artificial pacemakers. A long-term follow-up study of 101 patients. *Acta Med Scand* 1976;**200**:457–463.
12. Friedberg CK, Donoso E, Stein WG. Nonsurgical acquired heart block. *Ann N Y Acad Sci* 1964;**111**:835–847.
13. Shaw DB, Holman RR, Gowers JI. Survival in sinoatrial disorder (sick-sinus syndrome). *Br Med J* 1980;**280**:139–141.
14. Alboni P, Menozzi C, Brignole M, Paparella N, Gaggioli G, Lolli G, Cappato R. Effects of permanent pacemaker and oral theophylline in sick sinus syndrome the THEOPACE study: a randomized controlled trial. *Circulation* 1997;**96**:260–266.
15. Sutton R, Kenny RA. The natural history of sick sinus syndrome. *Pacing Clin Electrophysiol* 1986;**9**:1110–1114.
16. Hofer S, Anelli-Monti M, Berger T, Hintringer F, Oldridge N, Benzer W. Psychometric properties of an established heart disease specific health-related quality of life questionnaire for pacemaker patients. *Qual Life Res* 2005;**14**:1937–1942.
17. Fleischmann KE, Orav EJ, Lamas GA, Mangione CM, Schron E, Lee KL, Goldman L. Pacemaker implantation and quality of life in the Mode Selection Trial (MOST). *Heart Rhythm* 2006;**3**:653–659.
18. Lopez-Jimenez F, Goldman L, Orav EJ, Ellenbogen K, Stambler B, Marinchak R, Wilkoff BL, Mangione CM, Yoon C, Vitale K, Lamas GA. Health values before and after pacemaker implantation. *Am Heart J* 2002;**144**:687–692.
19. Newman D, Lau C, Tang AS, Irvine J, Paquette M, Woodend K, Dorian P, Gent M, Kerr C, Connolly SJ, CTOPP Investigators. Effect of pacing mode on health-related quality of life in the Canadian Trial of Physiologic Pacing. *Am Heart J* 2003;**145**:430–437.
20. Lamas GA, Orav EJ, Stambler BS, Ellenbogen KA, Sgarbossa EB, Huang SK, Marinchak RA, Estes NA 3rd, Mitchell GF, Lieberman EH, Mangione CM, Goldman L. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. *N Engl J Med* 1998;**338**:1097–1104.
21. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, Marinchak RA, Flaker G, Schron E, Orav EJ, Hellkamp AS, Greer S, McAnulty J, Ellenbogen K, Ehlert F, Freedman RA, Estes NA 3rd, Greenspon A, Goldman L, Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med* 2002;**346**:1854–1862.
22. Tjong FVY, Beurskens NEG, de Groot JR, Waweru C, Liu S, Ritter P, Reynolds D, Wilde AAM, Knops RE, MICRA Investigators. Health-related quality of life impact of a transcatheter pacing system. *J Cardiovasc Electrophysiol* 2018;**29**:1697–1704.
23. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S, Document Reviewers. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–1490.
24. Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. *J Cardiovasc Electrophysiol* 2012;**23**:797–799.
25. Sodeck GH, Domanovits H, Meron G, Rauscha F, Losert H, Thalmann M, Vlcek M, Laggner AN. Compromising bradycardia: management in the emergency department. *Resuscitation* 2007;**73**:96–102.
26. El-Sherif N, Jalife J. Paroxysmal atrioventricular block: are phase 3 and phase 4 block mechanisms or misnomers? *Heart Rhythm* 2009;**6**:1514–1521.
27. Lee S, Wellens HJ, Josephson ME. Paroxysmal atrioventricular block. *Heart Rhythm* 2009;**6**:1229–1234.
28. Narula OS, Samet P, Javier RP. Significance of the sinus-node recovery time. *Circulation* 1972;**45**:140–158.
29. Alboni P, Menozzi C, Brignole M, Paparella N, Lolli G, Oddone D, Dinelli M. An abnormal neural reflex plays a role in causing syncope in sinus bradycardia. *J Am Coll Cardiol* 1993;**22**:1130–1134.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

30. Brignole M, Menozzi C, Gianfranchi L, Oddone D, Lolli G, Bertulla A. Neurally mediated syncope detected by carotid sinus massage and head-up tilt test in sick sinus syndrome. *Am J Cardiol* 1991;**68**:1032–1036.
31. Brignole M, Deharo JC, De Roy L, Menozzi C, Blommaert D, Dabiri L, Ruf J, Guieu R. Syncope due to idiopathic paroxysmal atrioventricular block: long-term follow-up of a distinct form of atrioventricular block. *J Am Coll Cardiol* 2011;**58**:167–173.
32. Deharo JC, Brignole M, Guieu R. Adenosine hypersensitivity and atrioventricular block. *Herzschrittmacherther Elektrophysiol* 2018;**29**:166–170.
33. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, ESC Committee for Practice Guidelines. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;**34**:2281–2329.
34. Burri H, Starck C, Auricchio A, Biffi M, Burri M, D'Avila ALR, Deharo JC, Glikson M, Israel C, Lau CAR, Leclercq C, Love C, Nielsen JC, Vernooy K, Reviewers, Dagres NRC, Boveda SRC, Butter C, Marijon E, Braunschweig F, Mairesse GH, Gleva M, Defaye P, Zanon F, Lopez-Cabanillas N, Guerra JM, Vassilikos VP, Martins Oliveira M. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS). *Europace* 2021;doi: 10.1093/europace/euaa367.
35. Belott P, Reynolds D. Permanent pacemaker and implantable cardioverter-defibrillator implantation in adults. In: Ellenbogen KA, Wilcoff BL, Kay NG, Lau CP, Auricchio A, eds. *Clinical Cardiac Pacing, Defibrillation and Resynchronization Therapy*. 5th ed. Elsevier; 2017. p631–691.
36. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R, Tockman B, Pochet T, Spinelli J. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation* 1999;**99**:2993–3001.
37. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.
38. Saxon LA, Bristow MR, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, Feldman AM, Galle E, Ecklund F. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *Circulation* 2006;**114**:2766–2772.
39. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
40. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W, MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
41. Verma N, Knight BP. Update in cardiac pacing. *Arrhythm Electrophysiol Rev* 2019;**8**:228–233.
42. Abdelrahman M, Subzposh FA, Beer D, Durr B, Naperkowski A, Sun H, Oren JW, Dandamudi G, Vijayaraman P. Clinical outcomes of His bundle pacing compared to right ventricular pacing. *J Am Coll Cardiol* 2018;**71**:2319–2330.
43. Bhatt AG, Musat DL, Milstein N, Pimienta J, Flynn L, Sichrovsky T, Preminger MW, Mittal S. The efficacy of his bundle pacing: lessons learned from implementation for the first time at an experienced electrophysiology center. *JACC Clin Electrophysiol* 2018;**4**:1397–1406.
44. Ali N, Keene D, Arnold A, Shun-Shin M, Whinnett ZI, Afzal Sohaib SM. His bundle pacing: a new frontier in the treatment of heart failure. *Arrhythm Electrophysiol Rev* 2018;**7**:103–110.
45. Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongiorni MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P, Micra Transcatheter Pacing Study Group. A leadless intracardiac transcatheter pacing system. *N Engl J Med* 2016;**374**:533–541.
46. Reddy VY, Exner DV, Cantillon DJ, Doshi R, Bunch TJ, Tomassoni GF, Friedman PA, Estes NA 3rd, Ip J, Niazi I, Plunkitt K, Banker R, Porterfield J, Ip JE, Dukkipati SR, Leadless II Study Investigators. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med* 2015;**373**:1125–1135.
47. Knops RE, Tjong FV, Neuzil P, Sperzel J, Miller MA, Petru J, Simon J, Sediva L, de Groot JR, Dukkipati SR, Koruth JS, Wilde AA, Kautzner J, Reddy VY. Chronic performance of a leadless cardiac pacemaker: 1-year follow-up of the LEADLESS trial. *J Am Coll Cardiol* 2015;**65**:1497–1504.
48. Sperzel J, Defaye P, Delnoy PP, Garcia Guerrero JJ, Knops RE, Tondo C, Deharo JC, Wong T, Neuzil P. Primary safety results from the LEADLESS Observational Study. *Europace* 2018;**20**:1491–1497.
49. Roberts PR, Clementy N, Al Samadi F, Garweg C, Martinez-Sande JL, Iacopino S, Johansen JB, Vinolas Prat X, Kowal RC, Klug D, Mont L, Steffel J, Li S, Van Osch D, El-Chami MF. A leadless pacemaker in the real-world setting: The Micra Transcatheter Pacing System Post-Approval Registry. *Heart Rhythm* 2017;**14**:1375–1379.
50. El-Chami MF, Al-Samadi F, Clementy N, Garweg C, Martinez-Sande JL, Piccini JP, Iacopino S, Lloyd M, Vinolas Prat X, Jacobsen MD, Ritter P, Johansen JB, Tondo C, Liu F, Fagan DH, Eakley AK, Roberts PR. Updated performance of the Micra transcatheter pacemaker in the real-world setting: a comparison to the investigational study and a transvenous historical control. *Heart Rhythm* 2018;**15**:1800–1807.
51. Ovsyshcher I, Guetta V, Bondy C, Porath A. First derivative of right ventricular pressure, dP/dt, as a sensor for a rate adaptive VVI pacemaker: initial experience. *Pacing Clin Electrophysiol* 1992;**15**:211–218.
52. Lau CP, Butrous GS, Ward DE, Camm AJ. Comparison of exercise performance of six rate-adaptive right ventricular cardiac pacemakers. *Am J Cardiol* 1989;**63**:833–838.
53. Lau CP, Antoniou A, Ward DE, Camm AJ. Initial clinical experience with a minute ventilation sensing rate modulated pacemaker: improvements in exercise capacity and symptomatology. *Pacing Clin Electrophysiol* 1988;**11**:1815–1822.
54. Benditt DG, Mianulli M, Fetter J, Benson DW Jr, Dunnigan A, Molina E, Gornick CC, Almquist A. Single-chamber cardiac pacing with activity-initiated chronotropic response: evaluation by cardiopulmonary exercise testing. *Circulation* 1987;**75**:184–191.
55. Landzberg JS, Franklin JO, Mahawar SK, Himelman RB, Botvinick EH, Schiller NB, Springer MJ, Griffin JC. Benefits of physiologic atrioventricular synchronization for pacing with an exercise rate response. *Am J Cardiol* 1990;**66**:193–197.
56. Iwase M, Hatano K, Saito F, Kato K, Maeda M, Miyaguchi K, Aoki T, Yokota M, Hayashi H, Saito H, Murase M. Evaluation by exercise Doppler echocardiography of maintenance of cardiac output during ventricular pacing with or without chronotropic response. *Am J Cardiol* 1989;**63**:934–938.
57. Buckingham TA, Woodruff RC, Pennington DG, Redd RM, Janosik DL, Labovitz AJ, Graves R, Kennedy HL. Effect of ventricular function on the exercise hemodynamics of variable rate pacing. *J Am Coll Cardiol* 1988;**11**:1269–1277.
58. Padeletti L, Pieragnoli P, Di Biase L, Colella A, Landolina M, Moro E, Orazi S, Vicentini A, Maglia G, Pensabene O, Raciti G, Barold SS. Is a dual-sensor pacemaker appropriate in patients with sino-atrial disease? Results from the DUSISLOG study. *Pacing Clin Electrophysiol* 2006;**29**:34–40.
59. Nowak B, Misselwitz B, Expert committee 'Pacemaker Institute of Quality Assurance Hessen', Erdogan A, Funck R, Irnich W, Israel CW, Olbrich HG, Schmidt H, Sperzel J, Zegelman M. Do gender differences exist in pacemaker implantation?—results of an obligatory external quality control program. *Europace* 2010;**12**:210–215.
60. Mohamed MO, Volgman AS, Contractor T, Sharma PS, Kwok CS, Rashid M, Martin GP, Barker D, Patwala A, Mamas MA. Trends of sex differences in outcomes of cardiac electronic device implantations in the United States. *Can J Cardiol* 2020;**36**:69–78.
61. Moore K, Ganesan A, Labrosciano C, Heddle W, McGavigan A, Hossain S, Horton D, Hariharaputhiran S, Ranasinghe I. Sex differences in acute complications of cardiac implantable electronic devices: implications for patient safety. *J Am Heart Assoc* 2019;**8**:e010869.
62. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martin A, Probst V, Reed MJ, Rice CP, Sutton R, Ungar A, van Dijk JG. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:1883–1948.
63. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867.
64. Kaess BM, Andersson C, Duncan MS, Larson MG, Aasbjerg K, Gislason GH, Torp-Pedersen C, Vasan RS. Familial clustering of cardiac conduction defects and pacemaker insertion. *Circ Arrhythm Electrophysiol* 2019;**12**:e007150.
65. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm* 2011;**8**:1308–1339.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

66. Kerr SR, Pearce MS, Brayne C, Davis RJ, Kenny RA. Carotid sinus hypersensitivity in asymptomatic older persons: implications for diagnosis of syncope and falls. *Arch Intern Med* 2006;**166**:515–520.
67. Puggioni E, Guiducci V, Brignole M, Menozzi C, Oddone D, Donateo P, Croci F, Solano A, Lolli G, Tomasi C, Bottoni N. Results and complications of the carotid sinus massage performed according to the 'method of symptoms'. *Am J Cardiol* 2002;**89**:599–601.
68. Brignole M, Ungar A, Casagranda I, Gulizia M, Lunati M, Ammirati F, Del Rosso A, Sasdelli M, Santini M, Maggi R, Vitale E, Morrione A, Francese GM, Vecchi MR, Giada F. Prospective multicentre systematic guideline-based management of patients referred to the Syncope Units of general hospitals. *Europace* 2010;**12**:109–118.
69. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, Brignole M. Clinical context and outcome of carotid sinus syndrome diagnosed by means of the 'method of symptoms'. *Europace* 2014;**16**:928–934.
70. Solari D, Maggi R, Oddone D, Solano A, Croci F, Donateo P, Wieling W, Brignole M. Assessment of the vasodepressor reflex in carotid sinus syndrome. *Circ Arrhythm Electrophysiol* 2014;**7**:505–510.
71. Mangrum JM, DiMarco JP. The evaluation and management of bradycardia. *N Engl J Med* 2000;**342**:703–709.
72. Sutton R. Reflex atrioventricular block. *Front Cardiovasc Med* 2020;**7**:48.
72a. Da Costa D, Brady WJ, Edhouse J. Bradycardias and atrioventricular conduction block. *BMJ* 2002;**324**:535–538.
73. Steinberg JS, Varma N, Cygankiewicz I, Aziz P, Balsam P, Baranchuk A, Cantillon DJ, Dilaveris P, Dubner SJ, El-Sherif N, Krol J, Kurpesa M, La Rovere MT, Lobodzinski SS, Locati ET, Mittal S, Olshansky B, Piotrowicz E, Saxon L, Stone PH, Tereshchenko L, Turitto G, Wimmer NJ, Verrier RL, Zareba W, Piotrowicz R. 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry. *Heart Rhythm* 2017;**14**:e55-e96.
74. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation* 2011;**123**:1010–1020.
75. Savonen KP, Kiviniemi V, Laukkanen JA, Lakka TA, Rauramaa TH, Salonen JT, Rauramaa R. Chronotropic incompetence and mortality in middle-aged men with known or suspected coronary heart disease. *Eur Heart J* 2008;**29**:1896–1902.
76. Byrne JM, Marais HJ, Cheek GA. Exercise-induced complete heart block in a patient with chronic bifascicular block. *J Electrocardiol* 1994;**27**:339–342.
77. Wissocq L, Ennezat PV, Mouquet F. Exercise-induced high-degree atrioventricular block. *Arch Cardiovasc Dis* 2009;**102**:733–735.
78. Woelfel AK, Simpson RJ Jr, Gettes LS, Foster JR. Exercise-induced distal atrioventricular block. *J Am Coll Cardiol* 1983;**2**:578–581.
79. Sumiyoshi M, Nakata Y, Yasuda M, Tokano T, Ogura S, Nakazato Y, Yamaguchi H. Clinical and electrophysiologic features of exercise-induced atrioventricular block. *Am Heart J* 1996;**132**:1277–1281.
80. Oliveros RA, Seaworth J, Weiland FL, Boucher CA. Intermittent left anterior hemiblock during treadmill exercise test. Correlation with coronary arteriogram. *Chest* 1977;**72**:492–494.
81. Bharati S, Dhingra RC, Lev M, Towne WD, Rhimtoola SH, Rosen KM. Conduction system in a patient with Prinzmetal's angina and transient atrioventricular block. *Am J Cardiol* 1977;**39**:120–125.
82. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2019;**41**:407–477.
83. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, Khalique Z, Stirrat C, Auger D, Pareek N, Ismail TF, Rosen SD, Vazir A, Alpendurada F, Gregson J, Frenneaux MP, Cowie MR, Cleland JGF, Cook SA, Pennell DJ, Prasad SK. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. *Circulation* 2017;**135**:2106–2115.
84. Kazmirczak F, Chen KA, Adabag S, von Wald L, Roukoz H, Benditt DG, Okasha O, Farzaneh-Far A, Markowitz J, Nijjar PS, Velangi PS, Bhargava M, Perlman D, Duval S, Akcakaya M, Shenoy C. Assessment of the 2017 AHA/ACC/HRS Guideline Recommendations for Implantable Cardioverter-Defibrillator Implantation in Cardiac Sarcoidosis. *Circ Arrhythm Electrophysiol* 2019;**12**:e007488.
85. Aquaro GD, Perfetti M, Camastra G, Monti L, Dellegrottaglie S, Moro C, Pepe A, Todiere G, Lanzillo C, Scatteia A, Di Roma M, Pontone G, Perazzolo Marra M, Barison A, Di Bella G. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY Study. *J Am Coll Cardiol* 2017;**70**:1977–1987.
86. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, Friedrich MG. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol* 2018;**72**:3158–3176.
87. Zhou Y, Lower EE, Li HP, Costea A, Attari M, Baughman RP. Cardiac sarcoidosis: the impact of age and implanted devices on survival. *Chest* 2017;**151**:139–148.
88. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. *Circ Arrhythm Electrophysiol* 2011;**4**:303–309.
89. Turner JJO. Hypercalcaemia—presentation and management. *Clin Med (Lond)* 2017;**17**:270–273.
90. Chon SB, Kwak YH, Hwang SS, Oh WS, Bae JH. Severe hyperkalemia can be detected immediately by quantitative electrocardiography and clinical history in patients with symptomatic or extreme bradycardia: a retrospective cross-sectional study. *J Crit Care* 2013;**28**:1112.e7–1112.e13.
91. Mandell BF. Cardiovascular involvement in systemic lupus erythematosus. *Semin Arthritis Rheum* 1987;**17**:126–141.
92. Wan D, Blakely C, Branscombe P, Suarez-Fuster L, Glover B, Baranchuk A. Lyme carditis and high-degree atrioventricular block. *Am J Cardiol* 2018;**121**:1102–1104.
93. Nakayama Y, Ohno M, Yonemura S, Uozumi H, Kobayakawa N, Fukushima K, Takeuchi H, Aoyagi T. A case of transient 2:1 atrioventricular block, resolved by thyroxine supplementation for subclinical hypothyroidism. *Pacing Clin Electrophysiol* 2006;**29**:106–108.
94. Noble K, Isles C. Hyperkalaemia causing profound bradycardia. *Heart* 2006;**92**:1063.
95. Ishikawa T, Tsuji Y, Makita N. Inherited bradyarrhythmia: a diverse genetic background. *J Arrhythm* 2016;**32**:352–358.
96. Smits JP, Veldkamp MW, Wilde AA. Mechanisms of inherited cardiac conduction disease. *Europace* 2005;**7**:122–137.
97. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* 2013;**10**:1932–1963.
98. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol* 1977;**39**:390–395.
99. Clarke JM, Hamer J, Shelton JR, Taylor S, Venning GR. The rhythm of the normal human heart. *Lancet* 1976;**1**:508–512.
100. Fleg JL, Kennedy HL. Cardiac arrhythmias in a healthy elderly population: detection by 24-hour ambulatory electrocardiography. *Chest* 1982;**81**:302–307.
101. Grimm W, Hoffmann J, Menz V, Kohler U, Heitmann J, Peter JH, Maisch B. Electrophysiologic evaluation of sinus node function and atrioventricular conduction in patients with prolonged ventricular asystole during obstructive sleep apnea. *Am J Cardiol* 1996;**77**:1310–1314.
102. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea. Characteristics and mechanism. *J Clin Invest* 1982;**69**:1286–1292.
103. Guilleminault C, Pool P, Motta J, Gillis AM. Sinus arrest during REM sleep in young adults. *N Engl J Med* 1984;**311**:1006–1010.
104. Grimm W, Koehler U, Fus E, Hoffmann J, Menz V, Funck R, Peter JH, Maisch B. Outcome of patients with sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy. *Am J Cardiol* 2000;**86**:688–692.
105. Koehler U, Fus E, Grimm W, Pankow W, Schafer H, Stammnitz A, Peter JH. Heart block in patients with obstructive sleep apnoea: pathogenetic factors and effects of treatment. *Eur Respir J* 1998;**11**:434–439.
106. Simantirakis EN, Schiza SI, Marketou ME, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, Siafakas NS, Vardas PE. Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. *Eur Heart J* 2004;**25**:1070–1076.
107. Sutton R, Fedorowski A, Olshansky B, Gert van Dijk J, Abe H, Brignole M, de Lange F, Kenny RA, Lim PB, Moya A, Rosen SD, Russo V, Stewart JM, Thijs RD, Benditt DG. Tilt testing remains a valuable asset. *Eur Heart J* 2021;**42**:1654–1660.
108. Da Costa A, Defaye P, Romeyer-Bouchard C, Roche F, Dauphinot V, Deharo JC, Jacon P, Lamaison D, Bathelemy JC, Isaaz K, Laurent G. Clinical impact of the implantable loop recorder in patients with isolated syncope, bundle branch block and negative workup: a randomized multicentre prospective study. *Arch Cardiovasc Dis* 2013;**106**:146–154.
109. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. *Eur Heart J* 2006;**27**:351–356.
110. Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. *Circulation* 2001;**104**:46–51.
111. Podoleanu C, DaCosta A, Defaye P, Taieb J, Galley D, Bru P, Maury P, Mabo P, Boveda S, Cellarier G, Anselme F, Kouakam C, Delarche N, Deharo JC. Early use of an implantable loop recorder in syncope evaluation: a randomized study in the context of the French healthcare system (FRESH study). *Arch Cardiovasc Dis* 2014;**107**:546–552.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

112. Sulke N, Sugihara C, Hong P, Patel N, Freemantle N. The benefit of a remotely monitored implantable loop recorder as a first line investigation in unexplained syncope: the EaSyAS II trial. *Europace* 2016;**18**:912–918.
113. Gann D, Tolentino A, Samet P. Electrophysiologic evaluation of elderly patients with sinus bradycardia: a long-term follow-up study. *Ann Intern Med* 1979;**90**:24–29.
114. Menozzi C, Brignole M, Alboni P, Boni L, Paparella N, Gaggioli G, Lolli G. The natural course of untreated sick sinus syndrome and identification of the variables predictive of unfavorable outcome. *Am J Cardiol* 1998;**82**:1205–1209.
115. McAnulty JH, Rahimtoola SH, Murphy E, DeMots H, Ritzmann L, Kanarek PE, Kauffman S. Natural history of 'high-risk' bundle-branch block: final report of a prospective study. *N Engl J Med* 1982;**307**:137–143.
116. Gronda M, Magnani A, Occhetta E, Sauro G, D'Aulerio M, Carfora A, Rossi P. Electrophysiological study of atrio-ventricular block and ventricular conduction defects. Prognostic and therapeutical implications. *G Ital Cardiol* 1984;**14**:768–773.
117. Bergfeldt L, Edvardsson N, Rosenqvist M, Vallin H, Edhag O. Atrioventricular block progression in patients with bifascicular block assessed by repeated electrocardiography and a bradycardia-detecting pacemaker. *Am J Cardiol* 1994;**74**:1129–1132.
118. Kaul U, Dev V, Narula J, Malhotra AK, Talwar KK, Bhatia ML. Evaluation of patients with bundle branch block and 'unexplained' syncope: a study based on comprehensive electrophysiologic testing and ajmaline stress. *Pacing Clin Electrophysiol* 1988;**11**:289–297.
119. Moya A, Garcia-Civera R, Croci F, Menozzi C, Brugada J, Ammirati F, Del Rosso A, Bellver-Navarro A, Garcia-Sacristan J, Bortnik M, Mont L, Ruiz-Granell R, Navarro X. Diagnosis, management, and outcomes of patients with syncope and bundle branch block. *Eur Heart J* 2011;**32**:1535–1541.
120. Twidale N, Heddle WF, Tonkin AM. Procainamide administration during electrophysiology study—utility as a provocative test for intermittent atrioventricular block. *Pacing Clin Electrophysiol* 1988;**11**:1388–1397.
121. Scheinman MM, Peters RW, Suave MJ, Desai J, Abbott JA, Cogan J, Wohl B, Williams K. Value of the H–Q interval in patients with bundle branch block and the role of prophylactic permanent pacing. *Am J Cardiol* 1982;**50**:1316–1322.
122. Roca-Luque I, Oristrell G, Francisco-Pasqual J, Rodriguez-Garcia J, Santos-Ortega A, Martin-Sanchez G, Rivas-Gandara N, Perez-Rodon J, Ferreira-Gonzalez I, Garcia-Dorado D, Moya-Mitjans A. Predictors of positive electrophysiological study in patients with syncope and bundle branch block: PR interval and type of conduction disturbance. *Clin Cardiol* 2018;**41**:1537–1542.
123. Brignole M, Menozzi C, Moya A, Garcia-Civera R, Mont L, Alvarez M, Errazquin F, Beiras J, Bottoni N, Donateo P. Mechanism of syncope in patients with bundle branch block and negative electrophysiological test. *Circulation* 2001;**104**:2045–2050.
124. Rubenstein JJ, Schulman CL, Yurchak PM, DeSanctis RW. Clinical spectrum of the sick sinus syndrome. *Circulation* 1972;**46**:5–13.
125. Short DS. The syndrome of alternating bradycardia and tachycardia. *Br Heart J* 1954;**16**:208–214.
126. Goldberger JJ, Johnson NP, Gidea C. Significance of asymptomatic bradycardia for subsequent pacemaker implantation and mortality in patients >60 years of age. *Am J Cardiol* 2011;**108**:857–861.
127. Nielsen JC, Thomsen PE, Hojberg S, Moller M, Vesterlund T, Dalsgaard D, Mortensen LS, Nielsen T, Asklund M, Friis EV, Christensen PD, Simonsen EH, Eriksen UH, Jensen GV, Svendsen JH, Toff WD, Healey JS, Andersen HR, DANPACE Investigators. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. *Eur Heart J* 2011;**32**:686–696.
128. Breivik K, Ohm OJ, Segadal L. Sick sinus syndrome treated with permanent pacemaker in 109 patients. A follow-up study. *Acta Med Scand* 1979;**206**:153–159.
129. Hartel G, Talvensaari T. Treatment of sinoatrial syndrome with permanent cardiac pacing in 90 patients. *Acta Med Scand* 1975;**198**:341–347.
130. Rasmussen K. Chronic sinus node disease: natural course and indications for pacing. *Eur Heart J* 1981;**2**:455–459.
131. Sasaki Y, Shimotori M, Akahane K, Yonekura H, Hirano K, Endoh R, Koike S, Kawa S, Furuta S, Homma T. Long-term follow-up of patients with sick sinus syndrome: a comparison of clinical aspects among unpaced, ventricular inhibited paced, and physiologically paced groups. *Pacing Clin Electrophysiol* 1988;**11**:1575–1583.
132. Senturk T, Xu H, Puppala K, Krishnan B, Sakaguchi S, Chen LY, Karim R, Dickinson O, Benditt DG. Cardiac pauses in competitive athletes: a systematic review examining the basis of current practice recommendations. *Europace* 2016;**18**:1873–1879.
133. Brignole M, Menozzi C, Moya A, Andresen D, Blanc JJ, Krahn AD, Wieling W, Beiras X, Deharo JC, Russo V, Tomaino M, Sutton R, International Study on Syncope of Uncertain Etiology Investigators. Pacemaker therapy in patients with neurally mediated syncope and documented asystole: Third International Study on Syncope of Uncertain Etiology (ISSUE-3): a randomized trial. *Circulation* 2012;**125**:2566–2571.
134. Brignole M, Sutton R, Menozzi C, Garcia-Civera R, Moya A, Wieling W, Andresen D, Benditt DG, Vardas P, International Study on Syncope of Uncertain Etiology Group. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. *Eur Heart J* 2006;**27**:1085–1092.
135. Asseman P, Berzin B, Desry D, Vilarem D, Durand P, Delmotte C, Sarkis EH, Lekieffre J, Thery C. Persistent sinus nodal electrograms during abnormally prolonged postpacing atrial pauses in sick sinus syndrome in humans: sinoatrial block vs overdrive suppression. *Circulation* 1983;**68**:33–41.
136. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Cosedis Nielsen J, Curtis AB, Davies DW, Day JD, d'Avila A, Natasja de Groot NMS, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T, Document Reviewers. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2018;**20**:e1–e160.
137. Chen YW, Bai R, Lin T, Salim M, Sang CH, Long DY, Yu RH, Tang RB, Guo XY, Yan XL, Nie JG, Du X, Dong JZ, Ma CS. Pacing or ablation: which is better for paroxysmal atrial fibrillation-related tachycardia–bradycardia syndrome? *Pacing Clin Electrophysiol* 2014;**37**:403–411.
138. Inada K, Yamane T, Tokutake K, Yokoyama K, Mishima T, Hioki M, Narui R, Ito K, Tanigawa S, Yamashita S, Tokuda M, Matsuo S, Shibayama K, Miyanaga S, Date T, Sugimoto K, Yoshimura M. The role of successful catheter ablation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses: outcome during a 5-year follow-up. *Europace* 2014;**16**:208–213.
139. Jackson LR, 2nd, Rathakrishnan B, Campbell K, Thomas KL, Piccini JP, Bahnson T, Stiber JA, Daubert JP. Sinus node dysfunction and atrial fibrillation: a reversible phenomenon? *Pacing Clin Electrophysiol* 2017;**40**:442–450.
140. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med* 2000;**342**:1385–1391.
141. Healey JS, Toff WD, Lamas GA, Andersen HR, Thorpe KE, Ellenbogen KA, Lee KL, Skene AM, Schron EB, Skehan JD, Goldman L, Roberts RS, Camm AJ, Yusuf S, Connolly SJ. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. *Circulation* 2006;**114**:11–17.
142. Ross RA, Kenny RA. Pacemaker syndrome in older people. *Age Ageing* 2000;**29**:13–15.
143. Mitsuoka T, Kenny RA, Yeung TA, Chan SL, Perrins JE, Sutton R. Benefits of dual chamber pacing in sick sinus syndrome. *Br Heart J* 1988;**60**:338–347.
144. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, Sheldon T, Lamas GA, Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction Trial. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med* 2007;**357**:1000–1008.
145. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997;**350**:1210–1216.
146. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. *Lancet* 1994;**344**:1523–1528.
147. Kristensen L, Nielsen JC, Mortensen PT, Pedersen OL, Pedersen AK, Andersen HR. Incidence of atrial fibrillation and thromboembolism in a randomised trial of atrial versus dual chamber pacing in 177 patients with sick sinus syndrome. *Heart* 2004;**90**:661–666.
148. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A, Dual Chamber VVI Implantable Defibrillator Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;**288**:3115–3123.
149. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;**301**:2571–2577.
150. Nielsen JC, Thomsen PE, Hojberg S, Moller M, Riahi S, Dalsgaard D, Mortensen LS, Nielsen T, Asklund M, Friis EV, Christensen PD, Simonsen EH, Eriksen UH,

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Jensen GV, Svendsen JH, Toff WD, Healey JS, Andersen HR, DANPACE Investigators. Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing. *Europace* 2012;**14**:682–689.
151. Auricchio A, Ellenbogen KA. Reducing ventricular pacing frequency in patients with atrioventricular block: is it time to change the current pacing paradigm? *Circ Arrhythm Electrophysiol* 2016;**9**:e004404.
152. Shurrab M, Healey JS, Haj-Yahia S, Kaoutskaia A, Boriani G, Carrizo A, Botto G, Newman D, Padeletti L, Connolly SJ, Crystal E. Reduction in unnecessary ventricular pacing fails to affect hard clinical outcomes in patients with preserved left ventricular function: a meta-analysis. *Europace* 2017;**19**:282–288.
153. Jankelson L, Bordachar P, Strik M, Ploux S, Chinitz L. Reducing right ventricular pacing burden: algorithms, benefits, and risks. *Europace* 2019;**21**:539–547.
154. Pascale P, Pruvot E, Graf D. Pacemaker syndrome during managed ventricular pacing mode: what is the mechanism? *J Cardiovasc Electrophysiol* 2009;**20**:574–576.
155. Mansour F, Khairy P. Electrical storm due to managed ventricular pacing. *Heart Rhythm* 2012;**9**:842–843.
156. Sekita G, Hayashi H, Nakazato Y, Daida H. Ventricular fibrillation induced by short–long–short sequence during managed ventricular pacing. *J Cardiovasc Electrophysiol* 2011;**22**:1181.
157. Vavasis C, Slotwiner DJ, Goldner BG, Cheung JW. Frequent recurrent polymorphic ventricular tachycardia during sleep due to managed ventricular pacing. *Pacing Clin Electrophysiol* 2010;**33**:641–644.
158. van Mechelen R, Schoonderwoerd R. Risk of managed ventricular pacing in a patient with heart block. *Heart Rhythm* 2006;**3**:1384–1385.
159. Stockburger M, Boveda S, Moreno J, Da Costa A, Hatala R, Brachmann J, Butter C, Garcia Seara J, Rolando M, Defaye P. Long-term clinical effects of ventricular pacing reduction with a changeover mode to minimize ventricular pacing in a general pacemaker population. *Eur Heart J* 2015;**36**:151–157.
160. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–129.
161. Munawar DA, Mahajan R, Agbaedeng TA, Thiyagarajah A, Twomey DJ, Khokhar K, O'Shea C, Young GD, Roberts-Thomson KC, Munawar M, Lau DH, Sanders P. Implication of ventricular pacing burden and atrial pacing therapies on the progression of atrial fibrillation: a systematic review and meta-analysis of randomized controlled trials. *Heart Rhythm* 2019;**16**:1204–1214.
162. Padeletti L, Purerfellner H, Mont L, Tukkie R, Manolis AS, Ricci R, Inama G, Serra P, Scheffer MG, Martins V, Warman EN, Vimercati M, Grammatico A, Boriani G, MINERVA Investigators. New-generation atrial antitachycardia pacing (Reactive ATP) is associated with reduced risk of persistent or permanent atrial fibrillation in patients with bradycardia: results from the MINERVA randomized multicenter international trial. *Heart Rhythm* 2015;**12**:1717–1725.
163. Pujol-Lopez M, San Antonio R, Tolosana JM, Mont L. Programming pacemakers to reduce and terminate atrial fibrillation. *Curr Cardiol Rep* 2019;**21**:127.
164. Boriani G, Tukkie R, Manolis AS, Mont L, Purerfellner H, Santini M, Inama G, Serra P, de Sousa J, Botto GL, Mangoni L, Grammatico A, Padeletti L, MINERVA Investigators. Atrial antitachycardia pacing and managed ventricular pacing in bradycardia patients with paroxysmal or persistent atrial tachyarrhythmias: the MINERVA randomized multicentre international trial. *Eur Heart J* 2014;**35**:2352–2362.
165. Crossley GH, Padeletti L, Zweibel S, Hudnall JH, Zhang Y, Boriani G. Reactive atrial-based antitachycardia pacing therapy reduces atrial tachyarrhythmias. *Pacing Clin Electrophysiol* 2019;**42**:970–979.
166. Stockburger M, Gomez-Doblas JJ, Lamas G, Alzueta J, Fernandez-Lozano I, Cobo E, Wiegand U, Concha JF, Navarro X, Navarro-Lopez F, de Teresa E. Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: results from a multicentre international randomized trial (PREVENT-HF). *Eur J Heart Fail* 2011;**13**:633–641.
167. Stockburger M, Defaye P, Boveda S, Stancak B, Lazarus A, Sipotz J, Nardi S, Rolando M, Moreno J. Safety and efficiency of ventricular pacing prevention with an AAI-DDD changeover mode in patients with sinus node disease or atrioventricular block: impact on battery longevity—a sub-study of the ANSWER trial. *Europace* 2016;**18**:739–746.
168. Thibault B, Simpson C, Gagne CE, Blier L, Senaratne M, McNicoll S, Stuglin C, Williams R, Pinter A, Khaykin Y, Nitzsche R. Impact of AV conduction disorders on SafeR mode performance. *Pacing Clin Electrophysiol* 2009;**32 Suppl 1**:S231–235.
169. Thibault B, Ducharme A, Baranchuk A, Dubuc M, Dyrda K, Guerra PG, Macle L, Mondesert B, Rivard L, Roy D, Talajic M, Andrade J, Nitzsche R, Khairy P, CAN-SAVE R Study Investigators. Very low ventricular pacing rates can be achieved safely in a heterogeneous pacemaker population and provide clinical benefits: the CANadian Multi-Centre Randomised Study-Spontaneous AtrioVEntricular Conduction pReservation (CAN-SAVE R) *Trial. J Am Heart Assoc* 2015;**4**:e001983
170. Bellocci F, Spampinato A, Ricci R, Puglisi A, Capucci A, Dini P, Boriani G, Botto G, Curnis A, Moracchini PV, Nicotra G, Lisi F, Nigro P. Antiarrhythmic benefits of dual chamber stimulation with rate-response in patients with paroxysmal atrial fibrillation and chronotropic incompetence: a prospective, multicentre study. *Europace* 1999;**1**:220–225.
171. Santini M, Ricci R, Puglisi A, Mangiameli S, Proclemer A, Menozzi C, De Fabrizio G, Leoni G, Lisi F, De Seta F. Long-term haemodynamic and antiarrhythmic benefits of DDIR versus DDI pacing mode in sick sinus syndrome and chronotropic incompetence. *G Ital Cardiol* 1997;**27**:892–900.
172. Capucci A, Boriani G, Specchia S, Marinelli M, Santarelli A, Magnani B. Evaluation by cardiopulmonary exercise test of DDDR versus DDD pacing. *Pacing Clin Electrophysiol* 1992;**15**:1908–1913.
173. Lamas GA, Knight JD, Sweeney MO, Mianulli M, Jorapur V, Khalighi K, Cook JR, Silverman R, Rosenthal L, Clapp-Channing N, Lee KL, Mark DB. Impact of rate-modulated pacing on quality of life and exercise capacity—evidence from the Advanced Elements of Pacing Randomized Controlled Trial (ADEPT). *Heart Rhythm* 2007;**4**:1125–1132.
174. Hocini M, Sanders P, Deisenhofer I, Jais P, Hsu LF, Scavee C, Weerasoriya R, Raybaud F, Macle L, Shah DC, Garrigue S, Le Metayer P, Clementy J, Haissaguerre M. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation* 2003;**108**:1172–1175.
175. Mymin D, Mathewson FA, Tate RB, Manfreda J. The natural history of primary first-degree atrioventricular heart block. *N Engl J Med* 1986;**315**:1183–1187.
176. Barold SS, Ilercil A, Leonelli F, Herweg B. First-degree atrioventricular block. Clinical manifestations, indications for pacing, pacemaker management & consequences during cardiac resynchronization. *J Interv Card Electrophysiol* 2006;**17**:139–152.
177. Shaw DB, Gowers JI, Kekwick CA, New KH, Whistance AW. Is Mobitz type I atrioventricular block benign in adults? *Heart* 2004;**90**:169–174.
178. Coumbe AG, Naksuk N, Newell MC, Somasundaram PE, Benditt DG, Adabag S. Long-term follow-up of older patients with Mobitz type I second degree atrioventricular block. *Heart* 2013;**99**:334–338.
179. Strasberg B, Amat YLF, Dhingra RC, Palileo E, Swiryn S, Bauernfeind R, Wyndham C, Rosen KM. Natural history of chronic second-degree atrioventricular nodal block. *Circulation* 1981;**63**:1043–1049.
180. Dhingra RC, Denes P, Wu D, Chuquimia R, Rosen KM. The significance of second degree atrioventricular block and bundle branch block. Observations regarding site and type of block. *Circulation* 1974;**49**:638–646.
181. Toff WD, Camm AJ, Skehan JD, United Kingdom Pacing Cardiovascular Events Trial Investigators. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. *N Engl J Med* 2005;**353**:145–155.
182. Castelnuovo E, Stein K, Pitt M, Garside R, Payne E. The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation. *Health Technol Assess* 2005;**9**:iii, xi–xiii, 1–246.
183. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;**107**:2932–2937.
184. Nahlawi M, Waligora M, Spies SM, Bonow RO, Kadish AH, Goldberger JJ. Left ventricular function during and after right ventricular pacing. *J Am Coll Cardiol* 2004;**44**:1883–1888.
185. Sweeney MO, Prinzen FW. A new paradigm for physiologic ventricular pacing. *J Am Coll Cardiol* 2006;**47**:282–288.
186. Tayal B, Fruelund P, Sogaard P, Riahi S, Polcwiartek C, Atwater BD, Gislason G, Risum N, Torp-Pedersen C, Kober L, Kragholm KH. Incidence of heart failure after pacemaker implantation: a nationwide Danish Registry-based follow-up study. *Eur Heart J* 2019;**40**:3641–3648.
187. Khurshid S, Epstein AE, Verdino RJ, Lin D, Goldberg LR, Marchlinski FE, Frankel DS. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. *Heart Rhythm* 2014;**11**:1619–1625.
188. Kiehl EL, Makki T, Kumar R, Gumber D, Kwon DH, Rickard JW, Kanj M, Wazni OM, Saliba WI, Varma N, Wilkoff BL, Cantillon DJ. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. *Heart Rhythm* 2016;**13**:2272–2278.
189. Khurshid S, Obeng-Gyimah E, Supple GE, Schaller R, Lin D, Owens AT, Epstein AE, Dixit S, Marchlinski FE, Frankel DS. Reversal of pacing-induced cardiomyopathy following cardiac resynchronization therapy. *JACC Clin Electrophysiol* 2018;**4**:168–177.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

190. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS, Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;**368**:1585–1593.
191. Pitcher D, Papouchado M, James MA, Rees JR. Twenty four hour ambulatory electrocardiography in patients with chronic atrial fibrillation. *Br Med J (Clin Res Ed)* 1986;**292**:594.
192. Chatterjee NA, Upadhyay GA, Ellenbogen KA, McAlister FA, Choudhry NK, Singh JP. Atrioventricular nodal ablation in atrial fibrillation: a meta-analysis and systematic review. *Circ Arrhythm Electrophysiol* 2012;**5**:68–76.
193. Ozcan C, Jahangir A, Friedman PA, Patel PJ, Munger TM, Rea RF, Lloyd MA, Packer DL, Hodge DO, Gersh BJ, Hammill SC, Shen WK. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. *N Engl J Med* 2001;**344**:1043–1051.
194. Garcia B, Clementy N, Benhenda N, Pierre B, Babuty D, Olshansky B, Fauchier L. Mortality after atrioventricular nodal radiofrequency catheter ablation with permanent ventricular pacing in atrial fibrillation: outcomes from a controlled nonrandomized study. *Circ Arrhythm Electrophysiol* 2016;**9**.
195. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, Quartieri F, Calò L, Ungar A, Mont L. A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J* 2018;**39**:3999–4008.
196. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA, PAVE Study Group. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005;**16**:1160–1165.
197. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, Ellenbogen KA. Benefits of permanent His bundle pacing combined with atrioventricular node ablation in atrial fibrillation patients with heart failure with both preserved and reduced left ventricular ejection fraction. *J Am Heart Assoc* 2017;**6**:e005309.
198. Vijayaraman P, Subzposh FA, Naperkowski A. Atrioventricular node ablation and His bundle pacing. *Europace* 2017;**19**:iv10-iv16.
199. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His–Purkinje activation. *Circulation* 2000;**101**:869–877.
200. Occhetta E, Bortnik M, Magnani A, Francalacci G, Piccinino C, Plebani L, Marino P. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. *J Am Coll Cardiol* 2006;**47**:1938–1945.
201. Lau CP, Rushby J, Leigh-Jones M, Tam CY, Poloniecki J, Ingram A, Sutton R, Camm AJ. Symptomatology and quality of life in patients with rate-responsive pacemakers: a double-blind, randomized, crossover study. *Clin Cardiol* 1989;**12**:505–512.
202. Leung SK, Lau CP. Developments in sensor-driven pacing. *Cardiol Clin* 2000;**18**:113–155, ix.
203. Oto MA, Muderrisoglu H, Ozin MB, Korkmaz ME, Karamehmetoglu A, Oram A, Oram E, Ugurlu S. Quality of life in patients with rate responsive pacemakers: a randomized, cross-over study. *Pacing Clin Electrophysiol* 1991;**14**:800–806.
204. Proietti R, Manzoni G, Di Biase L, Castelnuovo G, Lombardi L, Fundaro C, Vegliante N, Pietrabissa G, Santangeli P, Canby RA, Sagone A, Viecca M, Natale A. Closed loop stimulation is effective in improving heart rate and blood pressure response to mental stress: report of a single-chamber pacemaker study in patients with chronotropic incompetent atrial fibrillation. *Pacing Clin Electrophysiol* 2012;**35**:990–998.
205. Barold SS. Indications for permanent cardiac pacing in first-degree AV block: class I, II, or III? *Pacing Clin Electrophysiol* 1996;**19**:747–751.
206. Brecker SJ, Xiao HB, Sparrow J, Gibson DG. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. *Lancet* 1992;**340**:1308–1312.
207. Carroz P, Delay D, Girod G. Pseudo-pacemaker syndrome in a young woman with first-degree atrio-ventricular block. *Europace* 2010;**12**:594–596.
208. Englund A, Bergfeldt L, Rehnqvist N, Astrom H, Rosenqvist M. Diagnostic value of programmed ventricular stimulation in patients with bifascicular block: a prospective study of patients with and without syncope. *J Am Coll Cardiol* 1995;**26**:1508–1515.
209. Morady F, Higgins J, Peters RW, Schwartz AB, Shen EN, Bhandari A, Scheinman MM, Sauve MJ. Electrophysiologic testing in bundle branch block and unexplained syncope. *Am J Cardiol* 1984;**54**:587–591.
210. Tabrizi F, Rosenqvist M, Bergfeldt L, Englund A. Long-term prognosis in patients with bifascicular block—the predictive value of noninvasive and invasive assessment. *J Intern Med* 2006;**260**:31–38.
211. Olshansky B, Hahn EA, Hartz VL, Prater SP, Mason JW. Clinical significance of syncope in the electrophysiologic study versus electrocardiographic monitoring (ESVEM) trial. The ESVEM Investigators. *Am Heart J* 1999;**137**:878–886.
212. Roca-Luque I, Francisco-Pasqual J, Oristrell G, Rodriguez-Garcia J, Santos-Ortega A, Martin-Sanchez G, Rivas-Gandara N, Perez-Rodon J, Ferreira-Gonzalez I, Garcia-Dorado D, Moya-Mitjans A. Flecainide versus procainamide in electrophysiological study in patients with syncope and wide QRS duration. *JACC Clin Electrophysiol* 2019;**5**:212–219.
213. Santini M, Castro A, Giada F, Ricci R, Inama G, Gaggioli G, Calo L, Orazi S, Viscusi M, Chiodi L, Bartoletti A, Foglia-Manzillo G, Ammirati F, Loricchio ML, Pedrinazzi C, Turreni F, Gasparini G, Accardi F, Raciti G, Raviele A. Prevention of syncope through permanent cardiac pacing in patients with bifascicular block and syncope of unexplained origin: the PRESS study. *Circ Arrhythm Electrophysiol* 2013;**6**:101–107.
214. Camm AJ, Lüscher TF, Maurer G, Serruys PW (eds). *ESC CardioMed*. 3rd ed. Oxford, UK: Oxford University Press; 2018.
215. Peters RW, Scheinman MM, Modin C, O'Young J, Somelofski CA, Mies C. Prophylactic permanent pacemakers for patients with chronic bundle branch block. *Am J Med* 1979;**66**:978–985.
216. Armaganijan LV, Toff WD, Nielsen JC, Andersen HR, Connolly SJ, Ellenbogen KA, Healey JS. Are elderly patients at increased risk of complications following pacemaker implantation? A meta-analysis of randomized trials. *Pacing Clin Electrophysiol* 2012;**35**:131–134.
217. Gadler F, Valzania C, Linde C. Current use of implantable electrical devices in Sweden: data from the Swedish pacemaker and implantable cardioverter-defibrillator registry. *Europace* 2015;**17**:69–77.
218. Shurrab M, Elitzur Y, Healey JS, Gula L, Kaoutskaia A, Israel C, Lau C, Crystal E. VDD vs DDD pacemakers: a meta-analysis. *Can J Cardiol* 2014;**30**:1385–1391.
219. Brignole M, Ammirati F, Arabia F, Quartieri F, Tomaino M, Ungar A, Lunati M, Russo V, Del Rosso A, Gaggioli G, Syncope Unit Project Two Investigators. Assessment of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncopes. *Eur Heart J* 2015;**36**:1529–1535.
220. Brignole M, Arabia F, Ammirati F, Tomaino M, Quartieri F, Rafanelli M, Del Rosso A, Rita Vecchi M, Russo V, Gaggioli G, Syncope Unit Project investigators. Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study. *Europace* 2016;**18**:1427–1433.
221. Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. *Eur Heart J* 2014;**35**:2211–2212.
222. Claesson JE, Kristensson BE, Edvardsson N, Wahrborg P. Less syncope and milder symptoms in patients treated with pacing for induced cardioinhibitory carotid sinus syndrome: a randomized study. *Europace* 2007;**9**:932–936.
223. Brignole M, Menozzi C, Lolli G, Bottoni N, Gaggioli G. Long-term outcome of paced and nonpaced patients with severe carotid sinus syndrome. *Am J Cardiol* 1992;**69**:1039–1043.
224. Sutton R, Brignole M, Menozzi C, Raviele A, Alboni P, Giani P, Moya A. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. *Circulation* 2000;**102**:294–299.
225. Ammirati F, Colivicchi F, Santini M, Syncope D, Treatment Study Investigators. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. *Circulation* 2001;**104**:52–57.
226. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, Martinez-Alday J, Ruiz-Granell R, Lacunza-Ruiz J, Garcia-Civera R, Gutierrez-Carretero E, Romero-Garrido R. Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope: the SPAIN study. *J Am Coll Cardiol* 2017;**70**:1720–1728.
227. Russo V, Rago A, Papa AA, Golino P, Calabro R, Russo MG, Nigro G. The effect of dual-chamber closed-loop stimulation on syncope recurrence in healthy patients with tilt-induced vasovagal cardioinhibitory syncope: a prospective, randomised, single-blind, crossover study. *Heart* 2013;**99**:1609–1613.
228. Brignole M, Russo V, Arabia F, Oliveira M, Pedrote A, Aerts A, Rapacciuolo A, Boveda S, Deharo JC, Maglia G, Nigro G, Giacopelli D, Gargaro A, Tomaino M, BioSync CSL trial Investigators. Cardiac pacing in severe recurrent reflex syncope and tilt-induced asystole. *Eur Heart J* 2020;**42**:508–516.
229. Russo V, Rago A, De Rosa M, Papa AA, Simova I, Petrov I, Bonev N, Gargaro A, Golino P, Nigro G. Does cardiac pacing reduce syncopal recurrences in cardioinhibitory vasovagal syncope patients selected with head-up tilt test? Analysis of a 5-year follow-up database. *Int J Cardiol* 2018;**270**:149–153.
230. Flammang D, Church TR, De Roy L, Blanc JJ, Leroy J, Mairesse GH, Otmani A, Graux PJ, Frank R, Purnode P, ATP Multicenter Study. Treatment of unexplained syncope: a multicenter, randomized trial of cardiac pacing guided by adenosine 5'-triphosphate testing. *Circulation* 2012;**125**:31–36.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

231. Connolly SJ, Sheldon R, Thorpe KE, Roberts RS, Ellenbogen KA, Wilkoff BL, Morillo C, Gent M, VPS II Investigators. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: Second Vasovagal Pacemaker Study (VPS II): a randomized trial. *JAMA* 2003;**289**:2224–2229.
232. Raviele A, Giada F, Menozzi C, Speca G, Orazi S, Gasparini G, Sutton R, Brignole M, Vasovagal Syncope Pacing Trial Investigators. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). *Eur Heart J* 2004;**25**:1741–1748.
233. Palmisano P, Dell'Era G, Russo V, Zaccaria M, Mangia R, Bortnik M, De Vecchi F, Giubertoni A, Patti F, Magnani A, Nigro G, Rago A, Occhetta E, Accogli M. Effects of closed-loop stimulation vs. DDD pacing on haemodynamic variations and occurrence of syncope induced by head-up tilt test in older patients with refractory cardioinhibitory vasovagal syncope: the Tilt test-Induced REsponse in Closed-loop Stimulation multicentre, prospective, single blind, randomized study. *Europace* 2018;**20**:859–866.
234. Proclemer A, Facchin D, Feruglio GA. [Syncope of unknown origin after electrophysiologic study: is the treatment with pacemaker useful?]. *G Ital Cardiol* 1990;**20**:195–201.
235. Raviele A, Proclemer A, Gasparini G, Di Pede F, Delise P, Piccolo E, Feruglio GA. Long-term follow-up of patients with unexplained syncope and negative electrophysiologic study. *Eur Heart J* 1989;**10**:127–132.
236. Parry SW, Steen N, Bexton RS, Tynan M, Kenny RA. Pacing in elderly recurrent fallers with carotid sinus hypersensitivity: a randomised, double-blind, placebo controlled crossover trial. *Heart* 2009;**95**:405–409.
237. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–1146.
238. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case–control study. *Am J Med* 2009;**122**:1023–1028.
239. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002;**347**:305–313.
240. Rawshani A, Rawshani A, Franzen S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjornsdottir S. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;**379**:633–644.
241. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;**391**:572–580.
242. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;doi:10.1093/eurheartj/ehab368.
243. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlstrom U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–625.
244. Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial. *Heart Rhythm* 2012;**9**:34–39.
245. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, Freemantle N, Cleland JG, Tavazzi L, Daubert C, CARE-HF investigators. Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. *Eur J Heart Fail* 2009;**11**:699–705.
246. Friedman DJ, Bao H, Spatz ES, Curtis JP, Daubert JP, Al-Khatib SM. Association Between a Prolonged PR interval and outcomes of cardiac resynchronization therapy: a report from the National Cardiovascular Data Registry. *Circulation* 2016;**134**:1617–1628.
247. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002;**39**:194–201.
248. Leclercq C, Hare JM. Ventricular resynchronization: current state of the art. *Circulation* 2004;**109**:296–299.
249. Patel N, Viles-Gonzalez J, Agnihotri K, Arora S, Patel NJ, Aneja E, Shah M, Badheka AO, Pothineni NV. Frequency of in-hospital adverse outcomes and cost utilization associated with cardiac resynchronization therapy defibrillator implantation in the United States. *J Cardiovasc Electrophysiol* 2018;**29**:1425–1435.
250. Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, Clark AL, de Silva R, Calvert MJ, Swedberg K, Komajda M, Mareev V, Follath F. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. *Eur J Heart Fail* 2007;**9**:491–501.
251. Cleland JG, McDonagh T, Rigby AS, Yassin A, Whittaker T, Dargie HJ. The national heart failure audit for England and Wales 2008–2009. *Heart* 2011;**97**:876–886.
252. Lund LH, Braunschweig F, Benson L, Stahlberg M, Dahlstrom U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2017;**19**:1270–1279.
253. Dickstein K, Normand C, Auricchio A, Bogale N, Cleland JG, Gitt AK, Stellbrink C, Anker SD, Filippatos G, Gasparini M, Hindricks G, Blomstrom Lundqvist C, Ponikowski P, Ruschitzka F, Botto GL, Bulava A, Duray G, Israel C, Leclercq C, Margitfalvi P, Cano O, Plummer C, Sarigul NU, Sterlinski M, Linde C. CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients—who is doing what to whom and how? *Eur J Heart Fail* 2018;**20**:1039–1051.
254. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schondube F, Wolfhard U, Bocker D, Krahnefeld O, Kirkels H. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;**39**:2026–2033.
255. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Bocker D, Block M, Kirkels JH, Kramer A, Huvelle E. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003;**42**:2109–2116.
256. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–880.
257. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, McKenna W, Fitzgerald M, Deharo JC, Alonso C, Walker S, Braunschweig F, Bailleul C, Daubert JC. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;**40**:111–118.
258. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
259. Abraham WT, Young JB, Leon AR, Adler S, Bank AJ, Hall SA, Lieberman R, Liem LB, O'Connell JB, Schroeder JS, Wheelan KR. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;**110**:2864–2868.
260. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
261. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;**27**:1928–1932.
262. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–1843.
263. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Torok T, Linde C. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol* 2009;**54**:1837–1846.
264. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J 3rd, Gras D, Krum H, Sogaard P, Holzmeister J. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405.
265. Goldenberg I, Kutyifa V, Moss AJ. Survival with cardiac-resynchronization therapy. *N Engl J Med* 2014;**371**:477–478.
266. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, Sherfesee L, Wells GA, Tang AS. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. *Eur Heart J* 2013;**34**:3547–3556.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

267. Leclercq C, Walker S, Linde C, Clementy J, Marshall AJ, Ritter P, Djiane P, Mabo P, Levy T, Gadler F, Bailleul C, Daubert JC. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;**23**:1780–1787.
268. Funck RC, Mueller HH, Lunati M, Piorkowski C, De Roy L, Paul V, Wittenberg M, Wuensch D, Blanc JJ. Characteristics of a large sample of candidates for permanent ventricular pacing included in the Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization Study (BioPace). *Europace* 2014;**16**:354–362.
269. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Arch Intern Med* 2011;**171**:1454–1462.
270. Sipahi I, Chou JC, Hyden M, Rowland DY, Simon DI, Fang JC. Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. *Am Heart J* 2012;**163**:260–267.e263.
271. Cunnington C, Kwok CS, Satchithananda DK, Patwala A, Khan MA, Zaidi A, Ahmed FZ, Mamas MA. Cardiac resynchronisation therapy is not associated with a reduction in mortality or heart failure hospitalisation in patients with non-left bundle branch block QRS morphology: meta-analysis of randomised controlled trials. *Heart* 2015;**101**:1456–1462.
272. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**123**:1061–1072.
273. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F, Thibault B, Wells G, Tang A. Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail* 2013;**6**:1190–1198.
274. Bilchick KC, Kamath S, DiMarco JP, Stukenborg GJ. Bundle-branch block morphology and other predictors of outcome after cardiac resynchronization therapy in Medicare patients. *Circulation* 2010;**122**:2022–2030.
275. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart* 2015;**101**:1800–1806.
276. Gold MR, Thebault C, Linde C, Abraham WT, Gerritse B, Ghio S, St John Sutton M, Daubert JC. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. *Circulation* 2012;**126**:822–829.
277. Fantoni C, Kawabata M, Massaro R, Regoli F, Raffa S, Arora V, Salerno-Uriarte JA, Klein HU, Auricchio A. Right and left ventricular activation sequence in patients with heart failure and right bundle branch block: a detailed analysis using three-dimensional non-fluoroscopic electroanatomic mapping system. *J Cardiovasc Electrophysiol* 2005;**16**:112–119; discussion 120–121.
278. Nery PB, Ha AC, Keren A, Birnie DH. Cardiac resynchronization therapy in patients with left ventricular systolic dysfunction and right bundle branch block: a systematic review. *Heart Rhythm* 2011;**8**:1083–1087.
279. Kutyifa V, Stockburger M, Daubert JP, Holmqvist F, Olshansky B, Schuger C, Klein H, Goldenberg I, Brenyo A, McNitt S, Merkely B, Zareba W, Moss AJ. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. *Circ Arrhythm Electrophysiol* 2014;**7**:645–651.
280. Kewcharoen J, Kanitsoraphan C. Prolonged PR interval and outcome in cardiac resynchronization therapy. *Arq Bras Cardiol* 2019;**113**:109–110.
281. Steffel J, Robertson M, Singh JP, Abraham WT, Bax JJ, Borer JS, Dickstein K, Ford I, Gorcsan J 3rd, Gras D, Krum H, Sogaard P, Holzmeister J, Brugada J, Ruschitzka F. The effect of QRS duration on cardiac resynchronization therapy in patients with a narrow QRS complex: a subgroup analysis of the EchoCRT trial. *Eur Heart J* 2015;**36**:1983–1989.
282. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, Greenberg H, Hall WJ, McNitt S, Zareba W, Solomon S, Steinberg JS. Cardiac resynchronization therapy is more effective in women than in men: the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. *J Am Coll Cardiol* 2011;**57**:813–820.
283. Zusterzeel R, Selzman KA, Sanders WE, Canos DA, O'Callaghan KM, Carpenter JL, Pina IL, Strauss DG. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. *JAMA Intern Med* 2014;**174**:1340–1348.
284. Zweerink A, Friedman DJ, Klem I, van de Ven PM, Vink C, Biesbroek PS, Hansen SM, Emerek K, Kim RJ, van Rossum AC, Atwater BD, Nijveldt R, Allaart CP. Size Matters: Normalization of QRS duration to left ventricular dimension improves prediction of long-term cardiac resynchronization therapy outcome. *Circ Arrhythm Electrophysiol* 2018;**11**:e006767.
285. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. *Am J Cardiol* 2011;**107**:927–934.
286. Lee AWC, O'Regan DP, Gould J, Sidhu B, Sieniewicz B, Plank G, Warriner DR, Lamata P, Rinaldi CA, Niederer SA. Sex-dependent QRS guidelines for cardiac resynchronization therapy using computer model predictions. *Biophysical Journal* 2019;**117**:2375–2381.
287. Caputo ML, van Stipdonk A, Illner A, D'Ambrosio G, Regoli F, Conte G, Moccetti T, Klersy C, Prinzen FW, Vernooy K, Auricchio A. The definition of left bundle branch block influences the response to cardiac resynchronization therapy. *Int J Cardiol* 2018;**269**:165–169.
288. van Stipdonk AMW, Vanbelle S, Ter Horst IAH, Luermans JG, Meine M, Maass AH, Auricchio A, Prinzen FW, Vernooy K. Large variability in clinical judgement and definitions of left bundle branch block to identify candidates for cardiac resynchronisation therapy. *Int J Cardiol* 2019;**286**:61–65.
289. Tomlinson DR, Bashir Y, Betts TR, Rajappan K. Accuracy of manual QRS duration assessment: its importance in patient selection for cardiac resynchronization and implantable cardioverter defibrillator therapy. *Europace* 2009;**11**:638–642.
290. Vancura V, Wichterle D, Ulc I, Smid J, Brabec M, Zarybnicka M, Rokyta R. The variability of automated QRS duration measurement. *Europace* 2017;**19**:636–643.
291. Sze E, Samad Z, Dunning A, Campbell KB, Loring Z, Atwater BD, Chiswell K, Kisslo JA, Velazquez EJ, Daubert JP. Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block. *J Am Coll Cardiol* 2018;**71**:306–317.
292. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
293. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
294. Nijst P, Martens P, Dauw J, Tang WHW, Bertrand PB, Penders J, Bruckers L, Voros G, Willems R, Vandervoort PM, Dupont M, Mullens W. Withdrawal of neurohumoral blockade after cardiac resynchronization therapy. *J Am Coll Cardiol* 2020;**75**:1426–1438.
295. Mullens W, Auricchio A, Martens P, Witte K, Cowie MR, Delgado V, Dickstein K, Linde C, Vernooy K, Leyva F, Bauersachs J, Israel CW, Lund LH, Donal E, Boriani G, Jaarsma T, Berruezo A, Traykov V, Yousef Z, Kalarus Z, Cosedis Nielsen J, Steffel J, Vardas P, Coats A, Seferovic P, Edvardsen T, Heidbuchel H, Ruschitzka F, Leclercq C. Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care: a joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:2349–2369.
296. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020;**42**:373–498.
297. Ousdigian KT, Borek PP, Koehler JL, Heywood JT, Ziegler PD, Wilkoff BL. The epidemic of inadequate biventricular pacing in patients with persistent or permanent atrial fibrillation and its association with mortality. *Circ Arrhythm Electrophysiol* 2014;**7**:370–376.
298. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? *J Am Coll Cardiol* 2009;**53**:355–360.
299. Hayes DL, Boehmer JP, Day JD, Gilliam FR 3rd, Heidenreich PA, Seth M, Jones PW, Saxon LA. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm* 2011;**8**:1469–1475.
300. Healey JS, Hohnloser SH, Exner DV, Birnie DH, Parkash R, Connolly SJ, Krahn AD, Simpson CS, Thibault B, Basta M, Philippon F, Dorian P, Nair GM, Sivakumaran S, Yetisir E, Wells GA, Tang AS. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail* 2012;**5**:566–570.
301. Ganesan AN, Brooks AG, Roberts-Thomson KC, Lau DH, Kalman JM, Sanders P. Role of AV nodal ablation in cardiac resynchronization in patients with

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

coexistent atrial fibrillation and heart failure a systematic review. *J Am Coll Cardiol* 2012;**59**:719–726.
302. Gasparini M, Leclercq C, Lunati M, Landolina M, Auricchio A, Santini M, Boriani G, Lamp B, Proclemer A, Curnis A, Klersy C, Leyva F. Cardiac resynchronization therapy in patients with atrial fibrillation: the CERTIFY study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry). *JACC Heart Fail* 2013;**1**:500–507.
303. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**:2235–2243.
304. Ziff OJ, Samra M, Howard JP, Bromage DI, Ruschitzka F, Francis DP, Kotecha D. Beta-blocker efficacy across different cardiovascular indications: an umbrella review and meta-analytic assessment. *BMC Med* 2020;**18**:103.
305. Docherty KF, Shen L, Castagno D, Petrie MC, Abraham WT, Bohm M, Desai AS, Dickstein K, Kober LV, Packer M, Rouleau JL, Solomon SD, Swedberg K, Vazir A, Zile MR, Jhund PS, McMurray JJV. Relationship between heart rate and outcomes in patients in sinus rhythm or atrial fibrillation with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2020;**22**:528–538.
306. Yin J, Hu H, Wang Y, Xue M, Li X, Cheng W, Li X, Yan S. Effects of atrioventricular nodal ablation on permanent atrial fibrillation patients with cardiac resynchronization therapy: a systematic review and meta-analysis. *Clin Cardiol* 2014;**37**:707–715.
307. Tolosana JM, Arnau AM, Madrid AH, Macias A, Lozano IF, Osca J, Quesada A, Toquero J, Francés RM, Bolao IG, Berruezo A, Sitges M, Alcalá MG, Brugada J, Mont L. Cardiac resynchronization therapy in patients with permanent atrial fibrillation. Is it mandatory to ablate the atrioventricular junction to obtain a good response? *Eur J Heart Fail* 2012;**14**:635–641.
308. Tolosana JM, Trucco E, Khatib M, Doltra A, Borras R, Castel M, Berruezo A, Arbelo E, Sitges M, Matas M, Guasch E, Brugada J, Mont L. Complete atrioventricular block does not reduce long-term mortality in patients with permanent atrial fibrillation treated with cardiac resynchronization therapy. *Eur J Heart Fail* 2013;**15**:1412–1418.
309. Kamath GS, Cotiga D, Koneru JN, Arshad A, Pierce W, Aziz EF, Mandava A, Mittal S, Steinberg JS. The utility of 12-lead Holter monitoring in patients with permanent atrial fibrillation for the identification of nonresponders after cardiac resynchronization therapy. *J Am Coll Cardiol* 2009;**53**:1050–1055.
310. Hernandez-Madrid A, Facchin D, Klepfer RN, Ghosh S, Matia R, Moreno J, Locatelli A. Device pacing diagnostics overestimate effective cardiac resynchronization therapy pacing results of the hOLter for Efficacy analysis of CRT (OLE CRT) study. *Heart Rhythm* 2017;**14**:541–547.
311. Plummer CJ, Frank CM, Bári Z, Al Hebaishi YS, Klepfer RN, Stadler RW, Ghosh S, Liu S, Mittal S. A novel algorithm increases the delivery of effective cardiac resynchronization therapy during atrial fibrillation: the CRTee randomized crossover trial. *Heart Rhythm* 2018;**15**:369–375.
312. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. *J Am Coll Cardiol* 2006;**48**:1642–1648.
313. Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**:2420–2429.
314. Brignole M, Botto GL, Mont L, Oddone D, Iacopino S, De Marchi G, Campoli M, Sebastiani V, Vincenti A, Garcia Medina D, Osca Asensi J, Mocini A, Grovale N, De Santo T, Menozzi C. Predictors of clinical efficacy of 'Ablate and Pace' therapy in patients with permanent atrial fibrillation. *Heart* 2012;**98**:297–302.
315. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. *Europace* 2012;**14**:1490–1497.
316. Sharma PS, Vijayaraman P, Ellenbogen KA. Permanent His bundle pacing: shaping the future of physiological ventricular pacing. *Nat Rev Cardiol* 2020;**17**:22–36.
317. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, Ellenbogen KA. A Novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol* 2017;**33**:1736.e1–1736.e73.
318. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A, Koneru JN, Ellenbogen KA, Vijayaraman P. Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. *Heart Rhythm* 2018;**15**:413–420.
319. Vijayaraman P, Herweg B, Ellenbogen KA, Gajek J. His-optimized cardiac resynchronization therapy to maximize electrical resynchronization: a feasibility study. *Circ Arrhythm Electrophysiol* 2019;**12**:e006934.
320. Boczar K, Sławuta A, Ząbek A, Dębski M, Vijayaraman P, Gajek J, Lelakowski J, Małecka B. Cardiac resynchronization therapy with His bundle pacing. *Pacing Clin Electrophysiol*. 2019;**42**:374–380.
321. Coluccia G, Vitale E, Corallo S, Aste M, Odaglia F, Donateo P, Oddone D, Brignole M. Additional benefits of nonconventional modalities of cardiac resynchronization therapy using His bundle pacing. *J Cardiovasc Electrophysiol* 2020;**31**:647–657.
322. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
323. Yu CM, Chan JY, Zhang Q, Omar R, Yip GW, Hussin A, Fang F, Lam KH, Chan HC, Fung JW. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med* 2009;**361**:2123–2134.
324. Tanaka H, Hara H, Adelstein EC, Schwartzman D, Saba S, Gorcsan J 3rd. Comparative mechanical activation mapping of RV pacing to LBBB by 2D and 3D speckle tracking and association with response to resynchronization therapy. *JACC Cardiovasc Imaging* 2010;**3**:461–471.
325. Marai I, Gurevitz O, Carasso S, Nof E, Bar-Lev D, Luria D, Arbel Y, Freimark D, Feinberg MS, Eldar M, Glikson M. Improvement of congestive heart failure by upgrading of conventional to resynchronization pacemakers. *Pacing Clin Electrophysiol* 2006;**29**:880–884.
326. Witte KK, Pipes RR, Nanthakumar K, Parker JD. Biventricular pacemaker upgrade in previously paced heart failure patients—improvements in ventricular dyssynchrony. *J Card Fail* 2006;**12**:199–204.
327. Duray GZ, Israel CW, Pajitnev D, Hohnloser SH. Upgrading to biventricular pacing/defibrillation systems in right ventricular paced congestive heart failure patients: prospective assessment of procedural parameters and response rate. *Europace* 2008;**10**:48–52.
328. Nagele H, Dodeck J, Behrens S, Azizi M, Hashagen S, Eisermann C, Castel MA. Hemodynamics and prognosis after primary cardiac resynchronization system implantation compared to 'upgrade' procedures. *Pacing Clin Electrophysiol* 2008;**31**:1265–1271.
329. Foley PW, Muhyaldeen SA, Chalil S, Smith RE, Sanderson JE, Leyva F. Long-term effects of upgrading from right ventricular pacing to cardiac resynchronization therapy in patients with heart failure. *Europace* 2009;**11**:495–501.
330. Wokhlu A, Rea RF, Asirvatham SJ, Webster T, Brooke K, Hodge DO, Wiste HJ, Dong Y, Hayes DL, Cha YM. Upgrade and de novo cardiac resynchronization therapy: impact of paced or intrinsic QRS morphology on outcomes and survival. *Heart Rhythm* 2009;**6**:1439–1447.
331. Frohlich G, Steffel J, Hurlimann D, Enseleit F, Luscher TF, Ruschitzka F, Abraham WT, Holzmeister J. Upgrading to resynchronization therapy after chronic right ventricular pacing improves left ventricular remodelling. *Eur Heart J* 2010;**31**:1477–1485.
332. Paparella G, Sciarra L, Capulzini L, Francesconi A, De Asmundis C, Sarkozy A, Cazzin R, Brugada P. Long-term effects of upgrading to biventricular pacing: differences with cardiac resynchronization therapy as primary indication. *Pacing Clin Electrophysiol* 2010;**33**:841–849.
333. Bogale N, Witte K, Priori S, Cleland J, Auricchio A, Gadler F, Gitt A, Limbourg T, Linde C, Dickstein K. The European Cardiac Resynchronization Therapy Survey: comparison of outcomes between *de novo* cardiac resynchronization therapy implantations and upgrades. *Eur J Heart Fail* 2011;**13**:974–983.
334. Gage RM, Burns KV, Bank AJ. Echocardiographic and clinical response to cardiac resynchronization therapy in heart failure patients with and without previous right ventricular pacing. *Eur J Heart Fail* 2014;**16**:1199–1205.
335. Tayal B, Gorcsan J 3rd, Delgado-Montero A, Goda A, Ryo K, Saba S, Risum N, Sogaard P. Comparative long-term outcomes after cardiac resynchronization therapy in right ventricular paced patients versus native wide left bundle branch block patients. *Heart Rhythm* 2016;**13**:511–518.
336. Ter Horst IA, Kuijpers Y, van 't Sant J, Tuinenburg AE, Cramer MJ, Meine M. 'Are CRT upgrade procedures more complex and associated with more complications than de novo CRT implantations?' A single centre experience. *Neth Heart J* 2016;**24**:75–81.
337. Lipar L, Srivathsan K, Scott LR. Short-term outcome of cardiac resynchronization therapy—a comparison between newly implanted and chronically right ventricle-paced patients. *Int J Cardiol* 2016;**219**:195–199.
338. Vamos M, Erath JW, Bari Z, Vagany D, Linzbach SP, Burmistrava T, Israel CW, Duray GZ, Hohnloser SH. Effects of upgrade versus de novo cardiac resynchronization therapy on clinical response and long-term survival: results from a multicenter study. *Circ Arrhythm Electrophysiol* 2017;**10**:e004471.
339. Cheung JW, Ip JE, Markowitz SM, Liu CF, Thomas G, Feldman DN, Swaminathan RV, Lerman BB, Kim LK. Trends and outcomes of cardiac resynchronization therapy upgrade procedures: a comparative analysis using a United States National Database 2003–2013. *Heart Rhythm* 2017;**14**:1043–1050.
340. Leon AR, Greenberg JM, Kanuru N, Baker CM, Mera FV, Smith AL, Langberg JJ, DeLurgio DB. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol* 2002;**39**:1258–1263.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

341. Baker CM, Christopher TJ, Smith PF, Langberg JJ, Delurgio DB, Leon AR. Addition of a left ventricular lead to conventional pacing systems in patients with congestive heart failure: feasibility, safety, and early results in 60 consecutive patients. *Pacing Clin Electrophysiol* 2002;**25**:1166–1171.
342. Valls-Bertault V, Fatemi M, Gilard M, Pennec PY, Etienne Y, Blanc JJ. Assessment of upgrading to biventricular pacing in patients with right ventricular pacing and congestive heart failure after atrioventricular junctional ablation for chronic atrial fibrillation. *Europace* 2004;**6**:438–443.
343. Eldadah ZA, Rosen B, Hay I, Edvardsen T, Jayam V, Dickfeld T, Meininger GR, Judge DP, Hare J, Lima JB, Calkins H, Berger RD. The benefit of upgrading chronically right ventricle-paced heart failure patients to resynchronization therapy demonstrated by strain rate imaging. *Heart Rhythm* 2006;**3**:435–442.
344. Shimano M, Tsuji Y, Yoshida Y, Inden Y, Tsuboi N, Itoh T, Suzuki H, Muramatsu T, Okada T, Harata S, Yamada T, Hirayama H, Nattel S, Murohara T. Acute and chronic effects of cardiac resynchronization in patients developing heart failure with long-term pacemaker therapy for acquired complete atrioventricular block. *Europace* 2007;**9**:869–874.
345. Laurenzi F, Achilli A, Avella A, Peraldo C, Orazi S, Perego GB, Cesario A, Valsecchi S, De Santo T, Puglisi A, Tondo C. Biventricular upgrading in patients with conventional pacing system and congestive heart failure: results and response predictors. *Pacing Clin Electrophysiol* 2007;**30**:1096–1104.
346. Vatankulu MA, Goktekin O, Kaya MG, Ayhan S, Kucukdurmaz Z, Sutton R, Henein M. Effect of long-term resynchronization therapy on left ventricular remodeling in pacemaker patients upgraded to biventricular devices. *Am J Cardiol* 2009;**103**:1280–1284.
347. Hoijer CJ, Meurling C, Brandt J. Upgrade to biventricular pacing in patients with conventional pacemakers and heart failure: a double-blind, randomized crossover study. *Europace* 2006;**8**:51–55.
348. Delnoy PP, Ottervanger JP, Vos DH, Elvan A, Misier AR, Beukema WP, Steendijk P, van Hemel NM. Upgrading to biventricular pacing guided by pressure–volume loop analysis during implantation. *J Cardiovasc Electrophysiol* 2011;**22**:677–683.
349. van Geldorp IE, Vernooy K, Delhaas T, Prins MH, Crijns HJ, Prinzen FW, Dijkman B. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. *Europace* 2010;**12**:223–229.
350. Leclercq C, Cazeau S, Lellouche D, Fossati F, Anselme F, Davy JM, Sadoul N, Klug D, Mollo L, Daubert JC. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: the RD-CHF Study. *Pacing Clin Electrophysiol* 2007;**30 Suppl 1**:S23–S30.
351. Kosztin A, Vamos M, Aradi D, Schwertner WR, Kovacs A, Nagy KV, Zima E, Geller L, Duray GZ, Kutyifa V, Merkely B. De novo implantation vs. upgrade cardiac resynchronization therapy: a systematic review and meta-analysis. *Heart Fail Rev* 2018;**23**:15–26.
352. Linde CM, Normand C, Bogale N, Auricchio A, Sterlinski M, Marinskis G, Sticherling C, Bulava A, Perez OC, Maass AH, Witte KK, Rekvava R, Abdelali S, Dickstein K. Upgrades from a previous device compared to *de novo* cardiac resynchronization therapy in the European Society of Cardiology CRT Survey II. *Eur J Heart Fail* 2018;**20**:1457–1468.
353. Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H, Camm J. A decade of information on the use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2017 report from the European Heart Rhythm Association. *Europace* 2017;**19**:ii1–ii90.
354. Kirkfeldt RE, Johansen JB, Nohr EA, Jorgensen OD, Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J* 2014;**35**:1186–1194.
355. Boriani G, Diemberger I. Cardiac resynchronization therapy in the real world: need to upgrade outcome research. *Eur J Heart Fail* 2018;**20**:1469–1471.
356. Merkely B, Kosztin A, Roka A, Geller L, Zima E, Kovacs A, Boros AM, Klein H, Wranicz JK, Hindricks G, Clemens M, Duray GZ, Moss AJ, Goldenberg I, Kutyifa V. Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicentre clinical trial. *Europace* 2017;**19**:1549–1555.
357. Kindermann M, Hennen B, Jung J, Geisel J, Bohm M, Frohlig G. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol* 2006;**47**:1927–1937.
358. Martinelli Filho M, de Siqueira SF, Costa R, Greco OT, Moreira LF, D'Avila A, Heist EK. Conventional versus biventricular pacing in heart failure and bradyarrhythmia: the COMBAT study. *J Card Fail* 2010;**16**:293–300.
359. Yu CM, Fang F, Luo XX, Zhang Q, Azlan H, Razali O. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. *Eur J Heart Fail* 2014;**16**:1016–1025.
360. Albertsen AE, Mortensen PT, Jensen HK, Poulsen SH, Egeblad H, Nielsen JC. Adverse effect of right ventricular pacing prevented by biventricular pacing during long-term follow-up: a randomized comparison. *Eur J Echocardiogr* 2011;**12**:767–772.
361. Chung ES, St John Sutton MG, Mealing S, Sidhu MK, Padhiar A, Tsintzos SI, Lu X, Verhees KJP, Lautenbach AA, Curtis AB. Economic value and cost-effectiveness of biventricular versus right ventricular pacing: results from the BLOCK-HF study. *J Med Econ* 2019;**22**:1088–1095.
362. Orlov MV, Gardin JM, Slawsky M, Bess RL, Cohen G, Bailey W, Plumb V, Flathmann H, de Metz K. Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients with symptomatic atrial fibrillation after atrioventricular node ablation. *Am Heart J* 2010;**159**:264–270.
363. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, Lwin A, Lindenfeld J, Ghali J, Barnet JH, Feldman AM, Bristow MR. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *J Am Coll Cardiol* 2005;**46**:2329–2334.
364. Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, Foster E, Huang DT, Klein HU, Zareba W, Eldar M, Goldenberg I. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011;**57**:2416–2423.
365. Gold MR, Linde C, Abraham WT, Gardiwal A, Daubert JC. The impact of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in mild heart failure. *Heart Rhythm* 2011;**8**:679–684.
366. Sapp JL, Parkash R, Wells GA, Yetisir E, Gardner MJ, Healey JS, Thibault B, Sterns LD, Birnie D, Nery PB, Sivakumaran S, Essebag V, Dorian P, Tang AS. Cardiac resynchronization therapy reduces ventricular arrhythmias in primary but not secondary prophylactic implantable cardioverter defibrillator patients: insight from the Resynchronization in Ambulatory Heart Failure trial. *Circ Arrhythm Electrophysiol* 2017;**10**:e004875.
367. Kutyifa V, Moss AJ, Solomon SD, McNitt S, Aktas MK, Barsheshet A, Merkely B, Zareba W, Goldenberg I. Reduced risk of life-threatening ventricular tachyarrhythmias with cardiac resynchronization therapy: relationship to left ventricular ejection fraction. *Eur J Heart Fail* 2015;**17**:971–978.
368. Gold MR, Daubert JC, Abraham WT, Hassager C, Dinerman JL, Hudnall JH, Cerkvenik J, Linde C. Implantable defibrillators improve survival in patients with mildly symptomatic heart failure receiving cardiac resynchronization therapy: analysis of the long-term follow-up of remodeling in systolic left ventricular dysfunction (REVERSE). *Circ Arrhythm Electrophysiol* 2013;**6**:1163–1168.
369. Al-Majed NS, McAlister FA, Bakal JA, Ezekowitz JA. Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure. *Ann Intern Med* 2011;**154**:401–412.
370. Lam SK, Owen A. Combined resynchronisation and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomised controlled trials. *BMJ* 2007;**335**:925.
371. Kutyifa V, Geller L, Bogyi P, Zima E, Aktas MK, Ozcan EE, Becker D, Nagy VK, Kosztin A, Szilagyi S, Merkely B. Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: results of a high-volume, single-centre experience. *Eur J Heart Fail* 2014;**16**:1323–1330.
372. Barra S, Boveda S, Providencia R, Sadoul N, Duehmke R, Reitan C, Borgquist R, Narayanan K, Hidden-Lucet F, Klug D, Defaye P, Gras D, Anselme F, Leclercq C, Hermida JS, Deharo JC, Looi KL, Chow AW, Virdee M, Fynn S, Le Heuzey JY, Marijon E, Agarwal S. Adding defibrillation therapy to cardiac resynchronization on the basis of the myocardial substrate. *J Am Coll Cardiol* 2017;**69**:1669–1678.
373. Leyva F, Zegard A, Umar F, Taylor RJ, Acquaye E, Gubran C, Chalil S, Patel K, Panting J, Marshall H, Qiu T. Long-term clinical outcomes of cardiac resynchronization therapy with or without defibrillation: impact of the aetiology of cardiomyopathy. *Europace* 2018;**20**:1804–1812.
374. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
375. Leyva F, Zegard A, Okafor O, de Bono J, McNulty D, Ahmed A, Marshall H, Ray D, Qiu T. Survival after cardiac resynchronization therapy: results from 50 084 implantations. *Europace* 2019;**21**:754–762.
376. Gras M, Bisson A, Bodin A, Herbert J, Babuty D, Pierre B, Clementy N, Fauchier L. Mortality and cardiac resynchronization therapy with or without defibrillation in primary prevention. *Europace* 2020;**22**:1224–1233.
377. Marijon E, Leclercq C, Narayanan K, Boveda S, Klug D, Lacaze-Gadonneix J, Defaye P, Jacob S, Piot O, Deharo JC, Perier MC, Mulak G, Hermida JS, Milliez P, Gras D, Cesari O, Hidden-Lucet F, Anselme F, Chevalier P, Maury P, Sadoul N, Bordachar P, Cazeau S, Chauvin M, Empana JP, Jouven X, Daubert JC, Le Heuzey JY. Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study. *Eur Heart J* 2015;**36**:2767–2776.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

378. Morani G, Gasparini M, Zanon F, Casali E, Spotti A, Reggiani A, Bertaglia E, Solimene F, Molon G, Accogli M, Tommasi C, Paoletti Perini A, Ciardiello C, Padeletti L. Cardiac resynchronization therapy-defibrillator improves long-term survival compared with cardiac resynchronization therapy-pacemaker in patients with a class IA indication for cardiac resynchronization therapy: data from the Contak Italian Registry. *Europace* 2013;**15**:1273–1279.
379. Acosta J, Fernandez-Armenta J, Borras R, Anguera I, Bisbal F, Marti-Almor J, Tolosana JM, Penela D, Andreu D, Soto-Iglesias D, Evertz R, Matiello M, Alonso C, Villuendas R, de Caralt TM, Perea RJ, Ortiz JT, Bosch X, Serra L, Planes X, Greiser A, Ekinci O, Lasalvia L, Mont L, Berruezo A. Scar characterization to predict life-threatening arrhythmic events and sudden cardiac death in patients with cardiac resynchronization therapy: the GAUDI-CRT study. *JACC Cardiovasc Imaging* 2018;**11**:561–572.
380. Leyva F, Zegard A, Acquaye E, Gubran C, Taylor R, Foley PWX, Umar F, Patel K, Panting J, Marshall H, Qiu T. Outcomes of cardiac resynchronization therapy with or without defibrillation in patients with nonischemic cardiomyopathy. *J Am Coll Cardiol* 2017;**70**:1216–1227.
381. Cleland JG, Freemantle N, Erdmann E, Gras D, Kappenberger L, Tavazzi L, Daubert JC. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. *Eur J Heart Fail* 2012;**14**:628–634.
382. Barra S, Looi KL, Gajendragadkar PR, Khan FZ, Virdee M, Agarwal S. Applicability of a risk score for prediction of the long-term benefit of the implantable cardioverter defibrillator in patients receiving cardiac resynchronization therapy. *Europace* 2016;**18**:1187–1193.
383. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, Zareba W, McNitt S, Andrews ML, MADIT-II Investigators. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008;**51**:288–296.
384. Lumens J, Tayal B, Walmsley J, Delgado-Montero A, Huntjens PR, Schwartzman D, Althouse AD, Delhaas T, Prinzen FW, Gorcsan J 3rd. Differentiating electromechanical from non-electrical substrates of mechanical discoordination to identify responders to cardiac resynchronization therapy. *Circ Cardiovasc Imaging* 2015;**8**:e003744.
385. Ploux S, Lumens J, Whinnett Z, Montaudon M, Strom M, Ramanathan C, Derval N, Zemmoura A, Denis A, De Guillebon M, Shah A, Hocini M, Jais P, Ritter P, Haissaguerre M, Wilkoff BL, Bordachar P. Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: beyond QRS duration and left bundle branch block morphology. *J Am Coll Cardiol* 2013;**61**:2435–2443.
386. Parsai C, Bijnens B, Sutherland GR, Baltabaeva A, Claus P, Marciniak M, Paul V, Scheffer M, Donal E, Derumeaux G, Anderson L. Toward understanding response to cardiac resynchronization therapy: left ventricular dyssynchrony is only one of multiple mechanisms. *Eur Heart J* 2009;**30**:940–949.
387. Adelstein EC, Tanaka H, Soman P, Miske G, Haberman SC, Saba SF, Gorcsan J 3rd. Impact of scar burden by single-photon emission computed tomography myocardial perfusion imaging on patient outcomes following cardiac resynchronization therapy. *Eur Heart J* 2011;**32**:93–103.
388. Taylor RJ, Umar F, Panting JR, Stegemann B, Leyva F. Left ventricular lead position, mechanical activation, and myocardial scar in relation to left ventricular reverse remodeling and clinical outcomes after cardiac resynchronization therapy: a feature-tracking and contrast-enhanced cardiovascular magnetic resonance study. *Heart Rhythm* 2016;**13**:481–489.
389. Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P, Oyenuga OA, Onishi T, Soman P, Gorcsan J 3rd. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. *Circ Heart Fail* 2013;**6**:427–434.
390. Stephansen C, Sommer A, Kronborg MB, Jensen JM, Norgaard BL, Gerdes C, Kristensen J, Jensen HK, Fyenbo DB, Bouchelouche K, Nielsen JC. Electrically vs. imaging-guided left ventricular lead placement in cardiac resynchronization therapy: a randomized controlled trial. *Europace* 2019;**21**:1369–1377.
391. Delgado-Montero A, Tayal B, Goda A, Ryo K, Marek JJ, Sugahara M, Qi Z, Althouse AD, Saba S, Schwartzman D, Gorcsan J 3rd. Additive prognostic value of echocardiographic global longitudinal and global circumferential strain to electrocardiographic criteria in patients with heart failure undergoing cardiac resynchronization therapy. *Circ Cardiovasc Imaging* 2016;**9**.
392. Gorcsan J 3rd, Anderson CP, Tayal B, Sugahara M, Walmsley J, Starling RC, Lumens J. Systolic stretch characterizes the electromechanical substrate responsive to cardiac resynchronization therapy. *JACC Cardiovasc Imaging* 2019;**12**:1741–1752.
393. Khidir MJH, Abou R, Yilmaz D, Ajmone Marsan N, Delgado V, Bax JJ. Prognostic value of global longitudinal strain in heart failure patients treated with cardiac resynchronization therapy. *Heart Rhythm* 2018;**15**:1533–1539.
394. Donal E, Delgado V, Bucciarelli-Ducci C, Galli E, Haugaa KH, Charron P, Voigt JU, Cardim N, Masci PG, Galderisi M, Gaemperli O, Gimelli A, Pinto YM, Lancellotti P, Habib G, Elliott P, Edvardsen T, Cosyns B, Popescu BA, EACVI Scientific Documents Committee. Multimodality imaging in the diagnosis, risk stratification, and management of patients with dilated cardiomyopathies: an expert consensus document from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1075–1093.
395. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation* 2006;**113**:969–976.
396. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de Roos A, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol* 2007;**99**:657–660.
397. van der Bijl P, Khidir M, Ajmone Marsan N, Delgado V, Leon MB, Stone GW, Bax JJ. Effect of functional mitral regurgitation on outcome in patients receiving cardiac resynchronization therapy for heart failure. *Am J Cardiol* 2019;**123**:75–83.
398. Leong DP, Hoke U, Delgado V, Auger D, Witkowski T, Thijssen J, van Erven L, Bax JJ, Schalij MJ, Marsan NA. Right ventricular function and survival following cardiac resynchronisation therapy. *Heart* 2013;**99**:722–728.
399. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616.
400. Beela AS, Unlu S, Duchenne J, Ciarka A, Daraban AM, Kotrc M, Aarones M, Szulik M, Winter S, Penicka M, Neskovic AN, Kukulski T, Aakhus S, Willems R, Fehske W, Faber L, Stankovic I, Voigt JU. Assessment of mechanical dyssynchrony can improve the prognostic value of guideline-based patient selection for cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging* 2019;**20**:66–74.
401. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, Bax JJ. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;**51**:1944–1952.
402. Risum N, Tayal B, Hansen TF, Bruun NE, Jensen MT, Lauridsen TK, Saba S, Kisslo J, Gorcsan J 3rd, Sogaard P. Identification of typical left bundle branch block contraction by strain echocardiography is additive to electrocardiography in prediction of long-term outcome after cardiac resynchronization therapy. *J Am Coll Cardiol* 2015;**66**:631–641.
403. Leenders GE, Lumens J, Cramer MJ, De Boeck BW, Doevendans PA, Delhaas T, Prinzen FW. Septal deformation patterns delineate mechanical dyssynchrony and regional differences in contractility: analysis of patient data using a computer model. *Circ Heart Fail* 2012;**5**:87–96.
404. Mafi-Rad M, Van't Sant J, Blaauw Y, Doevendans PA, Cramer MJ, Crijns HJ, Prinzen FW, Meine M, Vernooy K. Regional left ventricular electrical activation and peak contraction are closely related in candidates for cardiac resynchronization therapy. *JACC Clin Electrophysiol* 2017;**3**:854–862.
405. Maass AH, Vernooy K, Wijers SC, van 't Sant J, Cramer MJ, Meine M, Allaart CP, De Lange FJ, Prinzen FW, Gerritse B, Erdtsieck E, Scheerder COS, Hill MRS, Scholten M, Kloosterman M, Ter Horst IAH, Voors AA, Vos MA, Rienstra M, Van Gelder IC. Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodelling: results from the Markers and Response to CRT (MARC) study. *Europace* 2018;**20**:e1-e10.
406. van der Bijl P, Vo NM, Kostyukevich MV, Mertens B, Ajmone Marsan N, Delgado V, Bax JJ. Prognostic implications of global, left ventricular myocardial work efficiency before cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1388–1394.
407. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol* 2012;**59**:1509–1518.
408. Sommer A, Kronborg MB, Norgaard BL, Poulsen SH, Bouchelouche K, Bottcher M, Jensen HK, Jensen JM, Kristensen J, Gerdes C, Mortensen PT, Nielsen JC. Multimodality imaging-guided left ventricular lead placement in cardiac resynchronization therapy: a randomized controlled trial. *Eur J Heart Fail* 2016;**18**:1365–1374.
409. Cikes M, Sanchez-Martinez S, Claggett B, Duchateau N, Piella G, Butakoff C, Pouleur AC, Knappe D, Biering-Sorensen T, Kutyifa V, Moss A, Stein K, Solomon SD, Bijnens B. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy. *Eur J Heart Fail* 2019;**21**:74–85.
410. Di Biase L, Auricchio A, Mohanty P, Bai R, Kautzner J, Pieragnoli P, Regoli F, Sorgente A, Spinucci G, Ricciardi G, Michelucci A, Perrotta L, Faletra F, Mlcochova H, Sedlacek K, Canby R, Sanchez JE, Horton R, Burkhardt JD,

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Moccetti T, Padeletti L, Natale A. Impact of cardiac resynchronization therapy on the severity of mitral regurgitation. *Europace* 2011;**13**:829–838.
411. Auricchio A, Schillinger W, Meyer S, Maisano F, Hoffmann R, Ussia GP, Pedrazzini GB, van der Heyden J, Fratini S, Klersy C, Komtebedde J, Franzen O. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy by MitraClip improves symptoms and promotes reverse remodeling. *J Am Coll Cardiol* 2011;**58**:2183–2189.
412. D'Ancona G, Ince H, Schillinger W, Senges J, Ouarrak T, Butter C, Seifert M, Schau T, Lubos E, Boekstegers P, von Bardeleben RS, Safak E. Percutaneous treatment of mitral regurgitation in patients with impaired ventricular function: impact of intracardiac electronic devices (from the German Transcatheter Mitral Valve Interventions Registry). *Catheter Cardiovasc Interv* 2019;**94**:755–763.
413. Giaimo VL, Zappulla P, Cirasa A, Tempio D, Sanfilippo M, Rapisarda G, Trovato D, Grazia AD, Liotta C, Grasso C, Capodanno D, Tamburino C, Calvi V. Long-term clinical and echocardiographic outcomes of Mitraclip therapy in patients nonresponders to cardiac resynchronization. *Pacing Clin Electrophysiol* 2018;**41**:65–72.
414. Seifert M, Schau T, Schoepp M, Arya A, Neuss M, Butter C. MitraClip in CRT non-responders with severe mitral regurgitation. *Int J Cardiol* 2014;**177**:79–85.
415. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejjari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N, MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306.
416. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ, COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
417. Kaye GC, Linker NJ, Marwick TH, Pollock L, Graham L, Pouliot E, Poloniecki J, Gammage M, Protect-Pace trial investigators. Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study. *Eur Heart J* 2015;**36**:856–862.
418. Leclercq C, Sadoul N, Mont L, Defaye P, Osca J, Mouton E, Isnard R, Habib G, Zamorano J, Derumeaux G, Fernandez-Lozano I, SEPTAL CRT Study Investigators. Comparison of right ventricular septal pacing and right ventricular apical pacing in patients receiving cardiac resynchronization therapy defibrillators: the SEPTAL CRT Study. *Eur Heart J* 2016;**37**:473–483.
419. Hussain MA, Furuya-Kanamori L, Kaye G, Clark J, Doi SA. The Effect of right ventricular apical and nonapical pacing on the short- and long-term changes in left ventricular ejection fraction: a systematic review and meta-analysis of randomized-controlled trials. *Pacing Clin Electrophysiol* 2015;**38**:1121–1136.
420. Cano O, Andres A, Alonso P, Osca J, Sancho-Tello MJ, Olague J, Martinez-Dolz L. Incidence and predictors of clinically relevant cardiac perforation associated with systematic implantation of active-fixation pacing and defibrillation leads: a single-centre experience with over 3800 implanted leads. *Europace* 2017;**19**:96–102.
421. Sommer A, Kronborg MB, Norgaard BL, Gerdes C, Mortensen PT, Nielsen JC. Left and right ventricular lead positions are imprecisely determined by fluoroscopy in cardiac resynchronization therapy: a comparison with cardiac computed tomography. *Europace* 2014;**16**:1334–1341.
422. Zanon F, Ellenbogen KA, Dandamudi G, Sharma PS, Huang W, Lustgarten DL, Tung R, Tada H, Koneru JN, Bergemann T, Fagan DH, Hudnall JH, Vijayaraman P. Permanent His-bundle pacing: a systematic literature review and meta-analysis. *Europace* 2018;**20**:1819–1826.
423. Keene D, Arnold AD, Jastrzebski M, Burri H, Zweibel S, Crespo E, Chandrasekaran B, Bassi S, Joghetaei N, Swift M, Moskal P, Francis DP, Foley P, Shun-Shin MJ, Whinnett ZI. His bundle pacing, learning curve, procedure characteristics, safety, and feasibility: insights from a large international observational study. *J Cardiovasc Electrophysiol* 2019;**30**:1984–1993.
424. Vijayaraman P, Dandamudi G, Zanon F, Sharma PS, Tung R, Huang W, Koneru J, Tada H, Ellenbogen KA, Lustgarten DL. Permanent His bundle pacing: recommendations from a Multicenter His Bundle Pacing Collaborative Working Group for standardization of definitions, implant measurements, and follow-up. *Heart Rhythm* 2018;**15**:460–468.
425. Burri H, Jastrzebski M, Vijayaraman P. ECG analysis for His bundle pacing at implantation and follow-up. *JACC Clin Electrophysiol* 2020;**6**:883–900.
426. Teigeler T, Kolominsky J, Vo C, Shepard RK, Kalahasty G, Kron J, Huizar JF, Kaszala K, Tan AY, Koneru JN, Ellenbogen KA, Padala SK. Intermediate term performance and safety of His bundle pacing leads: a single center experience. *Heart Rhythm* 2021;**18**:743–749.
427. Vijayaraman P, Naperkowski A, Subzposh FA, Abdelrahman M, Sharma PS, Oren JW, Dandamudi G, Ellenbogen KA. Permanent His-bundle pacing: long-term lead performance and clinical outcomes. *Heart Rhythm* 2018;**15**:696–702.
428. Zanon F, Abdelrahman M, Marcantoni L, Naperkowski A, Subzposh FA, Pastore G, Baracca E, Boaretto G, Raffagnato P, Tiribello A, Dandamudi G, Vijayaraman P. Long term performance and safety of His bundle pacing: a multicenter experience. *J Cardiovasc Electrophysiol* 2019;**30**:1594–1601.
429. Kirkfeldt RE, Johansen JB, Nohr EA, Moller M, Arnsbo P, Nielsen JC. Risk factors for lead complications in cardiac pacing: a population-based cohort study of 28,860 Danish patients. *Heart Rhythm* 2011;**8**:1622–1628.
430. Starr N, Dayal N, Domenichini G, Stettler C, Burri H. Electrical parameters with His-bundle pacing: considerations for automated programming. *Heart Rhythm* 2019;**16**:1817–1824.
431. Burri H, Keene D, Whinnett Z, Zanon F, Vijayaraman P. Device programming for His bundle pacing. *Circ Arrhythm Electrophysiol* 2019;**12**:e006816.
432. Lustgarten DL, Sharma PS, Vijayaraman P. Troubleshooting and programming considerations for His bundle pacing. *Heart Rhythm* 2019;**16**:654–662.
433. Vijayaraman P, Naperkowski A, Ellenbogen KA, Dandamudi G. Electrophysiologic insights into site of atrioventricular block. *JACC Clin Electrophysiol* 2015;**1**:571–581.
434. Su L, Cai M, Wu S, Wang S, Xu T, Vijayaraman P, Huang W. Long-term performance and risk factors analysis after permanent His-bundle pacing and atrioventricular node ablation in patients with atrial fibrillation and heart failure. *Europace* 2020;**22**:ii19–ii26.
435. Narula OS. Longitudinal dissociation in the His bundle. Bundle branch block due to asynchronous conduction within the His bundle in man. *Circulation* 1977;**56**:996–1006.
436. Upadhyay GA, Cherian T, Shatz DY, Beaser AD, Aziz Z, Ozcan C, Broman MT, Nayak HM, Tung R. Intracardiac delineation of septal conduction in left bundle-branch block patterns. *Circulation* 2019;**139**:1876–1888.
437. Upadhyay GA, Vijayaraman P, Nayak HM, Verma N, Dandamudi G, Sharma PS, Saleem M, Mandrola J, Genovese D, Tung R. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. *J Am Coll Cardiol* 2019;**74**:157–159.
438. Upadhyay GA, Vijayaraman P, Nayak HM, Verma N, Dandamudi G, Sharma PS, Saleem M, Mandrola J, Genovese D, Oren JW, Subzposh FA, Aziz Z, Beaser A, Shatz D, Besser S, Lang RM, Trohman RG, Knight BP, Tung R, His-Sync Investigators. On-treatment comparison between corrective His bundle pacing and biventricular pacing for cardiac resynchronization: a secondary analysis of the His-SYNC Pilot Trial. *Heart Rhythm* 2019;**16**:1797–1807.
439. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J, Liberman E, Sheldon T. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. *Heart Rhythm* 2015;**12**:1548–1557.
440. Giraldi F, Cattadori G, Roberto M, Carbucicchio C, Pepi M, Ballerini G, Alamanni F, Della Bella P, Pontone G, Andreini D, Tondo C, Agostoni PG. Long-term effectiveness of cardiac resynchronization therapy in heart failure patients with unfavorable cardiac veins anatomy comparison of surgical versus hemodynamic procedure. *J Am Coll Cardiol* 2011;**58**:483–490.
441. Sharma PS, Naperkowski A, Bauch TD, Chan JYS, Arnold AD, Whinnett ZI, Ellenbogen KA, Vijayaraman P. Permanent His bundle pacing for cardiac resynchronization therapy in patients with heart failure and right bundle branch block. *Circ Arrhythm Electrophysiol* 2018;**11**:e006613.
442. Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm* 2019;**16**:1791–1796.
443. Barba-Pichardo R, Manovel Sanchez A, Fernandez-Gomez JM, Morina-Vazquez P, Venegas-Gamero J, Herrera-Carranza M. Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. *Europace* 2013;**15**:83–88.
444. Zweerink A, Bakelants E, Stettler C, Burri H. Cryoablation vs. radiofrequency ablation of the atrioventricular node in patients with His-bundle pacing. *Europace* 2020;**23**:421–430.
445. Valiton V, Graf D, Pruvot E, Carroz P, Fromer M, Bisch L, Tran VN, Cook S, Scharf C, Burri H. Leadless pacing using the transcatheter pacing system (Micra TPS) in the real world: initial Swiss experience from the Romandie region. *Europace* 2019;**21**:275–280.
446. Defaye P, Klug D, Anselme F, Gras D, Hermida JS, Piot O, Alonso C, Fauchier L, Gandjbakhch E, Marijon E, Maury P, Taieb J, Boveda S, Sadoul N. Recommendations for the implantation of leadless pacemakers from the French Working Group on Cardiac Pacing and Electrophysiology of the French Society of Cardiology. *Arch Cardiovasc Dis* 2018;**111**:53–58.
447. Leadless cardiac pacemaker therapy: design of pre- and post-market clinical studies. Recommendations from MHRA Expert Advisory Group. Version 3: Updated January 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/956252/Leadless-EAG-guidance.pdf (25 May 2021)
448. Steinwender C, Khelae SK, Garweg C, Sun Chan JY, Ritter P, Johansen JB, Sagi V, Epstein LM, Piccini JP, Pascual M, Mont L, Sheldon T, Splett V, Stromberg K, Wood N, Chinitz L. Atrioventricular synchronous pacing using a leadless

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

ventricular pacemaker: results from the MARVEL 2 study. *JACC Clin Electrophysiol* 2019;**6**:94–106.
449. Beurskens NE, Tjong FV, Knops RE. End-of-life management of leadless cardiac pacemaker therapy. *Arrhythm Electrophysiol Rev* 2017;**6**:129–133.
450. El-Chami MF, Johansen JB, Zaidi A, Faerestrand S, Reynolds D, Garcia-Seara J, Mansourati J, Pasquie JL, McElderry HT, Roberts PR, Soejima K, Stromberg K, Piccini JP. Leadless pacemaker implant in patients with pre-existing infections: results from the Micra postapproval registry. *J Cardiovasc Electrophysiol* 2019;**30**:569–574.
451. Zimetbaum PJ, Josephson ME. Use of the electrocardiogram in acute myocardial infarction. *N Engl J Med* 2003;**348**:933–940.
452. Pejkovic B, Krajnc I, Anderhuber F, Kosutic D. Anatomical aspects of the arterial blood supply to the sinoatrial and atrioventricular nodes of the human heart. *J Int Med Res* 2008;**36**:691–698.
453. Ritter WS, Atkins JM, Blomqvist CG, Mullins CB. Permanent pacing in patients with transient trifascicular block during acute myocardial infarction. *Am J Cardiol* 1976;**38**:205–208.
454. Ginks WR, Sutton R, Oh W, Leatham A. Long-term prognosis after acute anterior infarction with atrioventricular block. *Br Heart J* 1977;**39**:186–189.
455. Feigl D, Ashkenazy J, Kishon Y. Early and late atrioventricular block in acute inferior myocardial infarction. *J Am Coll Cardiol* 1984;**4**:35–38.
456. Jim MH, Chan AO, Tse HF, Barold SS, Lau CP. Clinical and angiographic findings of complete atrioventricular block in acute inferior myocardial infarction. *Ann Acad Med Singapore* 2010;**39**:185–190.
457. Sutton R, Davies M. The conduction system in acute myocardial infarction complicated by heart block. *Circulation* 1968;**38**:987–992.
458. Gang UJ, Hvelplund A, Pedersen S, Iversen A, Jøns C, Abildstrøm SZ, Haarbo J, Jensen JS, Thomsen PE. High-degree atrioventricular block complicating ST-segment elevation myocardial infarction in the era of primary percutaneous coronary intervention. *Europace* 2012;**14**:1639–1645.
459. Auffret V, Loirat A, Leurent G, Martins RP, Filippi E, Coudert I, Hacot JP, Gilard M, Castellant P, Rialan A, Delaunay R, Rouault G, Druelles P, Boulanger B, Treuil J, Avez B, Bedossa M, Boulmier D, Le Guellec M, Daubert JC, Le Breton H. High-degree atrioventricular block complicating ST segment elevation myocardial infarction in the contemporary era. *Heart* 2016;**102**:40–49.
460. Kim KH, Jeong MH, Ahn Y, Kim YJ, Cho MC, Kim W, Other Korea Acute Myocardial Infarction Registry Investigators. Differential clinical implications of high-degree atrioventricular block complicating ST-segment elevation myocardial infarction according to the location of infarction in the era of primary percutaneous coronary intervention. *Korean Circ J* 2016;**46**:315–323.
461. Kosmidou I, Redfors B, Dordi R, Dizon JM, McAndrew T, Mehran R, Ben-Yehuda O, Mintz GS, Stone GW. Incidence, predictors, and outcomes of high-grade atrioventricular block in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the HORIZONS-AMI Trial). *Am J Cardiol* 2017;**119**:1295–1301.
462. Singh SM, FitzGerald G, Yan AT, Brieger D, Fox KA, López-Sendón J, Yan RT, Eagle KA, Steg PG, Budaj A, Goodman SG. High-grade atrioventricular block in acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. *Eur Heart J* 2015;**36**:976–983.
463. Meine TJ, Al-Khatib SM, Alexander JH, Granger CB, White HD, Kilaru R, Williams K, Ohman EM, Topol E, Califf RM. Incidence, predictors, and outcomes of high-degree atrioventricular block complicating acute myocardial infarction treated with thrombolytic therapy. *Am Heart J* 2005;**149**:670–674.
464. Hindman MC, Wagner GS, JaRo M, Atkins JM, Scheinman MM, DeSanctis RW, Hutter AH, Yeatman L, Rubenfire M, Pujura C, Rubin M, Morris JJ. The clinical significance of bundle branch block complicating acute myocardial infarction. 1. Clinical characteristics, hospital mortality, and one-year follow-up. *Circulation* 1978;**58**:679–688.
465. Melgarejo-Moreno A, Galcerá-Tomás J, Garciá-Alberola A, Valdés-Chavarri M, Castillo-Soria FJ, Mira-Sánchez E, Gil-Sánchez J, Allegue-Gallego J. Incidence, clinical characteristics, and prognostic significance of right bundle-branch block in acute myocardial infarction: a study in the thrombolytic era. *Circulation* 1997;**96**:1139–1144.
466. Vivas D, Pérez-Vizcayno MJ, Hernández-Antolín R, Fernández-Ortiz A, Bañuelos C, Escaned J, Jiménez-Quevedo P, De Agustín JA, Núñez-Gil I, González-Ferrer JJ, Macaya C, Alfonso F. Prognostic implications of bundle branch block in patients undergoing primary coronary angioplasty in the stent era. *Am J Cardiol* 2010;**105**:1276–1283.
467. Xiong Y, Wang L, Liu W, Hankey GJ, Xu B, Wang S. The prognostic significance of right bundle branch block: a meta-analysis of prospective cohort studies. *Clin Cardiol* 2015;**38**:604–613.
468. Swart G, Brady WJ, DeBehnke DJ, MA OJ, Aufderheide TP. Acute myocardial infarction complicated by hemodynamically unstable bradyarrhythmia: prehospital and ED treatment with atropine. *Am J Emerg Med* 1999;**17**:647–652.
469. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
470. Watson RD, Glover DR, Page AJ, Littler WA, Davies P, de Giovanni J, Pentecost BL. The Birmingham Trial of permanent pacing in patients with intraventricular conduction disorders after acute myocardial infarction. *Am Heart J* 1984;**108**:496–501.
471. Kusumoto FM, Calkins H, Boehmer J, Buxton AE, Chung MK, Gold MR, Hohnloser SH, Indik J, Lee R, Mehra MR, Menon V, Page RL, Shen WK, Slotwiner DJ, Stevenson LW, Varosy PD, Welikovitch L. HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. *Circulation* 2014;**130**:94–125.
472. Brodell GK, Cosgrove D, Schiavone W, Underwood DA, Loop FD. Cardiac rhythm and conduction disturbances in patients undergoing mitral valve surgery. *Cleve Clin J Med* 1991;**58**:397–399.
473. Chung MK. Cardiac surgery: postoperative arrhythmias. *Crit Care Med* 2000;**28**:N136–N144.
474. Jaeger FJ, Trohman RG, Brener S, Loop F. Permanent pacing following repeat cardiac valve surgery. *Am J Cardiol* 1994;**74**:505–507.
475. Reade MC. Temporary epicardial pacing after cardiac surgery: a practical review. Part 1: general considerations in the management of epicardial pacing. *Anaesthesia* 2007;**62**:264–271.
476. Reade MC. Temporary epicardial pacing after cardiac surgery: a practical review. Part 2: selection of epicardial pacing modes and troubleshooting. *Anaesthesia* 2007;**62**:364–373.
477. Leyva F, Qiu T, McNulty D, Evison F, Marshall H, Gasparini M. Long-term requirement for pacemaker implantation after cardiac valve replacement surgery. *Heart Rhythm* 2017;**14**:529–534.
478. Merin O, Ilan M, Oren A, Fink D, Deeb M, Bitran D, Silberman S. Permanent pacemaker implantation following cardiac surgery: indications and long-term follow-up. *Pacing Clin Electrophysiol* 2009;**32**:7–12.
479. Glikson M, Dearani JA, Hyberger LK, Schaff HV, Hammill SC, Hayes DL. Indications, effectiveness, and long-term dependency in permanent pacing after cardiac surgery. *Am J Cardiol* 1997;**80**:1309–1313.
480. Kim MH, Deeb GM, Eagle KA, Bruckman D, Pelosi F, Oral H, Sticherling C, Baker RL, Chough SP, Wasmer K, Michaud GF, Knight BP, Strickberger SA, Morady F. Complete atrioventricular block after valvular heart surgery and the timing of pacemaker implantation. *Am J Cardiol* 2001;**87**:649–651, A610.
481. Hill TE, Kiehl EL, Shrestha NK, Gordon SM, Pettersson GB, Mohan C, Hussein A, Hussain S, Wazni O, Wilkoff BL, Menon V, Tarakji KG. Predictors of permanent pacemaker requirement after cardiac surgery for infective endocarditis. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:329–334.
482. DiBiase A, Tse TM, Schnittger I, Wexler L, Stinson EB, Valantine HA. Frequency and mechanism of bradycardia in cardiac transplant recipients and need for pacemakers. *Am J Cardiol* 1991;**67**:1385–1389.
483. Melton IC, Gilligan DM, Wood MA, Ellenbogen KA. Optimal cardiac pacing after heart transplantation. *Pacing Clin Electrophysiol* 1999;**22**:1510–1527.
484. Jacquet L, Ziady G, Stein K, Griffith B, Armitage J, Hardesty R, Kormos R. Cardiac rhythm disturbances early after orthotopic heart transplantation: prevalence and clinical importance of the observed abnormalities. *J Am Coll Cardiol* 1990;**16**:832–837.
485. Holt ND, McComb JM. Cardiac transplantation and pacemakers: when and what to implant. *Card Electrophysiol Rev* 2002;**6**:140–151.
486. Burger H, Pecha S, Hakmi S, Opalka B, Schoenburg M, Ziegelhoeffer T. Five-year follow-up of transvenous and epicardial left ventricular leads: experience with more than 1000 leads. *Interact Cardiovasc Thorac Surg* 2020;**30**:74–80.
487. Noheria A, van Zyl M, Scott LR, Srivathsan K, Madhavan M, Asirvatham SJ, McLeod CJ. Single-site ventricular pacing via the coronary sinus in patients with tricuspid valve disease. *Europace* 2018;**20**:636–642.
488. Sharma PS, Subzposh FA, Ellenbogen KA, Vijayaraman P. Permanent His-bundle pacing in patients with prosthetic cardiac valves. *Heart Rhythm* 2017;**14**:59–64.
489. Martins RP, Galand V, Leclercq C, Daubert JC. Cardiac electronic implantable devices after tricuspid valve surgery. *Heart Rhythm* 2018;**15**:1081–1088.
490. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607.
491. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ,

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;**364**:2187–2198.
492. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;**374**:1609–1620.
493. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;**380**:1695–1705.
494. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;**370**:1790–1798.
495. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchetche D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;**380**:1706–1715.
496. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;**376**:1321–1331.
497. Barbash IM, Finkelstein A, Barsheshet A, Segev A, Steinvil A, Assali A, Ben Gal Y, Vaknin Assa H, Fefer P, Sagie A, Guetta V, Kornowski R. Outcomes of patients at estimated low, intermediate, and high risk undergoing transcatheter aortic valve implantation for aortic stenosis. *Am J Cardiol* 2015;**116**:1916–1922.
498. Bekeredjian R, Szabo G, Balaban U, Bleiziffer S, Bauer T, Ensminger S, Frerker C, Herrmann E, Beyersdorf F, Hamm C, Beckmann A, Mollmann H, Karck M, Katus HA, Walther T. Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). *Eur Heart J* 2019;**40**:1323–1330.
499. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrie D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012;**366**:1705–1715.
500. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol* 2011;**58**:2130–2138.
501. Thomas M, Schymik G, Walther T, Himbert D, Lefevre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2010;**122**:62–69.
502. Werner N, Zahn R, Beckmann A, Bauer T, Bleiziffer S, Hamm CW, Berkeredjian R, Berkowitsch A, Mohr FW, Landwehr S, Katus HA, Harringer W, Ensminger S, Frerker C, Mollmann H, Walther T, Schneider S, Lange R. Patients at intermediate surgical risk undergoing isolated interventional or surgical aortic valve implantation for severe symptomatic aortic valve stenosis. *Circulation* 2018;**138**:2611–2623.
503. Fadahunsi OO, Olowoyeye A, Ukaigwe A, Li Z, Vora AN, Vemulapalli S, Elgin E, Donato A. Incidence, predictors, and outcomes of permanent pacemaker implantation following transcatheter aortic valve replacement: analysis from the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry. *JACC Cardiovasc Interv* 2016;**9**:2189–2199.
504. Regueiro A, Abdul-Jawad Altisent O, Del Trigo M, Campelo-Parada F, Puri R, Urena M, Philippon F, Rodes-Cabau J. Impact of new-onset left bundle branch block and periprocedural permanent pacemaker implantation on clinical outcomes in patients undergoing transcatheter aortic valve replacement: a systematic review and meta-analysis. *Circ Cardiovasc Interv* 2016;**9**:e003635.
505. Chamandi C, Barbanti M, Munoz-Garcia A, Latib A, Nombela-Franco L, Gutierrez-Ibanez E, Veiga-Fernandez G, Cheema AN, Cruz-Gonzalez I, Serra V, Tamburino C, Mangieri A, Colombo A, Jimenez-Quevedo P, Elizaga J, Laughlin G, Lee DH, Garcia Del Blanco B, Rodriguez-Gabella T, Marsal JR, Cote M, Philippon F, Rodes-Cabau J. Long-term outcomes in patients with new permanent pacemaker implantation following transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2018;**11**:301–310.
506. Mohananey D, Jobanputra Y, Kumar A, Krishnaswamy A, Mick S, White JM, Kapadia SR. Clinical and echocardiographic outcomes following permanent pacemaker implantation after transcatheter aortic valve replacement: meta-analysis and meta-regression. *Circ Cardiovasc Interv* 2017;**10**:e005046.
507. Ueshima D, Nai Fovino L, Mojoli M, Napodano M, Fraccaro C, Tarantini G. The interplay between permanent pacemaker implantation and mortality in patients treated by transcatheter aortic valve implantation: a systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2018;**92**:E159–E167.
508. Urena M, Webb JG, Tamburino C, Munoz-Garcia AJ, Cheema A, Dager AE, Serra V, Amat-Santos IJ, Barbanti M, Imme S, Briales JH, Benitez LM, Al Lawati H, Cucalon AM, Garcia Del Blanco B, Lopez J, Dumont E, Delarochelliere R, Ribeiro HB, Nombela-Franco L, Philippon F, Rodes-Cabau J. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. *Circulation* 2014;**129**:1233–1243.
509. Fujita B, Schmidt T, Bleiziffer S, Bauer T, Beckmann A, Bekeredjian R, Mollmann H, Walther T, Landwehr S, Hamm C, Beyersdorf F, Katus HA, Harringer W, Ensminger S, Frerker C, GARY Executive Board. Impact of new pacemaker implantation following surgical and transcatheter aortic valve replacement on 1-year outcome. *Eur J Cardiothorac Surg* 2020;**57**:151–159.
510. Zhang XH, Chen H, Siu CW, Yiu KH, Chan WS, Lee KL, Chan HW, Lee SW, Fu GS, Lau CP, Tse HF. New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. *J Cardiovasc Electrophysiol* 2008;**19**:136–141.
511. Dizon JM, Nazif TM, Hess PL, Biviano A, Garan H, Douglas PS, Kapadia S, Babaliaros V, Herrmann HC, Szeto WY, Jilaihawi H, Fearon WF, Tuzcu EM, Pichard AD, Makkar R, Williams M, Hahn RT, Xu K, Smith CR, Leon MB, Kodali SK. Chronic pacing and adverse outcomes after transcatheter aortic valve implantation. *Heart* 2015;**101**:1665–1671.
512. Abramowitz Y, Kazuno Y, Chakravarty T, Kawamori H, Maeno Y, Anderson D, Allison Z, Mangat G, Cheng W, Gopal A, Jilaihawi H, Mack MJ, Makkar RR. Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:1194–1203.
513. Al-Azzam F, Greason KL, Krittanawong C, Williamson EE, McLeod CJ, King KS, Mathew V. The influence of native aortic valve calcium and transcatheter valve oversize on the need for pacemaker implantation after transcatheter aortic valve insertion. *J Thorac Cardiovasc Surg* 2017;**153**:1056–1062.e1051.
514. Bagur R, Rodes-Cabau J, Gurvitch R, Dumont E, Velianou JL, Manazzoni J, Toggweiler S, Cheung A, Ye J, Natarajan MK, Bainey KR, DeLarochelliere R, Doyle D, Pibarot P, Voisine P, Cote M, Philippon F, Webb JG. Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. *JACC Cardiovasc Interv* 2012;**5**:540–551.
515. Boerlage-Van Dijk K, Kooiman KM, Yong ZY, Wiegerinck EM, Damman P, Bouma BJ, Tijssen JG, Piek JJ, Knops RE, Baan J Jr. Predictors and permanency of cardiac conduction disorders and necessity of pacing after transcatheter aortic valve implantation. *Pacing Clin Electrophysiol* 2014;**37**:1520–1529.
516. Calvi V, Conti S, Pruiti GP, Capodanno D, Puzzangara E, Tempio D, Di Grazia A, Ussia GP, Tamburino C. Incidence rate and predictors of permanent pacemaker implantation after transcatheter aortic valve implantation with self-expanding CoreValve prosthesis. *J Interv Card Electrophysiol* 2012;**34**:189–195.
517. De Carlo M, Giannini C, Bedogni F, Klugmann S, Brambilla N, De Marco F, Zucchelli G, Testa L, Oreglia J, Petronio AS. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. *Am Heart J* 2012;**163**:492–499.
518. Fraccaro C, Buja G, Tarantini G, Gasparetto V, Leoni L, Razzolini R, Corrado D, Bonato R, Basso C, Thiene G, Gerosa G, Isabella G, Iliceto S, Napodano M. Incidence, predictors, and outcome of conduction disorders after transcatheter self-expandable aortic valve implantation. *Am J Cardiol* 2011;**107**:747–754.
519. Gaede L, Kim WK, Liebetrau C, Dorr O, Sperzel J, Blumenstein J, Berkowitsch A, Walther T, Hamm C, Elsasser A, Nef H, Mollmann H. Pacemaker implantation after TAVI: predictors of AV block persistence. *Clin Res Cardiol* 2018;**107**:60–69.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

520. Guetta V, Goldenberg G, Segev A, Dvir D, Kornowski R, Finckelstein A, Hay I, Goldenberg I, Glikson M. Predictors and course of high-degree atrioventricular block after transcatheter aortic valve implantation using the CoreValve Revalving System. *Am J Cardiol* 2011;**108**:1600–1605.
521. Mangieri A, Lanzillo G, Bertoldi L, Jabbour RJ, Regazzoli D, Ancona MB, Tanaka A, Mitomo S, Garducci S, Montalto C, Pagnesi M, Giannini F, Giglio M, Montorfano M, Chieffo A, Rodes-Cabau J, Monaco F, Paglino G, Della Bella P, Colombo A, Latib A. Predictors of advanced conduction disturbances requiring a late (≥48 h) permanent pacemaker following transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2018;**11**:1519–1526.
522. Mauri V, Reimann A, Stern D, Scherner M, Kuhn E, Rudolph V, Rosenkranz S, Eghbalzadeh K, Friedrichs K, Wahlers T, Baldus S, Madershahian N, Rudolph TK. Predictors of permanent pacemaker implantation after transcatheter aortic valve replacement with the SAPIEN 3. *JACC Cardiovasc Interv* 2016;**9**:2200–2209.
523. Mouillet G, Lellouche N, Yamamoto M, Oguri A, Dubois-Rande JL, Van Belle E, Gilard M, Laskar M, Teiger E. Outcomes following pacemaker implantation after transcatheter aortic valve implantation with CoreValve® devices: results from the FRANCE 2 Registry. *Catheter Cardiovasc Interv* 2015;**86**:E158–E166.
524. Nazif TM, Dizon JM, Hahn RT, Xu K, Babaliaros V, Douglas PS, El-Chami MF, Herrmann HC, Mack M, Makkar RR, Miller DC, Pichard A, Tuzcu EM, Szeto WY, Webb JG, Moses JW, Smith CR, Williams MR, Leon MB, Kodali SK. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. *JACC Cardiovasc Interv* 2015;**8**:60–69.
525. Siontis GC, Juni P, Pilgrim T, Stortecky S, Bullesfeld L, Meier B, Wenaweser P, Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol* 2014;**64**:129–140.
526. van der Boon RM, Houthuizen P, Urena M, Poels TT, van Mieghem NM, Brueren GR, Altintas S, Nuis RJ, Serruys PW, van Garsse LA, van Domburg RT, Cabau JR, de Jaegere PP, Prinzen FW. Trends in the occurrence of new conduction abnormalities after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2015;**85**:E144–E152.
527. Gonska B, Seeger J, Kessler M, von Keil A, Rottbauer W, Wohrle J. Predictors for permanent pacemaker implantation in patients undergoing transfemoral aortic valve implantation with the Edwards Sapien 3 valve. *Clin Res Cardiol* 2017;**106**:590–597.
528. Maeno Y, Abramowitz Y, Kawamori H, Kazuno Y, Kubo S, Takahashi N, Mangat G, Okuyama K, Kashif M, Chakravarty T, Nakamura M, Cheng W, Friedman J, Berman D, Makkar RR, Jilaihawi H. A highly predictive risk model for pacemaker implantation after TAVR. *JACC Cardiovasc Imaging* 2017;**10**:1139–1147.
529. Giustino G, Van der Boon RM, Molina-Martin de Nicolas J, Dumonteil N, Chieffo A, de Jaegere PP, Tchetche D, Marcheix B, Millischer D, Cassagneau R, Carrie D, Van Mieghem NM, Colombo A. Impact of permanent pacemaker on mortality after transcatheter aortic valve implantation: the PRAGMATIC (Pooled Rotterdam-Milan-Toulouse in Collaboration) Pacemaker substudy. *EuroIntervention* 2016;**12**:1185–1193.
530. Hamdan A, Guetta V, Klempfner R, Konen E, Raanani E, Glikson M, Goitein O, Segev A, Barbash I, Fefer P, Spiegelstein D, Goldenberg I, Schwammenthal E. Inverse relationship between membranous septal length and the risk of atrioventricular block in patients undergoing transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2015;**8**:1218–1228.
531. Ledwoch J, Franke J, Gerckens U, Kuck KH, Linke A, Nickenig G, Krulls-Munch J, Vohringer M, Hambrecht R, Erbel R, Richardt G, Horack M, Zahn R, Senges J, Sievert H. Incidence and predictors of permanent pacemaker implantation following transcatheter aortic valve implantation: analysis from the German transcatheter aortic valve interventions registry. *Catheter Cardiovasc Interv* 2013;**82**:E569–E577.
532. Husser O, Pellegrini C, Kessler T, Burgdorf C, Thaller H, Mayr NP, Kasel AM, Kastrati A, Schunkert H, Hengstenberg C. Predictors of permanent pacemaker implantations and new-onset conduction abnormalities with the SAPIEN 3 balloon-expandable transcatheter heart valve. *JACC Cardiovasc Interv* 2016;**9**:244–254.
533. Toggweiler S, Stortecky S, Holy E, Zuk K, Cuculi F, Nietlispach F, Sabti Z, Suciu R, Maier W, Jamshidi P, Maisano F, Windecker S, Kobza R, Wenaweser P, Luscher TF, Binder RK. The electrocardiogram after transcatheter aortic valve replacement determines the risk for post-procedural high-degree AV block and the need for telemetry monitoring. *JACC Cardiovasc Interv* 2016;**9**:1269–1276.
534. Urena M, Webb JG, Cheema A, Serra V, Toggweiler S, Barbanti M, Cheung A, Ye J, Dumont E, DeLarochelliere R, Doyle D, Al Lawati HA, Peterson M, Chisholm R, Igual A, Ribeiro HB, Nombela-Franco L, Philippon F, Garcia Del Blanco B, Rodes-Cabau J. Impact of new-onset persistent left bundle branch block on late clinical outcomes in patients undergoing transcatheter aortic valve implantation with a balloon-expandable valve. *JACC Cardiovasc Interv* 2014;**7**:128–136.
535. Mouillet G, Lellouche N, Lim P, Meguro K, Yamamoto M, Deux JF, Monin JL, Bergoend E, Dubois-Rande JL, Teiger E. Patients without prolonged QRS after TAVI with CoreValve device do not experience high-degree atrio-ventricular block. *Catheter Cardiovasc Interv* 2013;**81**:882–887.
536. Rodes-Cabau J, Urena M, Nombela-Franco L, Amat-Santos I, Kleiman N, Munoz-Garcia A, Atienza F, Serra V, Deyell MW, Veiga-Fernandez G, Masson JB, Canadas-Godoy V, Himbert D, Castrodeza J, Elizaga J, Francisco Pascual J, Webb JG, de la Torre JM, Asmarats L, Pelletier-Beaumont E, Philippon F. Arrhythmic burden as determined by ambulatory continuous cardiac monitoring in patients with new-onset persistent left bundle branch block following transcatheter aortic valve replacement: the MARE study. *JACC Cardiovasc Interv* 2018;**11**:1495–1505.
537. Urena M, Webb JG, Eltchaninoff H, Munoz-Garcia AJ, Bouleti C, Tamburino C, Nombela-Franco L, Nietlispach F, Moris C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS, Lemos PA, Abizaid A, Sarmento-Leite R, Ribeiro HB, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Himbert D, Vahanian A, Imme S, Garcia E, Maisano F, del Valle R, Benitez LM, Garcia del Blanco B, Gutierrez H, Perin MA, Siqueira D, Bernardi G, Philippon F, Rodes-Cabau J. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. *J Am Coll Cardiol* 2015;**65**:437–448.
538. Auffret V, Puri R, Urena M, Chamandi C, Rodriguez-Gabella T, Philippon F, Rodes-Cabau J. Conduction disturbances after transcatheter aortic valve replacement: current status and future perspectives. *Circulation* 2017;**136**:1049–1069.
539. Rogers T, Devraj M, Thomaides A, Steinvil A, Lipinski MJ, Buchanan KD, Alraies MC, Koifman E, Gai J, Torguson R, Okubagzi P, Ben-Dor I, Pichard AD, Satler LF, Waksman R. Utility of invasive electrophysiology studies in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *Am J Cardiol* 2018;**121**:1351–1357.
540. Tovia-Brodie O, Ben-Haim Y, Joffe E, Finkelstein A, Glick A, Rosso R, Belhassen B, Michowitz Y. The value of electrophysiologic study in decision-making regarding the need for pacemaker implantation after TAVI. *J Interv Card Electrophysiol* 2017;**48**:121–130.
541. Rivard L, Schram G, Asgar A, Khairy P, Andrade JG, Bonan R, Dubuc M, Guerra PG, Ibrahim R, Macle L, Roy D, Talajic M, Dyrda K, Shohoudi A, le Polain de Waroux JB, Thibault B. Electrocardiographic and electrophysiological predictors of atrioventricular block after transcatheter aortic valve replacement. *Heart Rhythm* 2015;**12**:321–329.
542. Lilly SM, Deshmukh AJ, Epstein AE, Ricciardi MJ, Shreenivas S, Velagapudi P, Wyman JF. 2020 ACC Expert consensus decision pathway on management of conduction disturbances in patients undergoing transcatheter aortic valve replacement: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2020;**76**:2391–2411.
543. Rodes-Cabau J, Ellenbogen KA, Krahn AD, Latib A, Mack M, Mittal S, Muntane-Carol G, Nazif TM, Sondergaard L, Urena M, Windecker S, Philippon F. Management of conduction disturbances associated with transcatheter aortic valve replacement: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2019;**74**:1086–1106.
544. Costa G, Zappulla P, Barbanti M, Cirasa A, Todaro D, Rapisarda G, Picci A, Platania F, Tosto A, Di Grazia A, Sgroi C, Tamburino C, Calvi V. Pacemaker dependency after transcatheter aortic valve implantation: incidence, predictors and long-term outcomes. *EuroIntervention* 2019;**15**:875–883.
545. Kaplan RM, Yadlapati A, Cantey EP, Passman RS, Gajjar M, Knight BP, Sweis R, Ricciardi MJ, Pham DT, Churyla A, Malaisrie SC, Davidson CJ, Flaherty JD. Conduction recovery following pacemaker implantation after transcatheter aortic valve replacement. *Pacing Clin Electrophysiol* 2019;**42**:146–152.
546. Junquera L, Freitas-Ferraz AB, Padron R, Silva I, Nunes Ferreira-Neto A, Guimaraes L, Mohammadi S, Moris C, Philippon F, Rodes-Cabau J. Intraprocedural high-degree atrioventricular block or complete heart block in transcatheter aortic valve replacement recipients with no prior intraventricular conduction disturbances. *Catheter Cardiovasc Interv* 2019;**95**:982–990.
547. Auffret V, Webb JG, Eltchaninoff H, Munoz-Garcia AJ, Himbert D, Tamburino C, Nombela-Franco L, Nietlispach F, Moris C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS Jr, Lemos PA, Abizaid A, Sarmento-Leite R, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Vahanian A, Bouleti C, Imme S, Maisano F, Del Valle R, Benitez LM, Garcia Del Blanco B, Puri R, Philippon F, Urena M, Rodes-Cabau J. Clinical impact of baseline right bundle branch block in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2017;**10**:1564–1574.
548. Jorgensen TH, De Backer O, Gerds TA, Bieliauskas G, Svendsen JH, Sondergaard L. Immediate post-procedural 12-lead electrocardiography as predictor of late conduction defects after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2018;**11**:1509–1518.
549. Ream K, Sandhu A, Valle J, Weber R, Kaizer A, Wiktor DM, Borne RT, Tumolo AZ, Kunkel M, Zipse MM, Schuller J, Tompkins C, Rosenberg M, Nguyen DT,

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Cleveland JC Jr, Fullerton D, Carroll JD, Messenger J, Sauer WH, Aleong RG, Tzou WS. Ambulatory rhythm monitoring to detect late high-grade atrioventricular block following transcatheter aortic valve replacement. *J Am Coll Cardiol* 2019;**73**:2538–2547.
550. Kostopoulou A, Karyofillis P, Livanis E, Thomopoulou S, Stefopoulos C, Doudoumis K, Theodorakis G, Voudris V. Permanent pacing after transcatheter aortic valve implantation of a CoreValve prosthesis as determined by electrocardiographic and electrophysiological predictors: a single-centre experience. *Europace* 2016;**18**:131–137.
551. Khairy P, Landzberg MJ, Gatzoulis MA, Mercier L-Ae, Fernandes SM, Côté J-M, Lavoie J-P, Fournier A, Guerra PG, Frogoudaki A, Walsh EP, Dore A. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts. *Circulation* 2006;**113**:2391–2397.
552. Anand N. Chronotropic incompetence in young patients with late postoperative atrial flutter: a case–control study. *Eur Heart J* 2006;**27**:2069–2073.
553. Fishberger SB, Wernovsky G, Gentles TL, Gauvreau K, Burnetta J, Mayer JE, Walsh EP. Factors that influence the development of atrial flutter after the Fontan operation. *J Thorac Cardiovasc Surg* 1997;**113**:80–86.
554. Gillette PC, Shannon C, Garson A, Porter C-BJ, Ott D, Cooley DA, McNamara DG. Pacemaker treatment of sick sinus syndrome in children. *J Am Coll Cardiol* 1983;**1**:1325–1329.
555. Kay R, Estioko M, Wiener I. Primary sick sinus syndrome as an indication for chronic pacemaker therapy in young adults: incidence, clinical features, and long-term evaluation. *American Heart Journal* 1982;**103**:338–342.
556. Ragonese P, Drago F, Guccione P, Santilli A, Silvetti MS, Agostino DA. Permanent overdrive atrial pacing in the chronic management of recurrent postoperative atrial reentrant tachycardia in patients with complex congenital heart disease. *Pacing Clin Electrophysiol* 1997;**20**:2917–2923.
557. Opic P, Yap SC, Van Kranenburg M, Van Dijk AP, Budts W, Vliegen HW, Van Erven L, Can A, Sahin G, De Groot NM, Witsenburg M, Roos-Hesselink JW. Atrial-based pacing has no benefit over ventricular pacing in preventing atrial arrhythmias in adults with congenital heart disease. *Europace* 2013;**15**:1757–1762.
558. Skanes AC, Krahn AD, Yee R, Klein GJ, Connolly SJ, Kerr CR, Gent M, Thorpe KE, Roberts RS, Canadian Trial of Physiologic Pacing. Progression to chronic atrial fibrillation after pacing: the Canadian Trial of Physiologic Pacing. CTOPP Investigators. *J Am Coll Cardiol* 2001;**38**:167–172.
559. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, Lee R, Marine JE, McLeod CJ, Oken KR, Patton KK, Pellegrini CN, Selzman KA, Thompson A, Varosy PD. 2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *Circulation* 2019;**140**:e333-e381.
560. Kramer CC, Maldonado JR, Olson MD, Gingerich JC, Ochoa LA, Law IH. Safety and efficacy of atrial antitachycardia pacing in congenital heart disease. *Heart Rhythm* 2018;**15**:543–547.
561. Stephenson EA, Casavant D, Tuzi J, Alexander ME, Law I, Serwer G, Strieper M, Walsh EP, Berul CI, ATTEST Investigators. Efficacy of atrial antitachycardia pacing using the Medtronic AT500 pacemaker in patients with congenital heart disease. *Am J Cardiol* 2003;**92**:871–876.
562. Jaeggi ET, Hamilton RM, Silverman ED, Zamora SA, Hornberger LK. Outcome of children with fetal, neonatal, or childhood diagnosis of isolated congenital atrioventricular block: a single institution's experience of 30 years. *ACC Current Journal Review* 2002;**11**:95.
563. Villain E, Coastedoat-Chalumeau N, Marijon E, Boudjemline Y, Piette JC, Bonnet D. Presentation and prognosis of complete atrioventricular block in childhood, according to maternal antibody status. *J Am Coll Cardiol* 2006;**48**:1682–1687.
564. Dewey RC, Capeless MA, Levy AM. Use of ambulatory electrocardiographic monitoring to identify high-risk patients with congenital complete heart block. *N Engl J Med* 1987;**316**:835–839.
565. Karpawich PP, Gillette PC, Garson A Jr, Hesslein PS, Porter CB, McNamara DG. Congenital complete atrioventricular block: clinical and electrophysiologic predictors of need for pacemaker insertion. *Am J Cardiol* 1981;**48**:1098–1102.
566. Michaelsson M, Jonzon A, Riesenfeld T. Isolated congenital complete atrioventricular block in adult life. A prospective study. *Circulation* 1995;**92**:442–449.
567. Beaufort-Krol GC, Schasfoort-van Leeuwen MJ, Stienstra Y, Bink-Boelkens MT. Longitudinal echocardiographic follow-up in children with congenital complete atrioventricular block. *Pacing Clin Electrophysiol* 2007;**30**:1339–1343.
568. Breur JM, Udink Ten Cate FE, Kapusta L, Cohen MI, Crosson JE, Boramanand N, Lubbers LJ, Friedman AH, Brenner JI, Vetter VL, Sreeram N, Meijboom EJ. Pacemaker therapy in isolated congenital complete atrioventricular block. *Pacing Clin Electrophysiol* 2002;**25**:1685–1691.
569. Bonatti V, Agnetti A, Squarcia U. Early and late postoperative complete heart block in pediatric patients submitted to open-heart surgery for congenital heart disease. *Pediatr Med Chir* 1998;**20**:181–186.
570. Gross GJ, Chiu CC, Hamilton RM, Kirsh JA, Stephenson EA. Natural history of postoperative heart block in congenital heart disease: implications for pacing intervention. *Heart Rhythm* 2006;**3**:601–604.
571. Murphy D. Prognosis of complete atrioventricular dissociation in children after open-heart surgery. *Lancet* 1970;**295**:750–752.
572. Krongrad E. Prognosis for patients with congenital heart disease and postoperative intraventricular conduction defects. *Circulation* 1978;**57**:867–870.
573. Villain E. Indications for pacing in patients with congenital heart disease. *Pacing Clin Electrophysiol* 2008;**31 Suppl 1**:S17-20.
574. Diller GP, Okonko D, Uebing A, Ho SY, Gatzoulis MA. Cardiac resynchronization therapy for adult congenital heart disease patients with a systemic right ventricle: analysis of feasibility and review of early experience. *Europace* 2006;**8**:267–272.
575. Rapezzi C, Arbustini E, Caforio ALP, Charron P, Gimeno-Blanes J, Helio T, Linhart A, Mogensen J, Pinto Y, Ristic A, Seggewiss H, Sinagra G, Tavazzi L, Elliott PM. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2012;**34**:1448–1458.
576. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
577. Nishimura RA, Trusty JM, Hayes DL, Ilstrup DM, Larson DR, Hayes SN, Allison TG, Tajik AJ. Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. *J Am Coll Cardiol* 1997;**29**:435–441.
578. Kappenberger L, Linde C, Daubert C, McKenna W, Meisel E, Sadoul N, Chojnowska L, Guize L, Gras D, Jeanrenaud X, Ryden L. Pacing in hypertrophic obstructive cardiomyopathy: a randomized crossover study. *Eur Heart J* 1997;**18**:1249–1256.
579. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY). *Circulation* 1999;**99**:2927–2933.
580. Slade AK, Sadoul N, Shapiro L, Chojnowska L, Simon JP, Saumarez RC, Dodinot B, Camm AJ, McKenna WJ, Aliot E. DDD pacing in hypertrophic cardiomyopathy: a multicentre clinical experience. *Heart* 1996;**75**:44–49.
581. Megevand A, Ingles J, Richmond DR, Semsarian C. Long-term follow-up of patients with obstructive hypertrophic cardiomyopathy treated with dual-chamber pacing. *Am J Cardiol* 2005;**95**:991–993.
582. Linde C, Gadler F, Kappenberger L, Ryden L. Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy. PIC Study Group. Pacing In Cardiomyopathy. *Am J Cardiol* 1999;**83**:903–907.
583. Ommen SR, Nishimura RA, Squires RW, Schaff HV, Danielson GK, Tajik AJ. Comparison of dual-chamber pacing versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy: a comparison of objective hemodynamic and exercise end points. *J Am Coll Cardiol* 1999;**34**:191–196.
584. Arnold AD, Howard JP, Chiew K, Kerrigan WJ, de Vere F, Johns HT, Churlilov L, Ahmad Y, Keene D, Shun-Shin MJ, Cole GD, Kanagaratnam P, Sohaib SMA, Varnava A, Francis DP, Whinnett ZI. Right ventricular pacing for hypertrophic obstructive cardiomyopathy: meta-analysis and meta-regression of clinical trials. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:321–333.
585. Chang SM, Nagueh SF, Spencer WH 3rd, Lakkis NM. Complete heart block: determinants and clinical impact in patients with hypertrophic obstructive cardiomyopathy undergoing nonsurgical septal reduction therapy. *J Am Coll Cardiol* 2003;**42**:296–300.
586. Lawrenz T, Lieder F, Bartelsmeier M, Leuner C, Borchert B, Meyer zu Vilsendorf D, Strunk-Mueller C, Reinhardt J, Feuchtl A, Stellbrink C, Kuhn H. Predictors of complete heart block after transcoronary ablation of septal hypertrophy: results of a prospective electrophysiological investigation in 172 patients with hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 2007;**49**:2356–2363.
587. Topilski I, Sherez J, Keren G, Copperman I. Long-term effects of dual-chamber pacing with periodic echocardiographic evaluation of optimal atrioventricular delay in patients with hypertrophic cardiomyopathy >50 years of age. *Am J Cardiol* 2006;**97**:1769–1775.
588. Cui H, Schaff HV, Nishimura RA, Geske JB, Dearani JA, Lahr BD, Ommen SR. Conduction abnormalities and long-term mortality following septal myectomy in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2019;**74**:645–655.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

589. Rogers DP, Marazia S, Chow AW, Lambiase PD, Lowe MD, Frenneaux M, McKenna WJ, Elliott PM. Effect of biventricular pacing on symptoms and cardiac remodelling in patients with end-stage hypertrophic cardiomyopathy. *Eur J Heart Fail* 2008;**10**:507–513.
590. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Sorajja P. 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: Executive Summary: a Report of the American College of Cardiology/*American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation* 2020;**142**:e533-e557.
591. Cappelli F, Morini S, Pieragnoli P, Targetti M, Stefano P, Marchionni N, Olivotto I. Cardiac resynchronization therapy for end-stage hypertrophic cardiomyopathy: the need for disease-specific criteria. *J Am Coll Cardiol* 2018;**71**:464–466.
592. Killu AM, Park JY, Sara JD, Hodge DO, Gersh BJ, Nishimura RA, Asirvatham SJ, McLeod CJ. Cardiac resynchronization therapy in patients with end-stage hypertrophic cardiomyopathy. *Europace* 2018;**20**:82–88.
593. Gu M, Jin H, Hua W, Fan XH, Niu HX, Tian T, Ding LG, Wang J, Xue C, Zhang S. Clinical outcome of cardiac resynchronization therapy in dilated-phase hypertrophic cardiomyopathy. *J Geriatr Cardiol* 2017;**14**:238–244.
594. Fruh A, Siem G, Holmstrom H, Dohlen G, Haugaa KH. The Jervell and Lange–Nielsen syndrome; atrial pacing combined with β-blocker therapy, a favorable approach in young high-risk patients with long QT syndrome? *Heart Rhythm* 2016;**13**:2186–2192.
595. Aziz PF, Tanel RE, Zelster IJ, Pass RH, Wieand TS, Vetter VL, Vogel RL, Shah MJ. Congenital long QT syndrome and 2:1 atrioventricular block: an optimistic outcome in the current era. *Heart Rhythm* 2010;**7**:781–785.
596. Feingold B, Mahle WT, Auerbach S, Clemens P, Domenighetti AA, Jefferies JL, Judge DP, Lal AK, Markham LW, Parks WJ, Tsuda T, Wang PJ, Yoo SJ, American Heart Association Pediatric Heart Failure Committee of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Radiology Intervention, Council on Functional Genomics Translational Biology, Stroke Council. Management of cardiac involvement associated with neuromuscular diseases: a Scientific Statement from the American Heart Association. *Circulation* 2017;**136**:e200-e231.
597. Arbustini E, Di Toro A, Giuliani L, Favalli V, Narula N, Grasso M. Cardiac phenotypes in hereditary muscle disorders: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018;**72**:2485–2506.
598. Groh WJ. Arrhythmias in the muscular dystrophies. *Heart Rhythm* 2012;**9**:1890–1895.
599. Bhakta D, Shen C, Kron J, Epstein AE, Pascuzzi RM, Groh WJ. Pacemaker and implantable cardioverter-defibrillator use in a US myotonic dystrophy type 1 population. *J Cardiovasc Electrophysiol* 2011;**22**:1369–1375.
600. Wahbi K, Meune C, Porcher R, Becane HM, Lazarus A, Laforet P, Stojkovic T, Behin A, Radvanyi-Hoffmann H, Eymard B, Duboc D. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. *JAMA* 2012;**307**:1292–1301.
601. Lazarus A, Varin J, Babuty D, Anselme F, Coste J, Duboc D. Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing: a multicenter diagnostic pacemaker study. *J Am Coll Cardiol* 2002;**40**:1645–1652.
602. Laurent V, Pellieux S, Corcia P, Magro P, Pierre B, Fauchier L, Raynaud M, Babuty D. Mortality in myotonic dystrophy patients in the area of prophylactic pacing devices. *Int J Cardiol* 2011;**150**:54–58.
603. Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, Pourmand R, Otten RF, Bhakta D, Nair GV, Marashdeh MM, Zipes DP, Pascuzzi RM. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. *N Engl J Med* 2008;**358**:2688–2697.
604. Ha AH, Tarnopolsky MA, Bergstra TG, Nair GM, Al-Qubbany A, Healey JS. Predictors of atrio-ventricular conduction disease, long-term outcomes in patients with myotonic dystrophy types I and II. *Pacing Clin Electrophysiol* 2012;**35**:1262–1269.
605. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ Jr, Spudich S, De Girolami U, Seidman JG, Seidman C, Muntoni F, Muehle G, Johnson W, McDonough B. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–1724.
606. Arbustini E, Pilotto A, Repetto A, Grasso M, Negri A, Diegoli M, Campana C, Scelsi L, Baldini E, Gavazzi A, Tavazzi L. Autosomal dominant dilated cardiomyopathy with atrioventricular block: a lamin A/C defect-related disease. *J Am Coll Cardiol* 2002;**39**:981–990.
607. Taylor MR, Fain PR, Sinagra G, Robinson ML, Robertson AD, Carniel E, Di Lenarda A, Bohlmeyer TJ, Ferguson DA, Brodsky GL, Boucek MM, Lascor J, Moss AC, Li WL, Stetler GL, Muntoni F, Bristow MR, Mestroni L, Familial Dilated Cardiomyopathy Registry Research Group. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. *J Am Coll Cardiol* 2003;**41**:771–780.
608. Sanna T. Cardiac features of Emery–Dreifuss muscular dystrophy caused by lamin A/C gene mutations. *Eur Heart J* 2003;**24**:2227–2236.
609. Haas J, Frese KS, Peil B, Kloos W, Keller A, Nietsch R, Feng Z, Muller S, Kayvanpour E, Vogel B, Sedaghat-Hamedani F, Lim WK, Zhao X, Fradkin D, Kohler D, Fischer S, Franke J, Marquart S, Barb I, Li DT, Amr A, Ehlermann P, Mereles D, Weis T, Hassel S, Kremer A, King V, Wirsz E, Isnard R, Komajda M, Serio A, Grasso M, Syrris P, Wicks E, Plagnol V, Lopes L, Gadgaard T, Eiskjaer H, Jorgensen M, Garcia-Giustiniani D, Ortiz-Genga M, Crespo-Leiro MG, Deprez RH, Christiaans I, van Rijsingen IA, Wilde AA, Waldenstrom A, Bolognesi M, Bellazzi R, Morner S, Bermejo JL, Monserrat L, Villard E, Mogensen J, Pinto YM, Charron P, Elliott P, Arbustini E, Katus HA, Meder B. Atlas of the clinical genetics of human dilated cardiomyopathy. *Eur Heart J* 2015;**36**:1123–1135.
610. Gigli M, Merlo M, Graw SL, Barbati G, Rowland TJ, Slavov DB, Stolfo D, Haywood ME, Dal Ferro M, Altinier A, Ramani F, Brun F, Cocciolo A, Puggia I, Morea G, McKenna WJ, La Rosa FG, Taylor MRG, Sinagra G, Mestroni L. Genetic risk of arrhythmic phenotypes in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2019;**74**:1480–1490.
611. van Berlo JH, de Voogt WG, van der Kooi AJ, van Tintelen JP, Bonne G, Yaou RB, Duboc D, Rossenbacker T, Heidbuchel H, de Visser M, Crijns HJ, Pinto YM. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? *J Mol Med (Berl)* 2005;**83**:79–83.
612. Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D. Primary prevention of sudden death in patients with lamin A/C gene mutations. *N Engl J Med* 2006;**354**:209–210.
613. Anselme F, Moubarak G, Savoure A, Godin B, Borz B, Drouin-Garraud V, Gay A. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. *Heart Rhythm* 2013;**10**:1492–1498.
614. Hasselberg NE, Haland TF, Saberniak J, Brekke PH, Berge KE, Leren TP, Edvardsen T, Haugaa KH. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. *Eur Heart J* 2018;**39**:853–860.
615. Becane HM, Bonne G, Varnous S, Muchir A, Ortega V, Hammouda EH, Urtizberea JA, Lavergne T, Fardeau M, Eymard B, Weber S, Schwartz K, Duboc D. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. *Pacing Clin Electrophysiol* 2000;**23**:1661–1666.
616. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, Stalens C, Sacher F, Babuty D, Trochu JN, Moubarak G, Savvatis K, Porcher R, Laforet P, Fayssoil A, Marijon E, Stojkovic T, Behin A, Leonard-Louis S, Sole G, Labombarda F, Richard P, Metay C, Quijano-Roy S, Dabaj I, Klug D, Vantyghem MC, Chevalier P, Ambrosi P, Salort E, Sadoul N, Waintraub X, Chikhaoui K, Mabo P, Combes N, Maury P, Sellal JM, Tedrow UB, Kalman JM, Vohra J, Androulakis AFA, Zeppenfeld K, Thompson T, Barnerias C, Becane HM, Bieth E, Boccara F, Bonnet D, Bouhour F, Boule S, Brehin AC, Chapon F, Cintas P, Cuisset JM, Davy JM, De Sandre-Giovannoli A, Demurger F, Desguerre I, Dieterich K, Durigneux J, Echaniz-Laguna A, Eschalier R, Ferreiro A, Ferrer X, Francannet C, Fradin M, Gaborit B, Gay A, Hagege A, Isapof A, Jeru I, Juntas Morales R, Lagrue E, Lamblin N, Lascols O, Laugel V, Lazarus A, Leturcq F, Levy N, Magot A, Manel V, Martins R, Mayer M, Mercier S, Meune C, Michaud M, Minot-Myhie MC, Muchir A, Nadaj-Pakleza A, Pereon Y, Petiot P, Petit F, Praline J, Rollin A, Sabouraud P, Sarret C, Schaeffer S, Taithe F, Tard C, Tiffreau V, Toutain A, Vatier C, Walther-Louvier U, Eymard B, Charron P, Vigouroux C, Bonne G, Kumar S, Elliott P, Duboc D. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019;**140**:293–302.
617. van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, van den Berg MP, Pilotto A, Pasotti M, Jenkins S, Rowland C, Aslam U, Wilde AA, Perrot A, Pankuweit S, Zwinderman AH, Charron P, Pinto YM. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers a European cohort study. *J Am Coll Cardiol* 2012;**59**:493–500.
618. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, Waintraub X, Charron P, Rollin A, Richard P, Stevenson WG, Macintyre CJ, Ho CY, Thompson T, Vohra JK, Kalman JM, Zeppenfeld K, Sacher F, Tedrow UB, Lakdawala NK. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. *J Am Coll Cardiol* 2016;**68**:2299–2307.
619. Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, Mannarino S, Gambarin F, Favalli V, Grasso M, Agozzino M, Campana C, Gavazzi A, Febo O, Marini M, Landolina M, Mortara A, Piccolo G, Vigano M, Tavazzi L, Arbustini E. Long-term outcome and risk stratification in dilated cardiolaminopathies. *J Am Coll Cardiol* 2008;**52**:1250–1260.
620. Hasselberg NE, Edvardsen T, Petri H, Berge KE, Leren TP, Bundgaard H, Haugaa KH. Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. *Europace* 2014;**16**:563–571.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

621. Limongelli G, Tome-Esteban M, Dejthevaporn C, Rahman S, Hanna MG, Elliott PM. Prevalence and natural history of heart disease in adults with primary mitochondrial respiratory chain disease. *Eur J Heart Fail* 2010;**12**:114–121.
622. Anan R, Nakagawa M, Miyata M, Higuchi I, Nakao S, Suehara M, Osame M, Tanaka H. Cardiac involvement in mitochondrial diseases. A study on 17 patients with documented mitochondrial DNA defects. *Circulation* 1995;**91**:955–961.
623. Khambatta S, Nguyen DL, Beckman TJ, Wittich CM. Kearns–Sayre syndrome: a case series of 35 adults and children. *Int J Gen Med* 2014;**7**:325–332.
624. Kabunga P, Lau AK, Phan K, Puranik R, Liang C, Davis RL, Sue CM, Sy RW. Systematic review of cardiac electrical disease in Kearns–Sayre syndrome and mitochondrial cytopathy. *Int J Cardiol* 2015;**181**:303–310.
625. Polak PE, Zijlstra F, Roelandt JR. Indications for pacemaker implantation in the Kearns–Sayre syndrome. *Eur Heart J* 1989;**10**:281–282.
626. Nordenswan HK, Lehtonen J, Ekstrom K, Kandolin R, Simonen P, Mayranpaa M, Vihinen T, Miettinen H, Kaikkonen K, Haataja P, Kerola T, Rissanen TT, Kokkonen J, Alatalo A, Pietila-Effati P, Utriainen S, Kupari M. Outcome of cardiac sarcoidosis presenting with high-grade atrioventricular block. *Circ Arrhythm Electrophysiol* 2018;**11**:e006145.
627. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, McArdle BA, Davis D, Ohira H, Gollob MH, Leung E, Healey JS, Birnie DH. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. *J Cardiovasc Electrophysiol* 2014;**25**:875–881.
628. Yoshida Y, Morimoto S, Hiramitsu S, Tsuboi N, Hirayama H, Itoh T. Incidence of cardiac sarcoidosis in Japanese patients with high-degree atrioventricular block. *Am Heart J* 1997;**134**:382–386.
629. Mankad P, Mitchell B, Birnie D, Kron J. Cardiac sarcoidosis. *Curr Cardiol Rep* 2019;**21**:152.
630. Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. *Can J Cardiol* 2013;**29**:1034–1041.
631. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Cosedis Nielsen J, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;**11**:1305–1323.
632. Schuller JL, Zipse M, Crawford T, Bogun F, Beshai J, Patel AR, Sweiss NJ, Nguyen DT, Aleong RG, Varosy PD, Weinberger HD, Sauer WH. Implantable cardioverter defibrillator therapy in patients with cardiac sarcoidosis. *J Cardiovasc Electrophysiol* 2012;**23**:925–929.
633. Kron J, Sauer W, Schuller J, Bogun F, Crawford T, Sarsam S, Rosenfeld L, Mitiku TY, Cooper JM, Mehta D, Greenspon AJ, Ortman M, Delurgio DB, Valadri R, Narasimhan C, Swapna N, Singh JP, Danik S, Markowitz SM, Almquist AK, Krahn AD, Wolfe LG, Feinstein S, Ellenbogen KA. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. *Europace* 2013;**15**:347–354.
634. Birnie DH, Sauer WH, Judson MA. Consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart* 2016;**102**:411–414.
635. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GMC, Seeland U, Simoncini T, Swan L, Warnes CA, ESC Scientific Document Group. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**:3165–3241.
636. Tuzcu V, Gul EE, Erdem A, Kamali H, Saritas T, Karadeniz C, Akdeniz C. Cardiac interventions in pregnant patients without fluoroscopy. *Pediatr Cardiol* 2015;**36**:1304–1307.
637. Gudal M, Kervancioglu C, Oral D, Gurel T, Erol C, Sonel A. Permanent pacemaker implantation in a pregnant woman with the guidance of ECG and two-dimensional echocardiography. *Pacing Clin Electrophysiol* 1987;**10**:543–545.
638. Traykov V, Bongiorni MG, Boriani G, Burri H, Costa R, Dagres N, Deharo JC, Epstein LM, Erba PA, Snygg-Martin U, Nielsen JC, Poole JE, Saghy L, Starck C, Strathmore N, Blomstrom-Lundqvist C. Clinical practice and implementation of guidelines for the prevention, diagnosis and management of cardiac implantable electronic device infections: results of a worldwide survey under the auspices of the European Heart Rhythm Association. *Europace* 2019;**21**:1270–1279.
639. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey JL, Lande G, Lazarus A, Victor J, Barnay C, Grandbastien B, Kacet S, People Study Group. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation* 2007;**116**:1349–1355.
640. Enzler MJ, Berbari E, Osmon DR. Antimicrobial prophylaxis in adults. *Mayo Clin Proc* 2011;**86**:686–701.
641. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace* 2015;**17**:767–777.
642. Blomstrom-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG, Poole J, Boriani G, Costa R, Deharo JC, Epstein LM, Saghy L, Snygg-Martin U, Starck C, Tascini C, Strathmore N. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020;**41**:2012–2032.
643. de Oliveira JC, Martinelli M, Nishioka SA, Varejao T, Uipe D, Pedrosa AA, Costa R, D'Avila A, Danik SB. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;**2**:29–34.
644. Madadi S, Kafi M, Kheirkhah J, Azhari A, Kiarsi M, Mehryar A, Fazelifar A, Alizadehdiz A, Emkanjoo Z, Haghjoo M. Postoperative antibiotic prophylaxis in the prevention of cardiac implantable electronic device infection. *Pacing Clin Electrophysiol* 2019;**42**:161–165.
645. Krahn AD, Longtin Y, Philippon F, Birnie DH, Manlucu J, Angaran P, Rinne C, Coutu B, Low RA, Essebag V, Morillo C, Redfearn D, Toal S, Becker G, Degrace M, Thibault B, Crystal E, Tung S, LeMaitre J, Sultan O, Bennett M, Bashir J, Ayala-Paredes F, Gervais P, Rioux L, Hemels MEW, Bouwels LHR, van Vlies B, Wang J, Exner DV, Dorian P, Parkash R, Alings M, Connolly SJ. Prevention of arrhythmia device infection trial: the PADIT trial. *J Am Coll Cardiol* 2018;**72**:3098–3109.
646. Haines DE, Beheiry S, Akar JG, Baker JL, Beinborn D, Beshai JF, Brysiewicz N, Chiu-Man C, Collins KK, Dare M, Fetterly K, Fisher JD, Hongo R, Irefin S, Lopez J, Miller JM, Perry JC, Slotwiner DJ, Tomassoni GF, Weiss E. Heart Rythm Society expert consensus statement on electrophysiology laboratory standards: process, protocols, equipment, personnel, and safety. *Heart Rhythm* 2014;**11**:e9-51.
647. Mimoz O, Lucet J-C, Kerforne T, Pascal J, Souweine B, Goudet V, Mercat A, Bouadma L, Lasocki S, Alfandari S, Friggeri A, Wallet F, Allou N, Ruckly S, Balayn D, Lepape A, Timsit J-F. Skin antisepsis with chlorhexidine–alcohol versus povidone iodine–alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *Lancet* 2015;**386**:2069–2077.
648. Darouiche RO, Wall MJ Jr, Itani KM, Otterson MF, Webb AL, Carrick MM, Miller HJ, Awad SS, Crosby CT, Mosier MC, Alsharif A, Berger DH. Chlorhexidine–alcohol versus povidone-iodine for surgical-site antisepsis. *N Engl J Med* 2010;**362**:18–26.
649. Essebag V, Verma A, Healey JS, Krahn AD, Kalfon E, Coutu B, Ayala-Paredes F, Tang AS, Sapp J, Sturmer M, Keren A, Wells GA, Birnie DH, BRUISE CONTROL Investigators. Clinically significant pocket hematoma increases long-term risk of device infection: BRUISE CONTROL INFECTION Study. *J Am Coll Cardiol* 2016;**67**:1300–1308.
650. Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, Simpson CS, Ayala-Paredes F, Coutu B, Leiria TLL, Essebag V, BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013;**368**:2084–2093.
651. Malagu M, Trevisan F, Scalone A, Marcantoni L, Sammarco G, Bertini M. Frequency of 'pocket' hematoma in patients receiving vitamin K antagonist and antiplatelet therapy at the time of pacemaker or cardioverter defibrillator implantation (from the POCKET Study). *Am J Cardiol* 2017;**119**:1036–1040.
652. Birnie DH, Healey JS, Wells GA, Ayala-Paredes F, Coutu B, Sumner GL, Becker G, Verma A, Philippon F, Kalfon E, Eikelboom J, Sandhu RK, Nery PB, Lellouche N, Connolly SJ, Sapp J, Essebag V. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). *Eur Heart J* 2018;**39**:3973–3979.
653. Kutinsky IB, Jarandilla R, Jewett M, Haines DE. Risk of hematoma complications after device implant in the clopidogrel era. *Circ Arrhythm Electrophysiol* 2010;**3**:312–318.
654. Tompkins C, Cheng A, Dalal D, Brinker JA, Leng CT, Marine JE, Nazarian S, Spragg DD, Sinha S, Halperin H, Tomaselli GF, Berger RD, Calkins H, Henrikson CA. Dual antiplatelet therapy and heparin 'bridging' significantly increase the risk of bleeding complications after pacemaker or implantable cardioverter-defibrillator device implantation. *J Am Coll Cardiol* 2010;**55**:2376–2382.
655. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, ESC Scientific Document Group, ESC Committee for Practice Guidelines, ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.
656. Rossini R, Musumeci G, Visconti LO, Bramucci E, Castiglioni B, De Servi S, Lettieri C, Lettino M, Piccaluga E, Savonitto S, Trabattoni D, Capodanno D, Buffoli F, Parolari A, Dionigi G, Boni L, Biglioli F, Valdatta L, Droghetti A, Bozzani A, Setacci C, Ravelli P, Crescini C, Staurenghi G, Scarone P, Francetti L, D'Angelo F, Gadda F, Comel A, Salvi L, Lorini L, Antonelli M, Bovenzi F, Cremonesi A, Angiolillo DJ, Guagliumi G, Italian Society of Invasive Cardiology, Italian Association of Hospital Cardiologists, Italian Society for Cardiac Surgery, Italian Society of Vascular and Endovascular Surgery, Italian Association of Hospital Surgeons, Italian Society of Surgery, Italian Society of Anaesthesia, Intensive Care Medicine, Lombard Society of Surgery, Italian Society of Maxillofacial Surgery, Italian Society of Reconstructive Plastic Surgery and Aesthetics, Italian Society of Thoracic Surgeons, Italian Society of Urology, Italian Society of Orthopaedics and Traumatology, Italian Society of Periodontology, Italian Federation of Scientific Societies of Digestive System Diseases Lombardia, Association of Obstetricians Gynaecologists Italian Hospital Lombardia, Society of Ophthalmology Lombardia. Perioperative management of antiplatelet therapy in patients with coronary stents undergoing cardiac and non-cardiac surgery: a consensus document from Italian cardiological, surgical and anaesthesiological societies. *EuroIntervention* 2014;**10**:38–46.
657. Essebag V, Healey JS, Joza J, Nery PB, Kalfon E, Leiria TLL, Verma A, Ayala-Paredes F, Coutu B, Sumner GL, Becker G, Philippon F, Eikelboom J, Sandhu RK, Sapp J, Leather R, Yung D, Thibault B, Simpson CS, Ahmad K, Toal S, Sturmer M, Kavanagh K, Crystal E, Wells GA, Krahn AD, Birnie DH. Effect of direct oral anticoagulants, warfarin, and antiplatelet agents on risk of device pocket hematoma: combined analysis of BRUISE CONTROL 1 and 2. *Circ Arrhythm Electrophysiol* 2019;**12**:e007545.
658. Kirkfeldt RE, Johansen JB, Nohr EA, Moller M, Arnsbo P, Nielsen JC. Pneumothorax in cardiac pacing: a population-based cohort study of 28 860 Danish patients. *Europace* 2012;**14**:1132–1138.
659. Liu P, Zhou Y-F, Yang P, Gao Y-S, Zhao G-R, Ren S-Y, Li X-L. Optimized axillary vein technique versus subclavian vein technique in cardiovascular implantable electronic device implantation. *Chin Med J* 2016;**129**:2647–2651.
660. Liccardo M, Nocerino P, Gaia S, Ciardiello C. Efficacy of ultrasound-guided axillary/subclavian venous approaches for pacemaker and defibrillator lead implantation: a randomized study. *J Interv Card Electrophysiol* 2018;**51**:153–160.
661. Chan NY, Kwong NP, Cheong AP. Venous access and long-term pacemaker lead failure: comparing contrast-guided axillary vein puncture with subclavian puncture and cephalic cutdown. *Europace* 2017;**19**:1193–1197.
662. Deharo JC, Bongiorni MG, Rozkovec A, Bracke F, Defaye P, Fernandez-Lozano I, Golzio PG, Hansky B, Kennergren C, Manolis AS, Mitkowski P, Platou ES, Love C, Wilkoff B. Pathways for training and accreditation for transvenous lead extraction: a European Heart Rhythm Association position paper. *Europace* 2012;**14**:124–134.
663. Migliore F, Zorzi A, Bertaglia E, Leoni L, Siciliano M, De Lazzari M, Ignatiuk B, Veronese M, Verlato R, Tarantini G, Iliceto S, Corrado D. Incidence, management, and prevention of right ventricular perforation by pacemaker and implantable cardioverter defibrillator leads. *Pacing Clin Electrophysiol* 2014;**37**:1602–1609.
664. Segreti L, Di Cori A, Soldati E, Zucchelli G, Viani S, Paperini L, De Lucia R, Coluccia G, Valsecchi S, Bongiorni MG. Major predictors of fibrous adherences in transvenous implantable cardioverter-defibrillator lead extraction. *Heart Rhythm* 2014;**11**:2196–2201.
665. Behar JM, Bostock J, Zhu Li AP, Chin HMS, Jubb S, Lent E, Gamble J, Foley PWX, Betts TR, Rinaldi CA, Herring N. Cardiac resynchronization therapy delivered via a multipolar left ventricular lead is associated with reduced mortality and elimination of phrenic nerve stimulation: long-term follow-up from a multicenter registry. *J Cardiovasc Electrophysiol* 2015;**26**:540–546.
666. Forleo GB, Di Biase L, Panattoni G, Mantica M, Parisi Q, Martino A, Pappalardo A, Sergi D, Tesauro M, Papavasileiou LP, Santini L, Calò L, Tondo C, Natale A, Romeo F. Improved implant and postoperative lead performance in CRT-D patients implanted with a quadripolar left ventricular lead. A 6-month follow-up analysis from a multicenter prospective comparative study. *J Interv Card Electrophysiol* 2015;**42**:59–66.
667. Jackson KP, Faerestrand S, Philippon F, Yee R, Kong MH, Kloppe A, Bongiorni MG, Lee SF, Canby RC, Pouliot E, van Ginneken MME, Crossley GH. Performance of a novel active fixation quadripolar left ventricular lead for cardiac resynchronization therapy: Attain Stability Quad Clinical Study results. *J Cardiovasc Electrophysiol* 2020;**31**:1147–1154.
668. Ziacchi M, Diemberger I, Corzani A, Martignani C, Mazzotti A, Massaro G, Valzania C, Rapezzi C, Boriani G, Biffi M. Cardiac resynchronization therapy: a comparison among left ventricular bipolar, quadripolar and active fixation leads. *Sci Rep* 2018;**8**:13262.
669. Ziacchi M, Giannola G, Lunati M, Infusino T, Luzzi G, Rordorf R, Pecora D, Bongiorni MG, De Ruvo E, Biffi M. Bipolar active fixation left ventricular lead or quadripolar passive fixation lead? An Italian multicenter experience. *J Cardiovasc Med (Hagerstown)* 2019;**20**:192–200.
670. Shimony A, Eisenberg MJ, Filion KB, Amit G. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. *Europace* 2012;**14**:81–91.
671. Ng ACT, Allman C, Vidaic J, Tie H, Hopkins AP, Leung DY. Long-term impact of right ventricular septal versus apical pacing on left ventricular synchrony and function in patients with second- or third-degree heart block. *Am J Cardiol* 2009;**103**:1096–1101.
672. Hattori M, Naruse Y, Oginosawa Y, Matsue Y, Hanaki Y, Kowase S, Kurosaki K, Mizukami A, Kohno R, Abe H, Aonuma K, Nogami A. Prognostic impact of lead tip position confirmed via computed tomography in patients with right ventricular septal pacing. *Heart Rhythm* 2019;**16**:921–927.
673. Domenichini G, Sunthorn H, Fleury E, Foulkes H, Stettler C, Burri H. Pacing of the interventricular septum versus the right ventricular apex: a prospective, randomized study. *Eur J Intern Med* 2012;**23**:621–627.
674. Mahapatra S, Bybee KA, Bunch TJ, Espinosa RE, Sinak LJ, McGoon MD, Hayes DL. Incidence and predictors of cardiac perforation after permanent pacemaker placement. *Heart Rhythm* 2005;**2**:907–911.
675. Biffi M, de Zan G, Massaro G, Angeletti A, Martignani C, Boriani G, Diemberger I, Ziacchi M. Is ventricular sensing always right, when it is left? *Clin Cardiol* 2018;**41**:1238–1245.
676. Burri H, Muller H, Kobza R, Sticherling C, Ammann P, Zerlik H, Stettler C, Klersy C, Prinzen F, Auricchio A. RIght VErsus Left Apical transvenous pacing for bradycardia: results of the RIVELA randomized study. *Indian Pacing Electrophysiol J* 2017;**17**:171–175.
677. Tanabe K, Kotoda M, Nakashige D, Mitsui K, Ikemoto K, Matsukawa T. Sudden onset pacemaker-induced diaphragmatic twitching during general anesthesia. *JA Clin Rep* 2019;**5**:36.
678. Khan AA, Nash A, Ring NJ, Marshall AJ. Right hemidiaphragmatic twitching: a complication of bipolar atrial pacing. *Pacing Clin Electrophysiol* 1997;**20**:1732–1733.
679. Shali S, Su Y, Ge J. Interatrial septal pacing to suppress atrial fibrillation in patients with dual chamber pacemakers: a meta-analysis of randomized, controlled trials. *Int J Cardiol* 2016;**219**:421–427.
680. Zhang L, Jiang H, Wang W, Bai J, Liang Y, Su Y, Ge J. Interatrial septum versus right atrial appendage pacing for prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. *Herz* 2018;**43**:438–446.
681. Magnusson P, Wennstrom L, Kastberg R, Liv P. Placement Of Cardiac PacemaKEr Trial (POCKET)—rationale and design: a randomized controlled trial. *Heart Int* 2017;**12**:e8-e11.
682. Gold MR, Peters RW, Johnson JW, Shorofsky SR. Complications associated with pectoral cardioverter-defibrillator implantation: comparison of subcutaneous and submuscular approaches. *J Am Coll Cardiol* 1996;**28**:1278–1282.
683. Lakshmanadoss U, Nuanez B, Kutinsky I, Khalid R, Haines DE, Wong WS. Incidence of pocket infection postcardiac device implantation using antibiotic versus saline solution for pocket irrigation. *Pacing Clin Electrophysiol* 2016;**39**:978–984.
684. Mueller TC, Loos M, Haller B, Mihaljevic AL, Nitsche U, Wilhelm D, Friess H, Kleeff J, Bader FG. Intra-operative wound irrigation to reduce surgical site infections after abdominal surgery: a systematic review and meta-analysis. *Langenbeck's Arch Surg* 2015;**400**:167–181.
685. Tarakji KG, Mittal S, Kennergren C, Corey R, Poole JE, Schloss E, Gallastegui J, Pickett RA, Evonich R, Philippon F, McComb JM, Roark SF, Sorrentino D, Sholevar D, Cronin E, Berman B, Riggio D, Biffi M, Khan H, Silver MT, Collier J, Eldadah Z, Wright DJ, Lande JD, Lexcen DR, Cheng A, Wilkoff BL, WRAP-IT Investigators. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med* 2019;**380**:1895–1905.
686. Da Costa A, Kirkorian G, Cucherat M, Delahaye F, Chevalier P, Cerisier A, Isaaz K, Touboul P. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. *Circulation* 1998;**97**:1796–1801.
687. Leyva F, Zegard A, Qiu T, Acquaye E, Ferrante G, Walton J, Marshall H. Cardiac resynchronization therapy using quadripolar versus non-quadripolar left ventricular leads programmed to biventricular pacing with single-site left ventricular pacing: impact on survival and heart failure hospitalization. *J Am Heart Assoc* 2017;**6**:e007026.
688. Henrikson CA, Sohail MR, Acosta H, Johnson EE, Rosenthal L, Pachulski R, Dan D, Paladino W, Khairallah FS, Gleed K, Hanna I, Cheng A, Lexcen DR, Simons GR. Antibacterial envelope is associated with low infection rates after implantable cardioverter-defibrillator and cardiac resynchronization therapy device replacement: results of the Citadel and Centurion studies. *JACC Clin Electrophysiol* 2017;**3**:1158–1167.
689. Ghanbari H, Phard WS, Al-Ameri H, Latchamsetty R, Jongnarngsin K, Crawford T, Good E, Chugh A, Oral H, Bogun F, Morady F, Pelosi F Jr. Meta-analysis of safety and efficacy of uninterrupted warfarin compared to heparin-based bridging therapy during implantation of cardiac rhythm devices. *Am J Cardiol* 2012;**110**:1482–1488.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

690. Udo EO, Zuithoff NP, van Hemel NM, de Cock CC, Hendriks T, Doevendans PA, Moons KG. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE study. *Heart Rhythm* 2012;**9**:728–735.
691. Koneru JN, Jones PW, Hammill EF, Wold N, Ellenbogen KA. Risk factors and temporal trends of complications associated with transvenous implantable cardiac defibrillator leads. *J Am Heart Assoc* 2018;**7**:e007691.
692. Ellenbogen KA, Hellkamp AS, Wilkoff BL, Camunas JL, Love JC, Hadjis TA, Lee KL, Lamas GA. Complications arising after implantation of DDD pacemakers: the MOST experience. *Am J Cardiol* 2003;**92**:740–741.
693. Parsonnet V, Bernstein AD, Lindsay B. Pacemaker-implantation complication rates: an analysis of some contributing factors. *J Am Coll Cardiol* 1989;**13**:917–921.
694. Ranasinghe I, Labrosciano C, Horton D, Ganesan A, Curtis JP, Krumholz HM, McGavigan A, Hossain S, Air T, Hariharaputhiran S. Institutional variation in quality of cardiovascular implantable electronic device implantation: a cohort study. *Ann Intern Med* 2019;**171**:309–317.
695. Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R, Gottipaty V, Shinn T, Dan D, Feldman LA, Seide H, Winston SA, Gallagher JJ, Langberg JJ, Mitchell K, Holcomb R, REPLACE Registry Investigators. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation* 2010;**122**:1553–1561.
696. Biffi M, Ammendola E, Menardi E, Parisi Q, Narducci ML, De Filippo P, Manzo M, Stabile G, Potenza DR, Zanon F, Quartieri F, Rillo M, Saporito D, Zaca V, Berisso MZ, Bertini M, Tumietto F, Malacrida M, Diemberger I. Real-life outcome of implantable cardioverter-defibrillator and cardiac resynchronization defibrillator replacement/upgrade in a contemporary population: observations from the multicentre DECODE registry. *Europace* 2019;**21**:1527–1536.
697. Hosseini SM, Moazzami K, Rozen G, Vaid J, Saleh A, Heist KE, Vangel M, Ruskin JN. Utilization and in-hospital complications of cardiac resynchronization therapy: trends in the United States from 2003 to 2013. *Eur Heart J* 2017;**38**:2122–2128.
698. Zeitler EP, Patel D, Hasselblad V, Sanders GD, Al-Khatib SM. Complications from prophylactic replacement of cardiac implantable electronic device generators in response to United States Food and Drug Administration recall: a systematic review and meta-analysis. *Heart Rhythm* 2015;**12**:1558–1564.
699. Nowak B, Tasche K, Barnewold L, Heller G, Schmidt B, Bordignon S, Chun KR, Furnkranz A, Mehta RH. Association between hospital procedure volume and early complications after pacemaker implantation: results from a large, unselected, contemporary cohort of the German nationwide obligatory external quality assurance programme. *Europace* 2015;**17**:787–793.
700. van Rees JB, de Bie MK, Thijssen J, Borleffs CJ, Schalij MJ, van Erven L. Implantation-related complications of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials. *J Am Coll Cardiol* 2011;**58**:995–1000.
701. Wiegand UK, Bode F, Bonnemeier H, Eberhard F, Schlei M, Peters W. Long-term complication rates in ventricular, single lead VDD, and dual chamber pacing. *Pacing Clin Electrophysiol* 2003;**26**:1961–1969.
702. Olsen T, Jorgensen OD, Nielsen JC, Thogersen AM, Philbert BT, Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982–2018). *Eur Heart J* 2019;**40**:1862–1869.
703. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, Ho RT, Pavri BB, Kurtz SM. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol* 2011;**58**:1001–1006.
704. Rennert-May E, Chew D, Lu S, Chu A, Kuriachan V, Somayaji R. Epidemiology of cardiac implantable electronic device infections in the United States: a population-based cohort study. *Heart Rhythm* 2020;**17**:1125–1131.
705. Ozcan C, Raunso J, Lamberts M, Kober L, Lindhardt TB, Bruun NE, Laursen ML, Torp-Pedersen C, Gislason GH, Hansen ML. Infective endocarditis and risk of death after cardiac implantable electronic device implantation: a nationwide cohort study. *Europace* 2017;**19**:1007–1014.
706. Dai M, Cai C, Vaibhav V, Sohail MR, Hayes DL, Hodge DO, Tian Y, Asirvatham R, Cochuyt JJ, Huang C, Friedman PA, Cha YM. Trends of cardiovascular implantable electronic device infection in 3 decades: a population-based study. *JACC Clin Electrophysiol* 2019;**5**:1071–1080.
707. Palmisano P, Accogli M, Zaccaria M, Luzzi G, Nacci F, Anaclerio M, Favale S. Rate, causes, and impact on patient outcome of implantable device complications requiring surgical revision: large population survey from two centres in Italy. *Europace* 2013;**15**:531–540.
708. Sohail MR, Henrikson CA, Braid-Forbes MJ, Forbes KF, Lerner DJ. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* 2011;**171**:1821–1828.
709. Cantillon DJ, Dukkipati SR, Ip JH, Exner DV, Niazi IK, Banker RS, Rashtian M, Plunkitt K, Tomassoni GF, Nabutovsky Y, Davis KJ, Reddy VY. Comparative study of acute and mid-term complications with leadless and transvenous cardiac pacemakers. *Heart Rhythm* 2018;**15**:1023–1030.
710. Chahine J, Baranowski B, Tarakji K, Gad MM, Saliba W, Rickard J, Cantillon DJ, Diab M, Kanj M, Callahan T, Dresing T, Bhargava M, Chung M, Niebauer MJ, Varma N, Tchou P, Wilkoff BL, Wazni O, Hussein AA. Cardiac venous injuries: procedural profiles and outcomes during left ventricular lead placement for cardiac resynchronization therapy. *Heart Rhythm* 2020;**17**:1298–1303.
711. Seifert M, Schau T, Moeller V, Neuss M, Meyhoefer J, Butter C. Influence of pacing configurations, body mass index, and position of coronary sinus lead on frequency of phrenic nerve stimulation and pacing thresholds under cardiac resynchronization therapy. *Europace* 2010;**12**:961–967.
712. Biffi M, Moschini C, Bertini M, Saporito D, Ziacchi M, Diemberger I, Valzania C, Domenichini G, Cervi E, Martignani C, Sangiorgi D, Branzi A, Boriani G. Phrenic stimulation: a challenge for cardiac resynchronization therapy. *Circ Arrhythm Electrophysiol* 2009;**2**:402–410.
713. Rijal S, Wolfe J, Rattan R, Durrani A, Althouse AD, Marroquin OC, Jain S, Mulukutla S, Saba S. Lead related complications in quadripolar versus bipolar left ventricular leads. *Indian Pacing Electrophysiol J* 2017;**17**:3–7.
714. Nichols CI, Vose JG. Incidence of bleeding-related complications during primary implantation and replacement of cardiac implantable electronic devices. *J Am Heart Assoc* 2017;**6**:e004263.
715. Wiegand UKH, LeJeune D, Boguschewski F, Bonnemeier H, Eberhardt F, Schunkert H, Bode F. Pocket hematoma after pacemaker or implantable cardioverter defibrillator surgery: influence of patient morbidity, operation strategy, and perioperative antiplatelet/anticoagulation therapy. *Chest* 2004;**126**:1177–1186.
716. Van De Heyning CM, Elbarasi E, Masiero S, Brambatti M, Ghazal S, Al-Maashani S, Capucci A, Leong D, Shivalkar B, Saenen JB, Miljoen HP, Morillo CA, Divarakarmenon S, Amit G, Ribas S, Baiocco E, Maolo A, Romandini A, Maffei S, Connolly SJ, Healey JS, Dokainish H. Prospective study of tricuspid regurgitation associated with permanent leads after cardiac rhythm device implantation. *Can J Cardiol* 2019;**35**:389–395.
717. Cho MS, Kim J, Lee JB, Nam GB, Choi KJ, Kim YH. Incidence and predictors of moderate to severe tricuspid regurgitation after dual-chamber pacemaker implantation. *Pacing Clin Electrophysiol* 2019;**42**:85–92.
718. Lee RC, Friedman SE, Kono AT, Greenberg ML, Palac RT. Tricuspid regurgitation following implantation of endocardial leads: incidence and predictors. *Pacing Clin Electrophysiol* 2015;**38**:1267–1274.
719. Link MS, Hellkamp AS, Estes NA 3rd, Orav EJ, Ellenbogen KA, Ibrahim B, Greenspon A, Rizo-Patron C, Goldman L, Lee KL, Lamas GA, MOST Study Investigators. High incidence of pacemaker syndrome in patients with sinus node dysfunction treated with ventricular-based pacing in the Mode Selection Trial (MOST). *J Am Coll Cardiol* 2004;**43**:2066–2071.
720. van Rooden CJ, Molhoek SG, Rosendaal FR, Schalij MJ, Meinders AE, Huisman MV. Incidence and risk factors of early venous thrombosis associated with permanent pacemaker leads. *J Cardiovasc Electrophysiol* 2004;**15**:1258–1262.
721. Da Costa SSdC, Scalabrini Neto A, Costa R, Caldas JG, Martinelli Filho M. Incidence and risk factors of upper extremity deep vein lesions after permanent transvenous pacemaker implant: a 6-month follow-up prospective study. *Pacing Clin Electrophysiol* 2002;**25**:1301–1306.
722. Ascoeta MS, Marijon E, Defaye P, Klug D, Beganton F, Perier M-C, Gras D, Algalarrondo V, Deharo J-C, Leclercq C, Fauchier L, Babuty D, Bordachar P, Sadoul N, Boveda S, Piot O, DAI-PP Investigators. Impact of early complications on outcomes in patients with implantable cardioverter-defibrillator for primary prevention. *Heart Rhythm* 2016;**13**:1045–1051.
723. Reynolds MR, Cohen DJ, Kugelmass AD, Brown PP, Becker ER, Culler SD, Simon AW. The frequency and incremental cost of major complications among Medicare beneficiaries receiving implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2006;**47**:2493–2497.
724. Sridhar AR, Yarlagadda V, Yeruva MR, Kanmanthareddy A, Vallakati A, Dawn B, Lakkireddy D. Impact of haematoma after pacemaker and CRT device implantation on hospitalization costs, length of stay, and mortality: a population-based study. *Europace* 2015;**17**:1548–1554.
725. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL, ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**:3075–3128.
726. Clementy N, Carion PL, Leotoing L, Lamarsalle L, Wilquin-Bequet F, Brown B, Verhees KJP, Fernandes J, Deharo JC. Infections and associated costs following cardiovascular implantable electronic device implantations: a nationwide cohort study. *Europace* 2018;**20**:1974–1980.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

727. Rattanawong P, Kewcharoen J, Mekraksakit P, Mekritthikrai R, Prasitlumkum N, Vutthikraivit W, Putthapiban P, Dworkin J. Device infections in implantable cardioverter defibrillators versus permanent pacemakers: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2019;**30**:1053–1065.
728. Prutkin JM, Reynolds MR, Bao H, Curtis JP, Al-Khatib SM, Aggarwal S, Uslan DZ. Rates of and factors associated with infection in 200 909 Medicare implantable cardioverter-defibrillator implants: results from the National Cardiovascular Data Registry. *Circulation* 2014;**130**:1037–1043.
729. Uslan DZ, Sohail MR, St Sauver JL, Friedman PA, Hayes DL, Stoner SM, Wilson WR, Steckelberg JM, Baddour LM. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. *Arch Intern Med* 2007;**167**:669–675.
730. Chang JD, Manning WJ, Ebrille E, Zimetbaum PJ. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. *J Am Coll Cardiol* 2017;**69**:2331–2341.
731. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. *J Am Coll Cardiol* 2004;**43**:405–409.
732. Hoke U, Auger D, Thijssen J, Wolterbeek R, van der Velde ET, Holman ER, Schalij MJ, Bax JJ, Delgado V, Marsan NA. Significant lead-induced tricuspid regurgitation is associated with poor prognosis at long-term follow-up. *Heart* 2014;**100**:960–968.
733. Mutlak D, Aronson D, Lessick J, Reisner SA, Dabbah S, Agmon Y. Functional tricuspid regurgitation in patients with pulmonary hypertension: is pulmonary artery pressure the only determinant of regurgitation severity? *Chest* 2009;**135**:115–121.
734. Schleifer JW, Pislaru SV, Lin G, Powell BD, Espinosa R, Koestler C, Thome T, Polk L, Li Z, Asirvatham SJ, Cha YM. Effect of ventricular pacing lead position on tricuspid regurgitation: a randomized prospective trial. *Heart Rhythm* 2018;**15**:1009–1016.
735. Cheng Y, Gao H, Tang L, Li J, Yao L. Clinical utility of three-dimensional echocardiography in the evaluation of tricuspid regurgitation induced by implantable device leads. *Echocardiography* 2016;**33**:1689–1696.
736. Beurskens NEG, Tjong FVY, de Bruin-Bon RHA, Dasselaar KJ, Kuijt WJ, Wilde AAM, Knops RE. Impact of leadless pacemaker therapy on cardiac and atrioventricular valve function through 12 months of follow-up. *Circ Arrhythm Electrophysiol* 2019;**12**:e007124.
737. Addetia K, Harb SC, Hahn RT, Kapadia S, Lang RM. Cardiac implantable electronic device lead-induced tricuspid regurgitation. *JACC Cardiovasc Imaging* 2019;**12**:622–636.
738. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntane-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodes-Cabau J, Schafer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel KP, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M, Maisano F. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:2998–3008.
739. Auricchio A, Gasparini M, Linde C, Dobreanu D, Cano O, Sterlinski M, Bogale N, Stellbrink C, Refaat MM, Blomstrom-Lundqvist C, Lober C, Dickstein K, Normand C. Sex-related procedural aspects and complications in CRT Survey II: a multicenter European experience in 11,088 patients. *JACC Clin Electrophysiol* 2019;**5**:1048–1058.
740. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q* 1996;**74**:511–544.
741. Hendriks JM, de Wit R, Crijns HJ, Vrijhoef HJ, Prins MH, Pisters R, Pison LA, Blaauw Y, Tieleman RG. Nurse-led care vs. usual care for patients with atrial fibrillation: results of a randomized trial of integrated chronic care vs. routine clinical care in ambulatory patients with atrial fibrillation. *Eur Heart J* 2012;**33**:2692–2699.
742. Gallagher C, Elliott AD, Wong CX, Rangnekar G, Middeldorp ME, Mahajan R, Lau DH, Sanders P, Hendriks JML. Integrated care in atrial fibrillation: a systematic review and meta-analysis. *Heart* 2017;**103**:1947–1953.
743. Wijtvliet E, Tieleman RG, van Gelder IC, Pluymaekers N, Rienstra M, Folkeringa RJ, Bronzwaer P, Elvan A, Elders J, Tukkie R, Luermans J, Van Asselt A, Van Kuijk SMJ, Tijssen JG, Crijns H, RACE Investigators. Nurse-led vs. usual-care for atrial fibrillation. *Eur Heart J* 2020;**41**:634–641.
744. Russo RJ, Costa HS, Silva PD, Anderson JL, Arshad A, Biederman RW, Boyle NG, Frabizzio JV, Birgersdotter-Green U, Higgins SL, Lampert R, Machado CE, Martin ET, Rivard AL, Rubenstein JC, Schaerf RH, Schwartz JD, Shah DJ, Tomassoni GF, Tominaga GT, Tonkin AE, Uretsky S, Wolff SD. Assessing the risks associated with MRI in patients with a pacemaker or defibrillator. *N Engl J Med* 2017;**376**:755–764.
745. Indik JH, Gimbel JR, Abe H, Alkmim-Teixeira R, Birgersdotter-Green U, Clarke GD, Dickfeld TL, Froelich JW, Grant J, Hayes DL, Heidbuchel H, Idriss SF, Kanal E, Lampert R, Machado CE, Mandrola JM, Nazarian S, Patton KK, Rozner MA, Russo RJ, Shen WK, Shinbane JS, Teo WS, Uribe W, Verma A, Wilkoff BL, Woodard PK. 2017 HRS expert consensus statement on magnetic resonance imaging and radiation exposure in patients with cardiovascular implantable electronic devices. *Heart Rhythm* 2017;**14**:e97–e153.
746. Nazarian S, Hansford R, Rahsepar AA, Weltin V, McVeigh D, Gucuk Ipek E, Kwan A, Berger RD, Calkins H, Lardo AC, Kraut MA, Kamel IR, Zimmerman SL, Halperin HR. Safety of magnetic resonance imaging in patients with cardiac devices. *N Engl J Med* 2017;**377**:2555–2564.
747. Balmer C, Gass M, Dave H, Duru F, Luechinger R. Magnetic resonance imaging of patients with epicardial leads: *in vitro* evaluation of temperature changes at the lead tip. *J Interv Card Electrophysiol* 2019;**56**:321–326.
748. Higgins JV, Gard JJ, Sheldon SH, Espinosa RE, Wood CP, Felmlee JP, Cha YM, Asirvatham SJ, Dalzell C, Acker N, Watson RE Jr, Friedman PA. Safety and outcomes of magnetic resonance imaging in patients with abandoned pacemaker and defibrillator leads. *Pacing Clin Electrophysiol* 2014;**37**:1284–1290.
749. Padmanabhan D, Kella DK, Mehta R, Kapa S, Deshmukh A, Mulpuru S, Jaffe AS, Felmlee JP, Jondal ML, Dalzell CM, Asirvatham SJ, Cha YM, Watson RE Jr, Friedman PA. Safety of magnetic resonance imaging in patients with legacy pacemakers and defibrillators and abandoned leads. *Heart Rhythm* 2018;**15**:228–233.
750. Horwood L, Attili A, Luba F, Ibrahim EH, Parmar H, Stojanovska J, Gadoth-Goodman S, Fette C, Oral H, Bogun F. Magnetic resonance imaging in patients with cardiac implanted electronic devices: focus on contraindications to magnetic resonance imaging protocols. *Europace* 2017;**19**:812–817.
751. Vuorinen AM, Pakarinen S, Jaakkola I, Holmstrom M, Kivisto S, Kaasalainen T. Clinical experience of magnetic resonance imaging in patients with cardiac pacing devices: unrestricted patient population. *Acta Radiol* 2019;**60**:1414–1421.
752. Pulver AF, Puchalski MD, Bradley DJ, Minich LL, Su JT, Saarel EV, Whitaker P, Etheridge SP. Safety and imaging quality of MRI in pediatric and adult congenital heart disease patients with pacemakers. *Pacing Clin Electrophysiol* 2009;**32**:450–456.
753. Wilkoff BL, Bello D, Taborsky M, Vymazal J, Kanal E, Heuer H, Hecking K, Johnson WB, Young W, Ramza B, Akhtar N, Kuepper B, Hunold P, Luechinger R, Puererfellner H, Duru F, Gotte MJ, Sutton R, Sommer T, EnRhythm MRI SureScan Pacing System Study Investigators. Magnetic resonance imaging in patients with a pacemaker system designed for the magnetic resonance environment. *Heart Rhythm* 2011;**8**:65–73.
754. Shenthar J, Milasinovic G, Al Fagih A, Gotte M, Engel G, Wolff S, Tse HF, Herr J, Carrithers J, Cerkvenik J, Nahle CP. MRI scanning in patients with new and existing CapSureFix Novus 5076 pacemaker leads: randomized trial results. *Heart Rhythm* 2015;**12**:759–765.
755. Gimbel JR, Bello D, Schmitt M, Merkely B, Schwitter J, Hayes DL, Sommer T, Schloss EJ, Chang Y, Willey S, Kanal E. Randomized trial of pacemaker and lead system for safe scanning at 1.5 Tesla. *Heart Rhythm* 2013;**10**:685–691.
756. Homsi R, Mellert F, Luechinger R, Thomas D, Doerner J, Luetkens J, Schild HH, Naehle CP. Safety and feasibility of magnetic resonance imaging of the brain at 1.5 Tesla in patients with temporary transmyocardial pacing leads. *Thorac Cardiovasc Surg* 2019;**67**:86–91.
757. Zaremba T, Jakobsen AR, Sogaard M, Thogersen AM, Johansen MB, Madsen LB, Riahi S. Risk of device malfunction in cancer patients with implantable cardiac device undergoing radiotherapy: a population-based cohort study. *Pacing Clin Electrophysiol* 2015;**38**:343–356.
758. Harms W, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Krug D, Piroth MD, Sautter-Bihl ML, Sedlmayer F, Souchon R, Wenz F, Sauer R, Breast Cancer Expert Panel of the German Society of Radiation Oncology. DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. *Strahlenther Onkol* 2016;**192**:199–208.
759. Zecchin M, Severgnini M, Fiorentino A, Malavasi VL, Menegotti L, Alongi F, Catanzariti D, Jereczek-Fossa BA, Stasi M, Russi E, Boriani G. Management of patients with cardiac implantable electronic devices (CIED) undergoing radiotherapy: a consensus document from Associazione Italiana Aritmologia e Cardiostimolazione (AIAC), Associazione Italiana Radioterapia Oncologica (AIRO), Associazione Italiana Fisica Medica (AIFM). *Int J Cardiol* 2018;**255**:175–183.
760. Grant JD, Jensen GL, Tang C, Pollard JM, Kry SF, Krishnan S, Dougherty AH, Gomez DR, Rozner MA. Radiotherapy-induced malfunction in contemporary cardiovascular implantable electronic devices: clinical incidence and predictors. *JAMA Oncol* 2015;**1**:624–632.
761. Zaremba T, Jakobsen AR, Søgaard M, Thøgersen AM, Riahi S. Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators: a literature review. *Europace* 2016;**18**:479–491.
762. Hurkmans CW, Knegjens JL, Oei BS, Maas AJ, Uiterwaal GJ, van der Borden AJ, Ploegmakers MM, van Erven L, Dutch Society of Radiotherapy Oncology. Management of radiation oncology patients with a pacemaker or ICD: a new

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

comprehensive practical guideline in The Netherlands. Dutch Society of Radiotherapy and Oncology (NVRO). *Radiat Oncol* 2012;**7**:198.
763. Gomez DR, Poenisch F, Pinnix CC, Sheu T, Chang JY, Memon N, Mohan R, Rozner MA, Dougherty AH. Malfunctions of implantable cardiac devices in patients receiving proton beam therapy: incidence and predictors. *Int J Radiat Oncol Biol Phys* 2013;**87**:570–575.
764. Tjong FVY, de Ruijter UW, Beurskens NEG, Knops RE. A comprehensive scoping review on transvenous temporary pacing therapy. *Neth Heart J* 2019;**27**:462–473.
765. Hynes JK, Holmes DR Jr, Harrison CE. Five-year experience with temporary pacemaker therapy in the coronary care unit. *Mayo Clin Proc* 1983;**58**:122–126.
766. Ferri LA, Farina A, Lenatti L, Ruffa F, Tiberti G, Piatti L, Savonitto S. Emergent transvenous cardiac pacing using ultrasound guidance: a prospective study versus the standard fluoroscopy-guided procedure. *Eur Heart J Acute Cardiovasc Care* 2016;**5**:125–129.
767. Lang R, David D, Klein HO, Di Segni E, Libhaber C, Sareli P, Kaplinsky E. The use of the balloon-tipped floating catheter in temporary transvenous cardiac pacing. *Pacing Clin Electrophysiol* 1981;**4**:491–496.
768. Ferguson JD, Banning AP, Bashir Y. Randomised trial of temporary cardiac pacing with semirigid and balloon-flotation electrode catheters. *Lancet* 1997;**349**:1883.
769. Austin JL, Preis LK, Crampton RS, Beller GA, Martin RP. Analysis of pacemaker malfunction and complications of temporary pacing in the coronary care unit. *Am J Cardiol* 1982;**49**:301–306.
770. Hill PE. Complications of permanent transvenous cardiac pacing: a 14-year review of all transvenous pacemakers inserted at one community hospital. *Pacing Clin Electrophysiol* 1987;**10**:564–570.
771. Murphy JJ. Current practice and complications of temporary transvenous cardiac pacing. *BMJ* 1996;**312**:1134.
772. Bjornstad CC, Gjertsen E, Thorup F, Gundersen T, Tobiasson K, Otterstad JE. Temporary cardiac pacemaker treatment in five Norwegian regional hospitals. *Scand Cardiovasc J* 2012;**46**:137–143.
773. Lopez Ayerbe J, Villuendas Sabate R, Garcia Garcia C, Rodriguez Leor O, Gomez Perez M, Curos Abadal A, Serra Flores J, Larrousse E, Valle V. [Temporary pacemakers: current use and complications]. *Rev Esp Cardiol* 2004;**57**:1045–1052.
774. Ng ACC, Lau JK, Chow V, Adikari D, Brieger D, Kritharides L. Outcomes of 4838 patients requiring temporary transvenous cardiac pacing: a statewide cohort study. *Int J Cardiol* 2018;**271**:98–104.
775. Metkus TS, Schulman SP, Marine JE, Eid SM. Complications and outcomes of temporary transvenous pacing: an analysis of >360,000 patients from the National Inpatient Sample. *Chest* 2019;**155**:749–757.
776. Lever N, Ferguson JD, Bashir Y, Channon KM. Prolonged temporary cardiac pacing using subcutaneous tunnelled active-fixation permanent pacing leads. *Heart* 2003;**89**:209–210.
777. Rastan AJ, Doll N, Walther T, Mohr FW. Pacemaker dependent patients with device infection—a modified approach. *Eur J Cardiothorac Surg* 2005;**27**:1116–1118.
778. Zei PC, Eckart RE, Epstein LM. Modified temporary cardiac pacing using transvenous active fixation leads and external re-sterilized pulse generators. *J Am Coll Cardiol* 2006;**47**:1487–1489.
779. Kawata H, Pretorius V, Phan H, Mulpuru S, Gadiyaram V, Patel J, Steltzner D, Krummen D, Feld G, Birgersdotter-Green U. Utility and safety of temporary pacing using active fixation leads and externalized re-usable permanent pacemakers after lead extraction. *Europace* 2013;**15**:1287–1291.
780. Timothy PR, Rodeman BJ. Temporary pacemakers in critically ill patients: assessment and management strategies. *AACN Clin Issues* 2004;**15**:305–325.
781. Abd Elaziz ME, Allama AM. Temporary epicardial pacing after valve replacement: incidence and predictors. *Heart Surg Forum* 2018;**21**:E049–E053.
782. Lazarescu C, Mertes PM, Longrois D. [Temporary epicardial pacing following cardiac surgery: practical aspects]. *Ann Fr Anesth Reanim* 2013;**32**:592–601.
783. Bektas F, Soyuncu S. The efficacy of transcutaneous cardiac pacing in ED. *Am J Emerg Med* 2016;**34**:2090–2093.
784. Quast ABE, Beurskens NEG, Ebner A, Wasley R, Vehmeijer JT, Marcovecchio A, Sanghera R, Knops RE, Burke MC. Feasibility of an entirely extracardiac, minimally invasive, temporary pacing system. *Circ Arrhythm Electrophysiol* 2019;**12**:e007182.
785. Sherbino J, Verbeek PR, MacDonald RD, Sawadsky BV, McDonald AC, Morrison LJ. Prehospital transcutaneous cardiac pacing for symptomatic bradycardia or bradyasystolic cardiac arrest: a systematic review. *Resuscitation* 2006;**70**:193–200.
786. American Society of Anesthesiologists. Practice advisory for the perioperative management of patients with cardiac implantable electronic devices: pacemakers and implantable cardioverter-defibrillators: an updated report by the American Society of Anesthesiologists task force on perioperative management of patients with cardiac implantable electronic devices. *Anesthesiology* 2011;**114**:247–261.
787. Crossley GH, Poole JE, Rozner MA, Asirvatham SJ, Cheng A, Chung MK, Ferguson TB, Gallagher JD, Gold MR, Hoyt RH, Irefin S, Kusumoto FM, Moorman LP, Thompson A. The Heart Rhythm Society (HRS)/American Society of Anesthesiologists (ASA) Expert Consensus Statement on the perioperative management of patients with implantable defibrillators, pacemakers and arrhythmia monitors: facilities and patient management this document was developed as a joint project with the American Society of Anesthesiologists (ASA), and in collaboration with the American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). *Heart Rhythm* 2011;**8**:1114–1154.
788. Healey JS, Merchant R, Simpson C, Tang T, Beardsall M, Tung S, Fraser JA, Long L, van Vlymen JM, Manninen P, Ralley F, Venkatraghavan L, Yee R, Prasloski B, Sanatani S, Philippon F, Canadian Cardiovascular Society, Canadian Anesthesiologists' Society, Canadian Heart Rhythm Society. Canadian Cardiovascular Society/Canadian Anesthesiologists' Society/Canadian Heart Rhythm Society joint position statement on the perioperative management of patients with implanted pacemakers, defibrillators, and neurostimulating devices. *Can J Cardiol* 2012;**28**:141–151.
789. Boriani G, Fauchier L, Aguinaga L, Beattie JM, Blomstrom Lundqvist C, Cohen A, Dan GA, Genovesi S, Israel C, Joung B, Kalarus Z, Lampert R, Malavasi VL, Mansourati J, Mont L, Potpara T, Thornton A, Lip GYH, ESC Scientific Document Group. European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS). *Europace* 2019;**21**:7–8.
790. Schulman PM, Treggiari MM, Yanez ND, Henrikson CA, Jessel PM, Dewland TA, Merkel MJ, Sera V, Harukuni I, Anderson RB, Kahl E, Bingham A, Alkayed N, Stecker EC. Electromagnetic interference with protocolized electrosurgery dispersive electrode positioning in patients with implantable cardioverter defibrillators. *Anesthesiology* 2019;**130**:530–540.
791. Gifford J, Larimer K, Thomas C, May P. ICD-ON Registry for perioperative management of CIEDs: most require no change. *Pacing Clin Electrophysiol* 2017;**40**:128–134.
792. Heidbuchel H, Panhuyzen-Goedkoop N, Corrado D, Hoffmann E, Biffi A, Delise P, Blomstrom-Lundqvist C, Vanhees L, Ivarhoff P, Dorwarth U, Pelliccia A, Study Group on Sports Cardiology of the European Association for Cardiovascular Prevention Rehabilitation. Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions Part I: supraventricular arrhythmias and pacemakers. *Eur J Cardiovasc Prev Rehabil* 2006;**13**:475–484.
793. Lampert R. Managing with pacemakers and implantable cardioverter defibrillators. *Circulation* 2013;**128**:1576–1585.
794. Pelliccia A, Fagard R, Bjornstad HH, Anastassakis A, Arbustini E, Assanelli D, Biffi A, Borjesson M, Carre F, Corrado D, Delise P, Dorwarth U, Hirth A, Heidbuchel H, Hoffmann E, Mellwig KP, Panhuyzen-Goedkoop N, Pisani A, Solberg EE, van-Buuren F, Vanhees L, Blomstrom-Lundqvist C, Deligiannis A, Dugmore D, Glikson M, Hoff PI, Hoffmann A, Hoffmann E, Horstkotte D, Nordrehaug JE, Oudhof J, McKenna WJ, Penco M, Priori S, Reybrouck T, Senden J, Spataro A, Thiene G. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J* 2005;**26**:1422–1445.
795. Heidbuchel H, Adami PE, Antz M, Braunschweig F, Delise P, Scherr D, Solberg EE, Wilhelm M, Pelliccia A. Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions: Part 1: supraventricular arrhythmias. A position statement of the Section of Sports Cardiology and Exercise from the European Association of Preventive Cardiology (EAPC) and the European Heart Rhythm Association (EHRA), both associations of the European Society of Cardiology. *Eur J Prev Cardiol* 2020;doi: 10.1177/2047487320925635
796. Pelliccia A, Sharma S, Gati S, Back M, Borjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M, ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2020;**42**:17–96.
797. Lampert R, Olshansky B, Heidbuchel H, Lawless C, Saarel E, Ackerman M, Calkins H, Estes NAM, Link MS, Maron BJ, Marcus F, Scheinman M, Wilkoff BL, Zipes DP, Berul CI, Cheng A, Jordaens L, Law I, Loomis M, Willems R, Barth C, Broos K, Brandt C, Dziura J, Li F, Simone L, Vandenberghe K, Cannom D. Safety of sports for athletes with implantable cardioverter-defibrillators: long-term results of a prospective multinational registry. *Circulation* 2017;**135**:2310–2312.
798. Heidbuchel H, Arbelo E, D'Ascenzi F, Borjesson M, Boveda S, Castelletti S, Miljoen H, Mont L, Niebauer J, Papadakis M, Pelliccia A, Saenen J, Sanz de la

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Garza M, Schwartz PJ, Sharma S, Zeppenfeld K, Corrado D. Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions. Part 2: ventricular arrhythmias, channelopathies, and implantable defibrillators. *Europace* 2021;**23**:147–148.
799. Hauser RG, Hayes DL, Kallinen LM, Cannom DS, Epstein AE, Almquist AK, Song SL, Tyers GF, Vlay SC, Irwin M. Clinical experience with pacemaker pulse generators and transvenous leads: an 8-year prospective multicenter study. *Heart Rhythm* 2007;**4**:154–160.
800. Merchant FM, Tejada T, Patel A, El-Khalil J, Desai Y, Keeling B, Lattouf OM, Leon AR, El-Chami MF. Procedural outcomes and long-term survival associated with lead extraction in patients with abandoned leads. *Heart Rhythm* 2018;**15**:855–859.
801. Diemberger I, Mazzotti A, Giulia MB, Biffi M, Cristian M, Massaro G, Matteo M, Martignani C, Letizia ZM, Ziacchi M, Reggiani B, Reggiani ML, Battistini P, Boriani G. From lead management to implanted patient management: systematic review and meta-analysis of the last 15 years of experience in lead extraction. *Expert Rev Med Devices* 2013;**10**:551–573.
802. Bongiorni MG, Kennergren C, Butter C, Deharo JC, Kutarski A, Rinaldi CA, Romano SL, Maggioni AP, Andarala M, Auricchio A, Kuck KH, Blomström-Lundqvist C, ELECTRa Investigators. The European Lead Extraction ConTRolled (ELECTRa) study: a European Heart Rhythm Association (EHRA) registry of transvenous lead extraction outcomes. *Eur Heart J* 2017;**38**:2995–3005.
803. Segreti L, Rinaldi CA, Claridge S, Svendsen JH, Blomstrom-Lundqvist C, Auricchio A, Butter C, Dagres N, Deharo JC, Maggioni AP, Kutarski A, Kennergren C, Laroche C, Kempa M, Magnani A, Casteigt B, Bongiorni MG, ELECTRa Investigators. Procedural outcomes associated with transvenous lead extraction in patients with abandoned leads: an ESC-EHRA ELECTRa (European Lead Extraction ConTRolled) registry sub-analysis. *Europace* 2019;**21**:645–654.
804. Parthiban N, Esterman A, Mahajan R, Twomey DJ, Pathak RK, Lau DH, Roberts-Thomson KC, Young GD, Sanders P, Ganesan AN. Remote monitoring of implantable cardioverter-defibrillators: a systematic review and meta-analysis of clinical outcomes. *J Am Coll Cardiol* 2015;**65**:2591–2600.
805. Garcia-Fernandez FJ, Osca Asensi J, Romero R, Fernandez Lozano I, Larrazabal JM, Martinez Ferrer J, Ortiz R, Pombo M, Tornes FJ, Moradi Kolbolandi M. Safety and efficiency of a common and simplified protocol for pacemaker and defibrillator surveillance based on remote monitoring only: a long-term randomized trial (RM-ALONE). *Eur Heart J* 2019;**40**:1837–1846.
806. Mabo P, Victor F, Bazin P, Ahres S, Babuty D, Da Costa A, Binet D, Daubert JC, COMPAS Trial Investigators. A randomized trial of long-term remote monitoring of pacemaker recipients (the COMPAS trial). *Eur Heart J* 2012;**33**:1105–1111.
807. Vogtmann T, Stiller S, Marek A, Kespohl S, Gomer M, Kühlkamp V, Zach G, Löscher S, Baumann G. Workload and usefulness of daily, centralized home monitoring for patients treated with CIEDs: results of the MoniC (Model Project Monitor Centre) prospective multicentre study. *Europace* 2013;**15**:219–226.
808. Nielsen JC, Kautzner J, Casado-Arroyo R, Burri H, Callens S, Cowie MR, Dickstein K, Drossart I, Geneste G, Erkin Z, Hyafil F, Kraus A, Kutyifa V, Marin E, Schulze C, Slotwiner D, Stein K, Zanero S, Heidbuchel H, Fraser AG. Remote monitoring of cardiac implanted electronic devices: legal requirements and ethical principles—ESC Regulatory Affairs Committee/EHRA joint task force report. *Europace* 2020;**22**:1742–1758.
809. Perl S, Stiegler P, Rotman B, Prenner G, Lercher P, Anelli-Monti M, Sereinigg M, Riegelnik V, Kvas E, Kos C, Heinzel FR, Tscheliessnigg KH, Pieske B. Socio-economic effects and cost saving potential of remote patient monitoring (SAVE-HM trial). *Int J Cardiol* 2013;**169**:402–407.
810. Ricci RP, Morichelli L, Santini M. Remote control of implanted devices through Home Monitoring technology improves detection and clinical management of atrial fibrillation. *Europace* 2009;**11**:54–61.
811. McCance T, McCormack B, Dewing J. An exploration of person-centredness in practice. *Online J Issues Nurs* 2011;**16**:1.
812. Kitson A, Marshall A, Bassett K, Zeitz K. What are the core elements of patient-centred care? A narrative review and synthesis of the literature from health policy, medicine and nursing. *J Adv Nurs* 2013;**69**:4–15.
813. Ekman I, Swedberg K, Taft C, Lindseth A, Norberg A, Brink E, Carlsson J, Dahlin-Ivanoff S, Johansson IL, Kjellgren K, Liden E, Ohlen J, Olsson LE, Rosen H, Rydmark M, Sunnerhagen KS. Person-centered care—ready for prime time. *Eur J Cardiovasc Nurs* 2011;**10**:248–251.
814. Kiesler DJ, Auerbach SM. Optimal matches of patient preferences for information, decision-making and interpersonal behavior: evidence, models and interventions. *Patient Educ Couns* 2006;**61**:319–341.
815. Alston C, Paget L, Halvorson G, Novelli B, Guest J, McCabe P, Hoffman K, Koepke C, Simon M, Sutton S, Okun S, Wicks P, Undem T, Rohrbach V, von Kohorn I. *Communicating with Patients on Health Care Evidence*. Washington, DC: Institute of Medicine of the National Academies; 2012. http://www.iom.edu/evidence.
816. Hibbard JH, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences; fewer data on costs. *Health Aff (Millwood)* 2013;**32**:207–214.
817. Charles C, Gafni A, Whelan T. Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). *Soc Sci Med* 1997;**44**:681–692.
818. Towle A, Godolphin W. Framework for teaching and learning informed shared decision making. *BMJ* 1999;**319**:766–771.
819. Makoul G, Clayman ML. An integrative model of shared decision making in medical encounters. *Patient Educ Couns* 2006;**60**:301–312.
820. Pitcher D, Soar J, Hogg K, Linker N, Chapman S, Beattie JM, Jones S, George R, McComb J, Glancy J, Patterson G, Turner S, Hampshire S, Lockey A, Baker T, Mitchell S. Cardiovascular implanted electronic devices in people towards the end of life, during cardiopulmonary resuscitation and after death: guidance from the Resuscitation Council (UK), British Cardiovascular Society and National Council for Palliative Care. *Heart* 2016;**102 Suppl 7**:A1-a17.
821. The SHARE Approach. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html (25 May 2021)
822. International Patient Decision Aid Standards (IPDAS). IPDAS Collaboration Background Document,. ipdas.ohri.ca/IPDAS_Background.pdf (25 May 2021)
823. Stacey D, Legare F, Lewis K, Barry MJ, Bennett CL, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2017;**4**:Cd001431.
824. De Oliveira GS Jr, McCarthy RJ, Wolf MS, Holl J. The impact of health literacy in the care of surgical patients: a qualitative systematic review. *BMC Surg* 2015;**15**:86.
825. Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Viera A, Crotty K, Holland A, Brasure M, Lohr KN, Harden E, Tant E, Wallace I, Viswanathan M. Health literacy interventions and outcomes: an updated systematic review. *Evid Rep Technol Assess (Full Report)* 2011:1–941.
826. Wolf A, Vella R, Fors A. The impact of person-centred care on patients' care experiences in relation to educational level after acute coronary syndrome: secondary outcome analysis of a randomised controlled trial. *Eur J Cardiovasc Nurs* 2019;**18**:299–308.
827. Marcus C. Strategies for improving the quality of verbal patient and family education: a review of the literature and creation of the EDUCATE model. *Health Psychol Behav Med* 2014;**2**:482–495.
828. Friedman AJ, Cosby R, Boyko S, Hatton-Bauer J, Turnbull G. Effective teaching strategies and methods of delivery for patient education: a systematic review and practice guideline recommendations. *J Cancer Educ* 2011;**26**:12–21.
829. Sustersic M, Gauchet A, Foote A, Bosson JL. How best to use and evaluate Patient Information Leaflets given during a consultation: a systematic review of literature reviews. *Health Expect* 2017;**20**:531–542.
830. Elwyn G, Lloyd A, Joseph-Williams N, Cording E, Thomson R, Durand MA, Edwards A. Option grids: shared decision making made easier. *Patient Educ Couns* 2013;**90**:207–212.
831. Dwamena F, Holmes-Rovner M, Gaulden CM, Jorgenson S, Sadigh G, Sikorskii A, Lewin S, Smith RC, Coffey J, Olomu A. Interventions for providers to promote a patient-centred approach in clinical consultations. *Cochrane Database Syst Rev* 2012;**12**:Cd003267.
832. Olsson LE, Jakobsson Ung E, Swedberg K, Ekman I. Efficacy of person-centred care as an intervention in controlled trials—a systematic review. *J Clin Nurs* 2013;**22**:456–465.
833. McMillan SS, Kendall E, Sav A, King MA, Whitty JA, Kelly F, Wheeler AJ. Patient-centered approaches to health care: a systematic review of randomized controlled trials. *Med Care Res Rev* 2013;**70**:567–596.
834. Ekman I, Wolf A, Olsson LE, Taft C, Dudas K, Schaufelberger M, Swedberg K. Effects of person-centred care in patients with chronic heart failure: the PCC-HF study. *Eur Heart J* 2012;**33**:1112–1119.
835. Ulin K, Olsson LE, Wolf A, Ekman I. Person-centred care—an approach that improves the discharge process. *Eur J Cardiovasc Nurs* 2016;**15**:e19–e26.
836. Dudas K, Olsson LE, Wolf A, Swedberg K, Taft C, Schaufelberger M, Ekman I. Uncertainty in illness among patients with chronic heart failure is less in person-centred care than in usual care. *Eur J Cardiovasc Nurs* 2013;**12**:521–528.
837. Minchin M, Roland M, Richardson J, Rowark S, Guthrie B. Quality of care in the United Kingdom after removal of financial incentives. *N Engl J Med* 2018;**379**:948–957.
838. Song Z, Ji Y, Safran DG, Chernew ME. Health care spending, utilization, and quality 8 years into global payment. *N Engl J Med* 2019;**381**:252–263.
839. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B, Gale CP. European Society of

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021

Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Heart J Qual Care Clin Outcomes* 2020;TO BE UPDATED:doi: 10.1093/ehjqcco/qcaa1069. Online ahead of print.

840. Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP, Dagres N, Reviewers, Boveda S, Deneke T, Defaye P, Conte G, Lenarczyk R, Providencia R, Guerra JM, Takahashi Y, Pisani C, Nava S, Sarkozy A, Glotzer TV, Martins Oliveira M. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace* 2021;**23**:494–495.
841. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
842. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European unified registries on heart care evaluation and randomized trials. *Eur Heart J* 2019;**40**:2745–2749.
843. Zhang S, Gaiser S, Kolominsky-Rabas PL. Cardiac implant registries 2006–2016: a systematic review and summary of global experiences. *BMJ Open* 2018;**8**:e019039.
844. Aktaa S, Abdin A, Arbelo E, Burri H, Vernooy K, Blomström-Lundqvist C, Boriani G, Defaye P, Deharo J-C, Drossart I, Foldager D, Gold MR, Johansen JB, Leyva F, Linde C, Michowitz Y, Kronborg MB, Slotwiner D, Steen T, Tolosana JM, Tzeis S, Varma N, Glikson M, Nielsen J-C, Gale CP. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing Developed by the Working Group for Cardiac Pacing Quality Indicators in collaboration with the European Heart Rhythm Association of the European Society of Cardiology. *Europace* 2021;doi:10.1093/europace/euab193.

Downloaded from https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab364/6358547 by guest on 08 September 2021