



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias

use the right tool for the right outcome, in the right population

Nielsen, Jens Cosedis; Lin, Yenn Jiang; de Oliveira Figueiredo, Marcio Jansen; Sepehri Shamloo, Alireza; Alfie, Alberto; Boveda, Serge; Dagres, Nikolaos; Di Toro, Dario; Eckhardt, Lee L.; Ellenbogen, Kenneth; Hardy, Carina; Ikeda, Takanori; Jaswal, Aparna; Kaufman, Elizabeth; Krahm, Andrew; Kusano, Kengo; Kutyla, Valentina; Lim, Han S.; Lip, Gregory Y.H.; Nava-Townsend, Santiago; Pak, Hui Nam; Diez, Gerardo Rodríguez; Sauer, William; Saxena, Anil; Svendsen, Jesper Hastrup; Vanegas, Diego; Vaseghi, Marmar; Wilde, Arthur; Bunch, T Jared; ESC Scientific Document Group

Published in:
Europace

DOI (link to publication from Publisher):
[10.1093/europace/euaa065](https://doi.org/10.1093/europace/euaa065)

Creative Commons License
CC BY 4.0

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Nielsen, J. C., Lin, Y. J., de Oliveira Figueiredo, M. J., Sepehri Shamloo, A., Alfie, A., Boveda, S., Dagres, N., Di Toro, D., Eckhardt, L. L., Ellenbogen, K., Hardy, C., Ikeda, T., Jaswal, A., Kaufman, E., Krahm, A., Kusano, K., Kutyla, V., Lim, H. S., Lip, G. Y. H., ... ESC Scientific Document Group (2020). European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. *Europace*, 22(8), 1147–1148at.
<https://doi.org/10.1093/europace/euaa065>

European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population

Jens Cosedis Nielsen (EHRA Chair)^{1*}, Yenn-Jiang Lin (APHRS Co-Chair)², Marcio Jansen de Oliveira Figueiredo (LAHRS Co-Chair)³, Alireza Sepehri Shamloo⁴, Alberto Alfie⁵, Serge Boveda⁶, Nikolaos Dagres⁴, Dario Di Toro⁷, Lee L. Eckhardt⁸, Kenneth Ellenbogen⁹, Carina Hardy¹⁰, Takanori Ikeda¹¹, Aparna Jaswal¹², Elizabeth Kaufman¹³, Andrew Krahn¹⁴, Kengo Kusano¹⁵, Valentina Kutyifa^{16,17}, Han S. Lim^{18,19}, Gregory Y.H. Lip^{20,21}, Santiago Nava-Townsend²², Hui-Nam Pak²³, Gerardo Rodríguez Díez²⁴, William Sauer²⁵, Anil Saxena²⁶, Jesper Hastrup Svendsen^{27,28}, Diego Vanegas²⁹, Marmar Vaseghi³⁰, Arthur Wilde³¹, and T. Jared Bunch (HRS Co-Chair)³², ESC Scientific Document Group: Alfred E. Buxton³³, Gonzalo Calvimontes³⁴, Tze-Fan Chao², Lars Eckardt³⁵, Heidi Estner³⁶, Anne M. Gillis³⁷, Rodrigo Isa³⁸, Josef Kautzner³⁹, Philippe Maury⁴⁰, Joshua D. Moss⁴¹, Gi-Byung Nam⁴², Brian Olshansky⁴³, Luis Fernando Pava Molano⁴⁴, Mauricio Pimentel⁴⁵, Mukund Prabhu⁴⁶, Wendy S. Tzou⁴⁷, Philipp Sommer⁴⁸, Janice Swampillai⁴⁹, Alejandro Vidal⁵⁰, Thomas Deneke (Reviewer Coordinator)⁵¹, Gerhard Hindricks⁴, and Christophe Leclercq (ESC-CPG representative)⁵²

¹Department of Cardiology, Aarhus University Hospital, Skejby, Denmark; ²Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan;

³Department of Internal Medicine, Electrophysiology Service, University of Campinas Hospital, Campinas, Brazil; ⁴Department of Electrophysiology, Leipzig Heart Center at University of Leipzig, Leipzig, Germany; ⁵Division of Electrophysiology, Instituto Cardiovascular Adventista, Clinica Bazterrica, Buenos Aires, Argentina; ⁶Department of Cardiology, Clinique Pasteur, Toulouse, France; ⁷Department of Cardiology, Division of Electrophysiology, Argerich Hospital and CEMIC, Buenos Aires, Argentina; ⁸Department of Medicine, University of Wisconsin-Madison, Madison, WI, USA; ⁹Division of Cardiology, Virginia Commonwealth University School of Medicine, Richmond, USA; ¹⁰Arrhythmia Unit, Heart Institute, University of São Paulo Medical School, Instituto do Coração - InCor - Faculdade de Medicina de São Paulo-São Paulo, Brazil; ¹¹Department of Cardiovascular Medicine, Faculty of Medicine, Toho University, Japan; ¹²Department of Cardiac Electrophysiology, Fortis Escorts Heart Institute, Okhla Road, New Delhi, India;

*Corresponding author. Tel: +4578452039; fax: +4578452127. E-mail address: Jenniels@rm.dk

Developed in partnership with and endorsed by the European Heart Rhythm Association (EHRA), a branch of the European Society of Cardiology (ESC), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS).

This article has been co-published with permission in *EP Europace*, *Journal of Arrhythmia*, *Heart Rhythm*, and *Journal of Interventional Cardiac Electrophysiology*. © European Heart Rhythm Association, Asia Pacific Heart Rhythm Society, Heart Rhythm Society and Latin American Heart Rhythm Society, 2020.

These 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.

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

¹³The Heart and Vascular Research Center, Metrohealth Campus of Case Western Reserve University, Cleveland, OH, USA; ¹⁴Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, Canada; ¹⁵Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan; ¹⁶University of Rochester, Medical Center, Rochester, USA; ¹⁷Semmelweis University, Heart and Vascular Center, Budapest, Hungary; ¹⁸Department of Cardiology, Austin Health, Melbourne, VIC, Australia; ¹⁹University of Melbourne, Melbourne, VIC, Australia; ²⁰Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; ²¹Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; ²²Department of Electrocardiology, National Institute of Cardiology "Ignacio Chavez," Mexico City, Mexico; ²³Division of Cardiology, Department of Internal Medicine, Yonsei University Health System, Seoul, Republic of Korea; ²⁴Department of Electrophysiology and Hemodynamic, Arrhythmias Unity, CMN 20 de Noviembre, ISSSTE, Mexico City, Mexico; ²⁵Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, USA; ²⁶Department of Cardiac Electrophysiology, Fortis Escorts Heart Institute, Okhla Road, New Delhi, India; ²⁷Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; ²⁸Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; ²⁹Hospital Militar Central, Fundarritmia, Bogotá, Colombia; ³⁰Los Angeles UCLA Cardiac Arrhythmia Center, UCLA Health System, David Geffen School of Medicine, at UCLA, USA; ³¹Amsterdam UMC, University of Amsterdam, Heart Center; Department of Clinical and Experimental Cardiology, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands; ³²Department of Medicine, Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, USA; ³³Department of Medicine, The Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Boston, MA, USA; ³⁴Asociación Guatemalteca de Cardiología, Guatemala, Guatemala; ³⁵Department for Cardiology, Electrophysiology, University Hospital Münster, Münster, Germany; ³⁶Department of Medicine, I, University Hospital Munich, Ludwig-Maximilians University, Munich, Germany; ³⁷University of Calgary - Libin Cardiovascular Institute of Alberta, Calgary, AB, Canada; ³⁸Clínica RedSalud Vitacura and Hospital el Carmen de Maipú, Santiago, Chile; ³⁹Institute for Clinical and Experimental Medicine, Prague, Czech Republic; ⁴⁰Rangueil University Hospital, Toulouse, France; ⁴¹Department of Cardiac Electrophysiology, University of California San Francisco, San Francisco, USA; ⁴²Division of Cardiology, Asan Medical Center, University of Ulsan, College of Medicine, Seoul, Republic of Korea; ⁴³University of Iowa Carver College of Medicine, Iowa City, USA; ⁴⁴Fundación Valle del Lili, Cali, Colombia; ⁴⁵Cardiology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil; ⁴⁶Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India; ⁴⁷Department of Cardiology/Cardiac Electrophysiology, University of Colorado Anschutz Medical Campus, Aurora, USA; ⁴⁸Clinic for Electrophysiology, Herz- und Diabeteszentrum, Clinic for Electrophysiology, Ruhr-Universität Bochum, Bad Oeynhausen, Germany; ⁴⁹Waikato Hospital, Hamilton, New Zealand; ⁵⁰Division of Cardiology, McGill University Health Center, Montreal, Canada; ⁵¹Clinic for Cardiology II (Interventional Electrophysiology), Heart Center Bad Neustadt, Bad Neustadt a.d. Saale, Germany and ; and ⁵²Univ Rennes, CHU Rennes, INSERM, Rennes, France

Online publish-ahead-of-print 15 June 2020

Table of contents

Introduction	1148a
Evidence review	1148a
Relationships with industry and other conflicts	1148a
General tools for risk assessment, strengths, limitations, and pretest probability	1148b
Value of clinical history and characteristics including clinical risk scores such as CHA ₂ DS ₂ -VASc	1148b
Electrocardiographic methods including monitoring	1148c
Electrocardiographic methods	1148c
P wave and PR interval	1148c
QRS, QT interval, and T-wave	1148d
Ambulatory electrocardiogram monitoring	1148e
Imaging	1148e
Risk assessment of ventricular tachyarrhythmia using imaging modalities	1148e
Imaging modalities for atrial arrhythmias	1148e
Invasive electrophysiological study	1148f
Implantable loop recorders	1148g
Implantable loop recorder to diagnose unexplained syncope/atrial fibrillation with cryptogenic stroke	1148g
Implantable loop recorder to diagnose atrial and ventricular arrhythmia events	1148g
Wearables/direct to consumer	1148g
Biomarkers, tissue, genetics	1148h
Biomarkers	1148h
Tissue diagnostics	1148i
Genetics	1148i
Artificial intelligence	1148i
How to assess risk for atrial fibrillation in specific populations	1148i
Patients of advanced age	1148i
Patients with heart failure	1148k
Clinical risk factors	1148l
Electrocardiography	1148l
Biomarkers	1148l
Imaging	1148l
Genetics	1148l

Patients with obesity, hypertension, diabetes, sleep apnoea or structural heart disease	1148m
Patients who have undergone cardiac surgery	1148n
Patients with cryptogenic stroke	1148n
How to assess high risk of atrial fibrillation in professional athletes	1148o
Atrial fibrillation risk in athletes—general	1148o
Atrial fibrillation risk in athletes—exercise paradox	1148o
Atrial fibrillation risk in athletes—structural cardiac changes ...	1148p
Patients with inherited rhythm disease (long QT syndrome/short QT syndrome/catecholaminergic polymorphic ventricular tachyarrhythmia/Brugada syndrome)	1148p
How to assess risk for adverse outcomes in patients with atrial fibrillation	1148q
Risk assessment for stroke/transient ischaemic attack/cognitive decline	1148q
Risk assessment for stroke/transient ischaemic attack status post-left atrial appendage occlusion/ligation	1148q
Risk for heart failure incidence and progression	1148r
Risk for death in atrial fibrillation patients	1148s
Risk of adverse outcomes in patients treated with catheter ablation	1148t
Post-ablation atrial fibrillation recurrence	1148t
Other adverse outcomes	1148t
Catheter ablation in Wolff–Parkinson–White patients	1148u
Risk of adverse outcomes in patients treated with surgical Maze	1148u
Atrial fibrillation surgery	1148u
Surgical Maze in patients with concomitant heart surgery ...	1148u
Stand-alone surgical Maze	1148u
Left atrial appendage exclusion or removal during surgical Maze	1148u
How to assess risk for ventricular tachyarrhythmia in specific populations	1148u
Patients with ischaemic heart disease	1148u
Secondary prevention of ventricular tachyarrhythmia/ventricular fibrillation in patients with ICM	1148v
Primary prevention of ventricular tachyarrhythmia/ventricular fibrillation in patients with ICM and a left ventricular ejection fraction $\leq 35\%$	1148v

Primary prevention of ventricular tachyarrhythmia/ ventricular fibrillation in patients with ICM and left ventricular ejection fraction > 35%	1148v
Patients with non-ischaemic heart failure	1148w
Patients with inflammatory cardiomyopathies	1148x
Patients with congenital heart disease	1148x
Patients with inherited arrhythmia diseases (Inherited channelopathies and inherited structural diseases including arrhythmogenic right ventricular cardiomyopathy)	1148y
Risk stratification in patients with arrhythmogenic cardiomyopathy, specified for arrhythmogenic right ventricular cardiomyopathy	1148z
Patients with Chagas disease	1148aa
How to assess risk for adverse outcomes in patients with ventricular tachyarrhythmia	1148aa
Risk for appropriate and inappropriate implantable cardioverter-defibrillator therapies	1148aa
Appropriate shock predictors	1148ab
Inappropriate shock predictors	1148ab
Risk for heart failure incidence and progression	1148ab
Risk for death in ventricular tachyarrhythmia patients	1148ac
Risk of adverse outcomes in patients treated with catheter ablation	1148ad
How to assess risk for adverse outcome in patients with other specific cardiac conditions	1148ae
Patients with ventricular premature contractions	1148ae
Premature ventricular complex frequency	1148ae
Premature ventricular complex morphology	1148ae
Premature ventricular complex coupling interval	1148ae
Patients with supraventricular tachyarrhythmia such as Wolff–Parkinson–White syndrome and focal atrial tachycardia	1148ae
Summary	1148af
References	1148ah

Introduction

Patients with cardiac diseases or conditions with high risk of developing cardiac diseases undergo risk assessment by cardiologists, primary care physicians, and scientists based on referral for more advanced risk assessment strategies, institution of preventive treatments, counselling of patients and their relatives, and selection of patients for scientific trials. The various methods used for risk assessment differ with respect to availability, complexity, and usefulness in different patient populations. Parameters associated with increased risk of e.g. death may also be associated with higher risk of other adverse outcomes. However, risk assessment strategies including specific methods for risk assessment and risk scores should be used only for the purposes for which they are validated.

This expert consensus statement of the European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS) summarizes the consensus of the international writing group based on a thorough review of the medical literature regarding risk assessment in cardiac arrhythmias. To create a tool for clinicians to perform rational and evidence-based risk stratification, this task force was set down by EHRA, HRS, LAHRS, and APHRS, including representatives from each of the four societies.

With this document, we intend to describe and review status of performing risk assessment in different patient populations with cardiac diseases or conditions with high risk of developing such. Our objectives are to raise awareness of using the right risk assessment tool for a given outcome in a given population, and to provide physicians with practical proposals that may lead to improvement of patient care in this regard. For quick reference, sub-chapters start with a short section on consensus statements. The document concludes with a summary of consensus statements.

Evidence review

Members of the Task Force were asked to perform a detailed literature review using PubMed and EMBASE, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes for which data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests are considered, as are frequency of follow-up and cost-effectiveness. In controversial areas, or with regard to issues without evidence other than usual clinical practice, consensus was achieved by agreement of the expert panel after thorough deliberations. This document was prepared by the Task Force and peer-reviewed by official external reviewers representing EHRA, HRS, APHRS, and LAHRS.

Consensus statements are evidence-based and derived primarily from published data or determined through consensus opinion if no data available. Current systems of ranking level of evidence are becoming complicated in a way that might compromise their practical utility.¹ In contrast to guidelines, we opted for an easier user-friendly system of ranking using ‘coloured hearts’ that should allow physicians to easily assess the current status of the evidence and consequent guidance (Table 1). This EHRA grading of consensus statements does not have separate definitions of the level of evidence. The categorization used for consensus statements must not be considered directly similar to the one used for official society guideline recommendations which apply a classification (Class I–III) and level of evidence (A, B, and C) to recommendations used in official guidelines.




Thus, a green heart indicates a ‘should do this’ consensus statement or indicated risk assessment strategy based on at least one randomized trial or supported by strong observational evidence that it is beneficial and effective. A yellow heart indicates general agreement and/or scientific evidence favouring a ‘may do this’ statement or the usefulness/efficacy of a risk assessment strategy or procedure. A ‘yellow heart’ symbol may be supported by randomized trials based on a small number of patients or not widely applicable. Risk assessment strategies for which there is scientific evidence of no benefit or potential harm and should not be used (‘do not do this’) are indicated by a red heart.

Finally, this consensus document includes evidence and expert opinions from several countries. The risk assessment approaches discussed may therefore include tests not approved by governmental regulatory agencies in all countries.

Relationships with industry and other conflicts

All members of the writing group, as well as reviewers, have disclosed any potential conflicts of interest. Details are available in [Supplementary material online](#).

Table 1 Scientific rationale of consensus statements

Definitions related to a treatment or procedure	Consensus statement instruction	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk).	'Should do this'	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on a small number of patients or not widely applicable.	'May do this'	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	'Do not do this'	

The categorization for our consensus document should not be considered directly similar to the one used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

All consensus statements were voted upon by the writing committee independently and reached the predefined level of $\geq 75\%$ consensus for inclusion in consensus statement tables. Each partner society officially reviewed the document, and all reviewer comments were addressed. Each partner society approved the final document and consensus statements.

General tools for risk assessment, strengths, limitations, and pretest probability

Value of clinical history and characteristics including clinical risk scores such as CHA₂DS₂-VASc

Clinical assessment of the patient with cardiac arrhythmias starts with a good clinical history and basic investigations for an underlying aetiological factor for the arrhythmia or its associated complication(s). In addition, an assessment of the risks and benefits of any therapeutic intervention should be made, and appropriate management initiated.

Following on from clinical history and assessment, there is a proposal toward a more integrated and holistic approach to arrhythmia management, as evident in guidelines. Such an integrated approach requires multidisciplinary teams of healthcare professionals, patient involvement, access to treatment options, and decision-support tools

to optimize the patient journey. Many proposals have been made towards the operationalization of such an integrated approach to risk assessment and practical management in cardiac arrhythmias, which has been of varying complexity. As an example, the management of atrial fibrillation (AF) has been simplified into the ABC pathway ('A' Avoid stroke with Anticoagulation; 'B' Better symptom management, with patient-centred and symptom-directed decisions on rate or rhythm control; 'C' Cardiovascular and comorbidity risk management), which has been shown to be associated with improved clinical outcomes and reduced healthcare costs.^{2–6}

This makes a strong argument for using the right approaches and clinical tools for patient assessment, but using them appropriately for the reasons they were first proposed (e.g. stroke risk scores to assess stroke risk, and not other outcomes).

Taking AF as an *illustrative example* with regard to using the right score for the right reason there are many risk factors for stroke (but the more common and validated ones have been used to formulate risk stratification tools).⁷ The most common in use is the CHA₂DS₂-VASc score⁸ but it is not meant to include every possible stroke risk factor, and was designed to be simple, reductionist and practical to help decision-making for stroke risk. As with all clinical scores based on clinical factors, the CHA₂DS₂-VASc score only performs modestly for predicting high-risk patients who sustain events. The use of more clinical factors and biomarkers improves prediction (at least statistically) but the practical added value is marginal, and less impressive in real-world cohorts.^{9,10} Use of simplified scores to artificially categorize patients into low-, moderate- and high-risk strata can be problematic, as in the real-world patients do not necessarily fall into three neat categories of risk. Also, not all risk factors carry equal weight, hence, the move to focus the initial decision-making on identifying low-risk patients who do not need antithrombotic therapy first, following which stroke prevention can be offered to AF patients with ≥ 1 stroke risk factors.⁹ Stroke risk is also highly dynamic, and although logistically challenging, a clinical reassessment may be needed every 4–6 months to optimize risk re-assessment.^{11–13} As the CHA₂DS₂-VASc is a cluster of common cardiovascular risk factors, it is predictive of death, cardiovascular hospitalizations, and other adverse outcomes that the CHA₂DS₂-VASc score was not designed for. Also, given that many components of the CHA₂DS₂-VASc score are associated with incident AF, the CHA₂DS₂-VASc score is used to predict new onset AF, again something it was not designed for. Another misuse of the CHA₂DS₂-VASc score is the prediction of bleeding risk. Nevertheless, formal comparisons show that the CHA₂DS₂-VASc (and older CHA₂DS₂) score are inferior to a formal bleeding risk score such as the HAS-BLED score, for the prediction of major bleeding in AF patients.¹⁴

Indeed, bleeding risk is also highly dynamic, and the appropriate use of bleeding risk scores such as HAS-BLED is to address modifiable bleeding risk factors (e.g. uncontrolled hypertension, labile INR, concomitant aspirin, or NSAID use) then to schedule the 'high risk' patients for early and more frequent follow-up visits (e.g. 4 weeks rather than 4 months).¹⁵ Only focusing on modifiable bleeding risk factors is an inferior strategy for bleeding risk assessment, compared to the HAS-BLED score.⁸








We should use the scores only for the purposes they were designed for. Attention to appropriate methodology, statistics, etc.—as well as other clinical states merits consideration e.g. sudden death

prediction (or failed ablation, device infection, etc.), Charlson Comorbidity Index, frailty etc.—but using the right score designed for that purpose.

If appropriately used, some of these (simplified) tools help with clinical management. Indeed, the value of a medical test is measured by its accuracy as well as how it impacts medical decisions and ultimately patient health. As medical tests are considered and new ones emerge, they should be considered and evaluated in a framework of accuracy and patient impact.¹⁶ A test must not only be accurate, but also feasible. Tests that are difficult to reproduce, subject to technical failures, or difficult to interpret are likely to impact patient care as a consequence of a primary failure to produce a definitive and actionable result.

Electrocardiographic methods including monitoring

development of AF, where maximum P wave duration was a significant independent risk marker for the development of AF over 10 years.²⁰ This observation was confirmed by epidemiologic/population studies (including ARIC and the Copenhagen ECG studies) that showed increased risk of AF in patients with prolonged P wave duration and PR interval prolongation,^{21–23} and summarized in a review by Nikolaidou *et al.*²⁴ Moreover, a prolonged P wave duration was determined as a sensitive predictor of post-operative AF in patients undergoing coronary artery bypass grafting (CABG).²⁵ The definition of an abnormal P wave varies greatly depending on how it is measured, and definitions vary depending on whether P wave area, duration, terminal forces in lead V1 or signal-averaged P wave are analysed. Abnormal P wave morphology was associated with incident stroke in the Multi-Ethnic Study of Atherosclerosis.²⁶ The prognostic significance of PR interval prolongation, which is variably defined as PR intervals greater than 196–220 ms, is controversial and depends

Electrocardiographic methods including monitoring	Class	References
Twelve-lead electrocardiogram (ECG) should be obtained in all patients undergoing evaluation for known or suspected heart disease.		17
The 12-lead ECG provides diagnostic and prognostic information in patients with inherited high-risk syndromes including long QT syndrome (LQTS), short QT syndrome, Brugada Syndrome, and arrhythmogenic cardiomyopathy (ACM) and should be obtained.		17
Exercise ECG provides diagnostic and prognostic information for patients with LQTS ACM, hypertrophic cardiomyopathy (HCM), catecholaminergic polymorphic ventricular tachycardia, and documented or suspected arrhythmias related to exertion, and should be obtained.		17
Ambulatory ECG evidence of non-sustained ventricular tachycardia provides prognostic information in ischaemic cardiomyopathy, ACM, and HCM and should be obtained.		17
The signal-averaged ECG and QRS fragmentation may aid in the diagnosis of ACM.		18
The signal-averaged ECG and QRS fragmentation may be useful in risk stratification of Brugada syndrome.		18
Heart rate variability, heart rate turbulence, signal-averaged ECG, and T wave alternans analysis, when used in combination with additional clinical, electrocardiographic, and structural measures, may be useful for identifying high- and low-risk groups among patients with acquired structural heart disease.		19

Electrocardiographic methods

The ECG is the gold standard for risk assessment in patients with or at risk of developing cardiac arrhythmias. The 12-lead ECG is inexpensive and widely available. Risk stratification with the ECG is limited in general by its low positive predictive value (PPV) determined to a large extent by the low prevalence of cardiovascular events in the general population. However, the prognostic significance of the ECG is enhanced in patients with heart disease.

P wave and PR interval

The prognostic value of P wave characteristics has been examined in subjects enrolled in clinical trials of AF for prediction of the

on the patient population studied. Most studies show that PR interval prolongation is not associated with increased mortality in healthy middle-aged individuals during medium term follow-up. On the other hand, a number of reports show worse survival in patients with suspected heart failure (acute and chronic) or heart disease [coronary artery disease (CAD)]. Additionally, PR prolongation and P wave prolongation predict increased risk of AF and the greater degrees of PR prolongation and P wave duration predicted higher risks of AF.^{27,28} An increased PR interval is also associated with poor cardiovascular outcomes in patients with AF.²⁹ Several studies have shown that PR prolongation in patients undergoing cardiac pacing or receiving cardiac resynchronization therapy (CRT) is an independent

predictor of worse prognosis and lower probability of reverse remodelling as well as an increased risk of AF, death, and hospitalization.^{30,31} There are no data indicating whether the degree of PR prolongation portends a worse outcome compared to patients who have lesser degrees of PR prolongation, nor is there information on its prognostic value in acute inferior wall myocardial infarction (MI).

QRS, QT interval, and T-wave

Over the years, a number of ECG techniques have been developed to assess risk of ventricular tachyarrhythmias (VTs). These have the advantage of being non-invasive and, often, inexpensive. For almost all of these techniques, there are conflicting data, and not one technique has proven beneficial in patients with structural heart disease. Moreover, studies have varied in their reporting of sudden arrhythmic death vs. total mortality. Among the risk predictors shown to have value are QRS widening and fragmentation, QT prolongation, T-wave abnormalities, and ventricular ectopy. Although the prognostic value of each ECG parameter in isolation is limited, in combination with additional ECG, imaging, and genetic testing, these parameters can contribute to effective risk stratification.

QRS

QRS prolongation has been associated with all-cause mortality in heart failure patients, implantable cardioverter-defibrillator (ICD) shocks, and inducibility of sustained VT. QRS prolongation in patients on Class IC antiarrhythmic drugs is a predictor of pro-arrhythmia, and should be monitored, particularly during exercise. QRS prolongation predicts risk in patients with myotonic dystrophy and in Brugada Syndrome. Additional prognostic information from the QRS is obtained from the signal-averaged ECG, which amplifies the QRS, averages multiple complexes to reduce noise, and filters out the T-wave in order to detect late potentials, and provides evidence of slow conduction substrate that associates with risk of re-entry tachyarrhythmias.¹⁷ The signal-averaged ECG has been used to detect risk of ventricular arrhythmias in post-infarction patients, ACM, and Brugada Syndrome. Although its specificity is limited, its negative predictive value is high, particularly in survivors of inferior wall myocardial infarction. The signal-averaged ECG is not useful in patients with underlying bundle branch block. QRS fragmentation, which includes abnormally notched narrow and wide QRS complexes, is associated with the presence of myocardial scar and is also associated with mortality in patients with cardiomyopathy and with Brugada Syndrome.³² The presence of an unprovoked type 1 Brugada Syndrome pattern is associated with increased risk as is discussed later in the document.

QT interval

Measurement of the QT interval can be complicated by QRS prolongation and by the need to correct for heart rate, as has been described elsewhere.³³ Despite these limitations, prolongation of the heart rate-corrected QT interval (QTc) has been associated with mortality in several population studies.^{34,35} In congenital long QT syndrome (LQTS), the length of the QT interval is a major predictor of risk of cardiac events, including sudden cardiac death (SCD). When initiating QT-prolonging drugs such as sotalol or dofetilide, a QT

interval of 500 ms or higher should prompt reduction or discontinuation of the offending drug(s).

QT dispersion

This measure of ventricular repolarization heterogeneity is typically defined from the 12-lead ECG as the $QT_{max} - QT_{min}$. It has been used to predict a wide variety of events, including ventricular pro-arrhythmia, VTs, although the sensitivity, specificity, and accuracy are poorly defined and highly dependent on the patient population studied.³⁶

T wave

T wave inversions are common and may be non-specific or may signal important abnormalities such as ischaemia or hypertrophy. Widespread deep T wave inversions in combination with QT prolongation, such as may occur in acute stress cardiomyopathy, can be associated with torsades de pointes. Abnormal T wave notching can be a clue to abnormal repolarization and is often seen in patients with QT prolongation. Computerized T-wave analytic techniques such as principal component analysis, T-wave residuum, flatness, asymmetry, and notching have been developed in an effort to detect and quantify abnormal repolarization and may have particular value in identifying patients with LQTS.^{37,38} Moreover, it has been shown that adding T-wave morphology characterizations to age, gender, and QTc in a support vector machine model can improve LQTS diagnosis.³⁹ However, these additional analytic techniques are not used in routine clinical practice.

The Tpeak-end interval, measured from the peak to the end of the T-wave, thought to reflect heterogeneity of repolarization in the heart, has been associated with arrhythmic risk in various populations.⁴⁰ However, considerable controversy remains as to how it should be measured and applied.⁴¹

T-wave alternans is a beat-to-beat alternation of T wave morphology. When seen with the naked eye, it usually accompanies marked QT prolongation and is a harbinger of imminent torsades de pointes. Analysis of more subtle T-wave alternans has been used for assessing abnormal and heterogeneous repolarization to predict mortality and arrhythmic risk. Abnormal microvolt T-wave alternans assessed using the spectral method during graded exercise has a high negative predictive value and has been used to identify a subgroup of patients with reduced ejection fraction who are not likely to benefit from defibrillator implantation.¹⁸ Microvolt T-wave alternans analysis cannot be performed when the rhythm is AF, and patients with ventricular pacing have not been studied extensively.

Early repolarization




Early repolarization pattern, highly prevalent in the overall population, defined as an elevation of the J point of at least 0.1 mV, may occur in the anteroseptal or inferolateral leads. In 2008, Haissaguerre reported an association of inferolateral early repolarization with increased risk of idiopathic ventricular fibrillation (VF) in a case-control study⁴² and subsequently confirmed in other case-control studies. Exercise testing or isoproterenol testing improved the pattern of repolarization, and the pattern was accentuated with exposure to beta-adrenergic blockers. In a meta-analysis of population-based studies, inferolateral early repolarization was associated with increased risk of arrhythmic death, but the risk was still quite low in

general (70/100 000 patient-years).⁴³ It appears that individuals at highest risk have early repolarization in multiple (especially inferior) leads, with high voltage (at least 0.2 mV), and with notching or horizontal/down-sloping ST segments. Early repolarization is especially prevalent in young men, particularly young black men, and in athletes.⁴⁴ Because the absolute risk of arrhythmic death is so low, asymptomatic individuals with early repolarization, even those with higher risk ECG patterns, do not require further evaluation except when there is a strong family history of sudden cardiac death or when the J point elevation is associated with Brugada syndrome (discussed later in this document) or short QT syndrome (SQT).

Ambulatory electrocardiographic monitoring

In 1984, Bigger *et al.* showed that ventricular ectopy recorded on a Holter monitor, especially when combined with a low left ventricular ejection fraction (LVEF), predicted a higher risk of mortality in post-infarction patients compared to those without ectopy.⁴⁵ Non-sustained VT is also associated with increased risk in patients with arrhythmogenic and hypertrophic cardiomyopathy (HCM). Other data that can be extracted from ambulatory monitoring include heart rate, heart rate variability, and heart rate turbulence measurements, which can predict mortality risk at least in ischaemic cardiomyopathy (ICM), but have not been incorporated into clinical practice.^{19,46}

Imaging

Imaging (echo, computed tomography (CT), magnetic resonance imaging (MRI), perfusion)	Class	References
Echocardiography should be used to evaluate EF for risk assessment for primary prevention of sudden cardiac death and the presence of structural heart disease. Alternatively, MRI or cardiac CT can be used.		47,48
Cardiac MRI is useful in assessing aetiology-driven risk of VT and for the presence of scar or myocardial inflammation.		49–51
Cardiac positron emission tomography may be useful for the assessment of aetiology-driven risk of ventricular arrhythmias and the presence of scar or myocardial inflammation in patients without CAD.		52,53

Risk assessment of ventricular tachyarrhythmia using imaging modalities

Evaluation for the presence of structural heart disease (SHD) is important for patients suspected of being at risk for sudden cardiac death. Left ventricular ejection fraction remains the key independent parameter for risk stratification of sudden cardiac death and to guide implantation of an ICD.^{47,48} Randomized controlled trials have

shown a survival benefit from ICDs in patients with SHD and an EF $\leq 35\%$.^{54–56} Although EF is currently the only proven imaging modality demonstrated to risk stratify for sudden cardiac death, only 1–5% of patients with ICDs, implanted based upon a low EF, require therapies each year and the large majority of patients who receive ICDs will not have ICD therapies over the 3-year period after implantation.^{57,58} In addition, up to 70% of all sudden cardiac deaths in the community occur in individuals with EF $>35\%$.^{58–60} Although the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure (DANISH) trial showed that primary prevention ICD in the setting of severe non-ICM did not reduce all-cause mortality in patients on optimal medical therapy for heart failure, ICD implantation was associated with a 50% reduction in arrhythmic death. Of note, within this non-ICM population, younger patients (<68 years old) experienced a mortality benefit of 36% if treated with an ICD.⁶¹

Ejection fraction is most readily evaluated with echocardiography (recommendation level: green), given both lower cost, availability of equipment, and available expertise; however, cardiac MRI or CT can also be used to evaluate EF and SHD, particularly if obtained in combination of other assessment aims, such as CAD or if there is controversy over the quantified EF with echo (recommendation level: green). The imaging modality used to estimate EF has not been shown to determine benefit from ICD.⁴⁸

Additional parameters beyond EF remain to be tested in large studies. Cardiac MRI with late gadolinium enhancement (LGE) can provide important prognostic information and may allow for more accurate assessment of scar. Presence and location of scar can portend a higher risk of sustained VT.^{49–51,62,63} In a study of 452 non-ICM patients with New York Heart Association Class II or III and EF $<35\%$, ICD implantation was only associated with reduced mortality in the population that had presence of scar on cardiac MRI.⁶⁴ Cardiac positron emission tomography (PET) may elucidate areas of inflammation which may identify inflammatory cardiomyopathies and sarcoidosis, a condition that is associated with higher risk of ventricular arrhythmias in patients without CAD (increased F-2-fluorodeoxyglucose uptake) or can be used to identify sympathetic denervation (carbon-11-metahydroxyephedrine imaging) or regions of inflammation. Greater sympathetic denervation on PET in a prospective study of ICM patients was a better predictor of ICD shocks than EF.⁶⁵ Uptake of iodine-123 meta-iodobenzylguanidine (MIBG) to evaluate heart to mediastinum ratio (H/M ratio) has shown mixed results in predicting arrhythmic death with some studies suggesting additional prognostic benefit for this parameter, while others have not demonstrated additional value.^{66,67} Importantly, the value of these additional parameters in determining risk of sustained VT, VF, or benefit from ICD in various population remains to be clarified. Finally, routine use of viability assessment using PET to guide revascularization in order to reduce risk of SCD remains an area of investigation. In patients with an EF $<35\%$ and CAD amenable to revascularization, routine use of PET to guide revascularization was not beneficial in reducing overall mortality.⁶⁸










Imaging modalities for atrial arrhythmias

Echocardiography (transthoracic or transoesophageal) is a valuable tool in patients who present with atrial arrhythmias, specifically atrial flutter and AF, to evaluate for the presence of structural heart

disease, left atrial enlargement, and valvular heart disease in order to better define treatment options. Cardiac MRI or CT may also be used if images obtained at echocardiography are not reliable. However, routine use of echocardiography, including atrial strain or atrial function in patients who do not have atrial arrhythmias to assess risk for the development of AF or atrial flutter is not warranted, unless other structural cardiac abnormalities are suspected.

Invasive electrophysiological study

Patients with ICM without a primary indication for an ICD, EF $\leq 40\%$, and non-sustained VT on ambulatory cardiac monitoring are candidates for an EPS according to the findings in the MUSTT trial,⁷³ in which, 35% of patients with inducible sustained VT had a significantly lower risk of death with an ICD.⁶⁶ The MADIT trial initially also utilized an EPS in post-MI patients with an EF $\leq 30\%$, and non-sustained VT events to implant an ICD, and showed survival benefit with the ICD.⁵⁴ However, MADIT-II subsequently eliminated the need for an EPS in post-MI patients with an EF $\leq 30\%$ and similarly showed the life-saving benefit of the ICD in a broader patient co-

Invasive electrophysiological study (EPS)	Class	References
EPS is indicated in patients with syncope and previous myocardial infarction, or other scar-related conditions when syncope remains unexplained after non-invasive evaluation.		69
EPS may be considered in patients with syncope and asymptomatic sinus bradycardia, in a few instances when non-invasive tests (e.g. ECG monitoring) have failed to show a correlation between syncope and bradycardia		70–72
EPS may be considered in patients with EF $\leq 40\%$, without a primary prophylactic ICD indication, and non-sustained VT in ICM (MUSTT criteria) to ascertain the presence of sustained VT events.		73
EPS may be helpful in patients with syncope and presence of a cardiac scar, including those with a previous myocardial infarction, or other scar-related conditions, when the mechanism of syncope remains unexplained after non-invasive evaluation.		66,70,71,73
EPS may be considered in patients with syncope and bifascicular block, when the mechanism of syncope remains unexplained after non-invasive evaluation.		67,70,71,74
EPS may be considered for risk stratification of SCD in patients with tetralogy of Fallot who have one or more risk factors among LV dysfunction, non-sustained VT and QRS duration exceeding 180 ms.		67,70,71,74
EPS may be considered in patients with congenital heart disease and non-sustained VT to determine the risk of sustained VT or identify SVT that could be ablate.		67,70,71,74
EPS may be considered in asymptomatic patients with spontaneous type 1 Brugada ECG pattern, or drug-induced type 1 ECG pattern and additional risk factors.		75–77
EPS is not recommended for additional risk stratification in patients with either long or short QT, catecholaminergic VT or early repolarization.		70,71
EPS is not recommended for risk stratification in patients with ischaemic or non-ischaemic DCM who meet criteria for ICD implantation.		70,71

Currently, there are a few indications to perform an electrophysiological study (EPS) to further assess the risk of arrhythmias in at-risk cardiac patients. Such patients include those with structural heart disease, LVEF $>35\%$, pre-syncope, syncope, palpitations, or markedly abnormal ECG suggesting severe conduction disease. These patients can be considered for an EPS to assess the risk of ventricular arrhythmias and sudden cardiac death to decide on need of an ICD, or to identify conduction disturbances or supraventricular tachycardias that can be treated with ablation or pacing.^{70,71}




hort.⁵⁵ Therefore, post-MI patients with an EF $\leq 30\%$ do not currently need to undergo an EPS to guide decisions on whether to implant an ICD.

In patients with heart failure and EF $\leq 35\%$, an EPS is not recommended for risk assessment for the decision on ICD indication. Some centres perform an EPS for inducibility to better characterize induced, sustained VT events, and their response to anti-tachycardia pacing, which may potentially help to tailor ICD programming. Furthermore, in patients who have syncope of uncertain origin, an

EPS could identify ventricular arrhythmias or document electrical conduction disorders.^{67,70,71,74}

In the case of channelopathies, there is no indication for an EPS, except for Brugada syndrome. In Brugada syndrome, EPS may be useful in asymptomatic patients with spontaneous or drug-induced type 1 pattern, especially when there is a family history of sudden death.^{75–77}

Implantable loop recorders

Implantable cardiac devices	Class	References
An ILR is indicated in the evaluation of patients with infrequent recurrent syncope of uncertain origin especially when ambulatory monitoring is inconclusive.		78–80
An ILR is indicated in patients with syncope and high-risk criteria in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment, and who do not have conventional indications for primary prevention ICD or pacemaker.		78–80
An ILR can be considered in patients with palpitations, dizziness, pre-syncope, frequent premature ventricular complexes (PVCs)/non-sustained VT, and in those with suspected AF, and following AF ablation.		78–80

Implantable loop recorder to diagnose unexplained syncope/atrial fibrillation with cryptogenic stroke

The implantable loop recorder (ILR) provides long-term continuous monitoring and improves the diagnosis in patients with unexplained syncope.⁸¹ In a meta-analysis of 49 studies that included 4381 participants, the diagnostic yield for the detection of arrhythmogenic syncope was 26.5%.⁷⁸ Moreover, the CRYSTAL-AF trial⁸⁰ revealed that the ILR can detect subclinical AF following cryptogenic stroke. Still, any benefit of these findings needs to be confirmed in large randomized trials. Early use of the ILR has been advocated by the European guidelines⁸² and in the American guidelines following inconclusive non-invasive monitoring.⁸³ The indications for ILR have been expanded in the current guidelines (Table 2).

Implantable loop recorder to diagnose atrial and ventricular arrhythmia events

While the ILR can be useful to detect atrial and ventricular arrhythmias, a large cohort study indicated that most of the current use of ILRs is primarily in patients with unexplained syncope (84%), followed by

Table 2 High-risk and low-risk criteria for syncope at initial evaluation (Adapted from 2018 ESC Guidelines for the diagnosis and management of syncope⁸²)

Syncopal events

Low-risk

- Associated with prodrome typical of reflex syncope (e.g. lightheadedness, feeling of warmth, sweating, nausea, vomiting)
- After sudden unexpected unpleasant sight, sound, smell, or pain^a
- After prolonged standing or crowded, hot places
- During a meal or postprandial
- Triggered by cough, defaecation, or micturition
- With head rotation or pressure on carotid sinus (e.g. tumour, shaving, tight collars)
- Standing from supine/sitting position

High-risk

Major

- New onset of chest discomfort, breathlessness, abdominal pain, or headache
- Syncope during exertion or when supine
- Sudden onset palpitation immediately followed by syncope
- Presence of structural heart disease especially left ventricular dysfunction and/or history of myocardial infarction


Minor (high-risk only if associated with structural heart disease or abnormal ECG):

- No warning symptoms or short (<10 s) prodrome
- Family history of sudden cardiac death at young age
- Syncope in the sitting position

^aSudden loud sounds (as an alarm clock) may trigger VF in some long QT syndrome patients.
ECG, electrocardiogram; VF, ventricular fibrillation.

palpitations (13%), and suspected AF (12%).⁷⁹ Another smaller study specifically studying the risk of SCD and arrhythmias in patients with haemodialysis, found that 20% of these patients had SCD or bradyarrhythmia events necessitating pacemaker implantation, and 33% of these patients had an arrhythmic endpoint. Interestingly, the median time to event was 2.6 years, confirming the need for long-term monitoring. Surprisingly however, bradyarrhythmias were very commonly diagnosed in this cohort suspected to be at high risk for ventricular arrhythmias and sudden cardiac death.⁸⁴ Further studies are needed to establish the role of ILR in risk stratification.

Wearables/direct to consumer

Wearables/direct to consumer	Class	References
Wearables may provide diagnostic data that contribute to disease detection and management when integrated into the clinical context and physician judgement.		85,86





The direct to consumer or wearable technology market, comprised of devices that monitor physiological parameters such as heart rate and sleep pattern, is anticipated to grow to 929 million connected devices by 2021.⁸⁷ These devices encompass wristbands, glasses, in-ear monitors, chest straps, and smart phone-enabled recording electrode systems or electronic shirts, with varying capacity to monitor heart rate, heart rhythm, blood pressure, physical activity, respiratory rate, blood glucose, and sleep patterns.^{88–90} For heart rate monitoring, most wearable devices use photoplethysmography (PPG) technology, meaning they are inherently less accurate than conventional electrocardiography monitoring techniques. Accuracy of various devices varies, with correlation to reference standard ECG monitoring ranging from 0.76 to 0.99.⁹¹ Recent advances in wearable ECG acquisition include use of direct electrode recording that represents a regulatory approved medical device generating a lead I like rhythm strip, blurring the lines between consumer and medical devices.⁹²

A growing body of evidence suggests that these technologies can be harnessed to facilitate arrhythmia detection in the appropriate context. Although marketed as consumer devices, many wearable devices may generate health data comparable to that of medical grade ECG monitors, with several devices migrating to approved medical use.⁸⁵ Despite this promise, there are clear concerns regarding accuracy, particularly false positives in asymptomatic patients where device-based alerts can raise unwarranted concern and generate low yield screening for disease, with associated costs. Wearable technologies represent an important frontier in health evaluation, with the potential to provide readily accessible health data for large segments of the population, including those not captured by conventional monitoring techniques. Though intended for personal use focused on health promotion and physical activity, wearable technologies promise to invert the traditional paradigm of healthcare delivery, with data collection and health queries often initiated by consumers and not providers. Providers may see wearables as accessible risk stratification tools for detection of AF in high-risk cohorts (such as high CHADS₂-VASC₂ score patients), and patients may equally present for evaluation after device-based observations that call into question whether they are at risk. The confluence of these factors is illustrated in the recently presented Apple Heart Study, wherein 419 297 participants were recruited in only 8 months to participate in an AF screening study that deployed a PPG-based algorithm followed by a 7-day patch if AF was suspected.⁹³ Using a complex tachogram algorithm, 2126 individuals were sent irregular pulse notifications and prompted for a telemedicine visit and 7-day ECG patch. The authors reported a PPV of 84% for each irregular pulse notification, and 71% for each irregular tachogram. The burden of notifications and the performance of the technology showed promise to inform AF detection in the broader public. Similarly, the Huawei Heart Study evaluated 187 912 individuals that used smart devices to monitor their pulse rhythm, with notification of suspected AF in 424 participants, with a strong relationship between advancing age and detecting AF. The predictive value of the algorithm in the 62% of notified participants that pursued medical evaluation was promising (87%).⁹⁴

Studies evaluating PPG-based wearables in conjunction with machine-learning algorithms have shown promise in arrhythmia detection, such as AF.⁸⁶ Studies to date have not focused on ventricular arrhythmia detection. Future wearables will benefit from improved reliability and accuracy, collect additional health and fitness

parameters, support chronic disease management, and provide real-time connectivity and feedback that may supplant conventional medical monitoring. Wearables have the potential to become truly disruptive in our healthcare sector, with large segments of the population accessing cardiac monitoring that the physician must interpret. Currently, we have no data on how the information provided by PPG-based wearables will affect management and outcomes of patients, or how risk scores derived in other populations such as the CHA₂DS₂VASc score apply in these previously undetected subjects.

Biomarkers, tissue, genetics

Biomarkers, tissue, genetics	Class	References
Genetic testing should be considered in several inherited arrhythmic diseases associated with an increased risk of ventricular arrhythmia and SCD.		95–97
MRI with LGE to detect fibrosis and scar may be useful in assessing the risk of arrhythmic events in AF patients and patients with cardiomyopathies.		98–100
Plasma NT-proBNP may be useful in differentiating patients with higher vs. lower burden of AF.		101–105
Plasma CRP or other inflammatory markers may be useful in risk assessment, for identifying individuals with increased risk of future AF and for identifying individuals with high degree of atrial fibrosis.		106–108

The use of biomarkers, tissue biopsy, and genetic assessment can be used for risk assessment in patients suspected of specific arrhythmias or syndromes. The utility of using these tools broadly spans determining arrhythmic risk, refining a clinical diagnosis and estimating prognosis.

Biomarkers

Cardiac myocytes express and secrete natriuretic hormones that have a central function on blood pressure regulation, blood volume, and plasma sodium balance. Levels of B-type natriuretic peptide (BNP) and its stable N-terminal peptide pro-BNP (NT-proBNP) are increased in AF.¹⁰¹ AF burden has been shown to be associated with increased NT-proBNP.¹⁰² In a large meta-analysis consortium, BNP and C-reactive protein (CRP) associate with AF but only BNP was superior to well-known clinical variables in AF risk prediction.¹⁰³ Inflammatory processes and fibrosis are central to pathogenesis of AF,^{106,109} and the inflammatory marker CRP is associated with longer

AF duration and atrial remodelling.¹¹⁰ CRP levels are elevated in patients with permanent AF compared to persistent AF patients and are predictive of recurrent AF after catheter ablation,^{111,112} indicating that CRP levels can be used to identify AF subtypes and evaluate prognosis. Higher levels of CRP correlated to an increased risk of developing AF in general and after acute myocardial infarction.^{107,113} Similarly, the plasma protein YKL-40 may have diagnostic and prognostic use in AF patients¹⁰⁸ because plasma serum chondrex (YKL-40) is associated with atrial fibrosis severity in patients with lone AF.¹¹⁴ Patients who experience recurrent AF following ablation have significantly increased YKL-40 baseline levels, although plasma YKL-40 is not an independent predictor of recurrent AF.^{108,115} Increasing levels of YKL-40 have been shown to associate with a two-fold increased risk of future AF.¹¹⁶ Other simple AF biomarkers include body weight and blood pressure, which are also major intervention targets.^{117–122}

Tissue diagnostics

Tissue diagnostics can be beneficial to differentiate various infiltrative myopathic processes that can contribute to the risk for arrhythmic events. Fibrosis and scarring are well-recognized substrates for arrhythmia both in atria and ventricles.¹⁰⁹ Fibrosis may be assessed in atria as well as in ventricular myocardium and its quantification can be used in evaluating the risk of arrhythmia in AF and cardiomyopathies.^{98,99} Specific patterns of scarring can assist in refinement of the diagnosis for infiltrative myopathies, hypertrophic cardiomyopathy, sarcoidosis, ACM, and amyloidosis. The development and validation of advanced imaging techniques including bio-metabolic imaging (sarcoid), and contrast enhanced cardiac MRI (amyloid) have largely replaced the need for invasive diagnostics.

Genetics

The majority of clinically applicable genetic testing is intended to be driven by phenotype and the pre-test probability of specific diagnosis determines the utility of genetic investigation.⁹⁵ Due to incomplete penetrance of genetic arrhythmia syndromes, harbouring a genetic variant with known pathogenicity is almost never solely enough to meet diagnostic criteria for a particular syndrome.¹²³

For LQTS, part of the diagnostic framework (along with the ECG biomarker of QT prolongation) can include a positive genetic test.¹²³ Moreover, understanding the genetic diagnosis is important for treatment and prognostication. For example, patients with Jervell and Lange-Nielsen and Timothy Syndrome patients (LQT8) have more malignant clinical courses,^{124,125} and for LQT1 the arrhythmic risk depends partly on which region of the channel the mutation affects.¹²⁶ In catecholaminergic polymorphic ventricular tachyarrhythmia (CPVT),¹²⁷ genetic testing of suspected individuals has a moderately high yield.⁹⁵ Identification of an at risk first-degree relative of a CPVT affected individual is essential due to the high penetrance but more so the lethality of this syndrome.^{123,128} Similar to LQT1, CPVT due to RYR2 mutations may have some degree of risk depending on where in the ryanodine receptor the mutation falls.¹²⁹ Brugada syndrome can be particularly difficult to clinically diagnose and the utility of genetic testing for improving diagnosis is poor. For patients who are clinically diagnosed with Brugada Syndrome the yield of genetic testing is ~30%,¹³⁰ the

majority of whom harbour SCN5a mutations, a gene associated with a plethora of arrhythmia syndromes.^{131,132} Genetic testing can be useful for family members of an appropriately genotype identified proband but is not recommended in the absence of a diagnostic ECG.⁹⁵ Using genetics as part of diagnostic criteria for arrhythmogenic cardiomyopathies will be discussed later in the document. Lastly, genetics in AF is a developing area, but certain primary electrical sudden death syndromes have increased AF association as discussed in Patients with inherited rhythm disease (long QT syndrome/short QT syndrome/catecholaminergic polymorphic ventricular tachyarrhythmia/Brugada syndrome) section. For families with a substantial number of AF cases or in early onset AF, genetic testing can be considered but the yield is low.^{133–136}

Artificial intelligence

Machine learning is a broad term of artificial intelligence derived from the extraction of patterns from large data sets. The marriage with healthcare analytics and decision processes has been rapidly forwarded with computerized medical records and the creation of large data warehouses.

A deep neural network was created to analyse raw ECG data from an ambulatory heart monitor and classify it into 12 categories based upon the presence of arrhythmia. Machine learning performed very well with an average under the reviewer operating characteristic curve (ROC) of 0.97 and an average F1 score (mean of the PPV and sensitivity) of 0.837; a score better than an average cardiologist (0.780).¹³⁷

Machine learning has been applied to standard ECG characteristics in sinus rhythm to predict incident AF using the eight independent ECG leads (leads I, II, V1–6) through a convolutional neural network.¹³⁸ The ROC area under the curve for the detection of AF was 0.87 (0.86–0.88) using the internal validation dataset and 0.87 (0.86–0.88) using the testing dataset.

In an analysis of the Atrial Fibrillation Prediction Database, a machine learning approach based upon heart rate variability predicted onset of AF with sensitivity of 100%, specificity of 95.6%, and accuracy of 96.2%.¹³⁹ Machine learning based upon ECG characteristics identified left ventricular dysfunction with an area under the curve of 0.93, sensitivity of 86.3%, and specificity of 85.7% including risk of left ventricular dysfunction in those without.¹⁴⁰

Machine learning has shown accuracy in predicting mortality and risk stratification of patients with CAD.¹⁴¹ Machine learning has also been shown to accurately discriminate between athletic hearts compared to hypertrophic cardiomyopathy hearts.¹⁴² Machine learning has great potential in this area of risk assessment because of the large amount of data contained in the large ECG and clinical datasets available to determine rules.

How to assess risk for atrial fibrillation in specific populations

Patients of advanced age

There is agreement that the prevalence of AF in the general population in the Western world is in the order of 1–2%.^{143–145} It is estimated that in 2010 there were 33.5 million people in

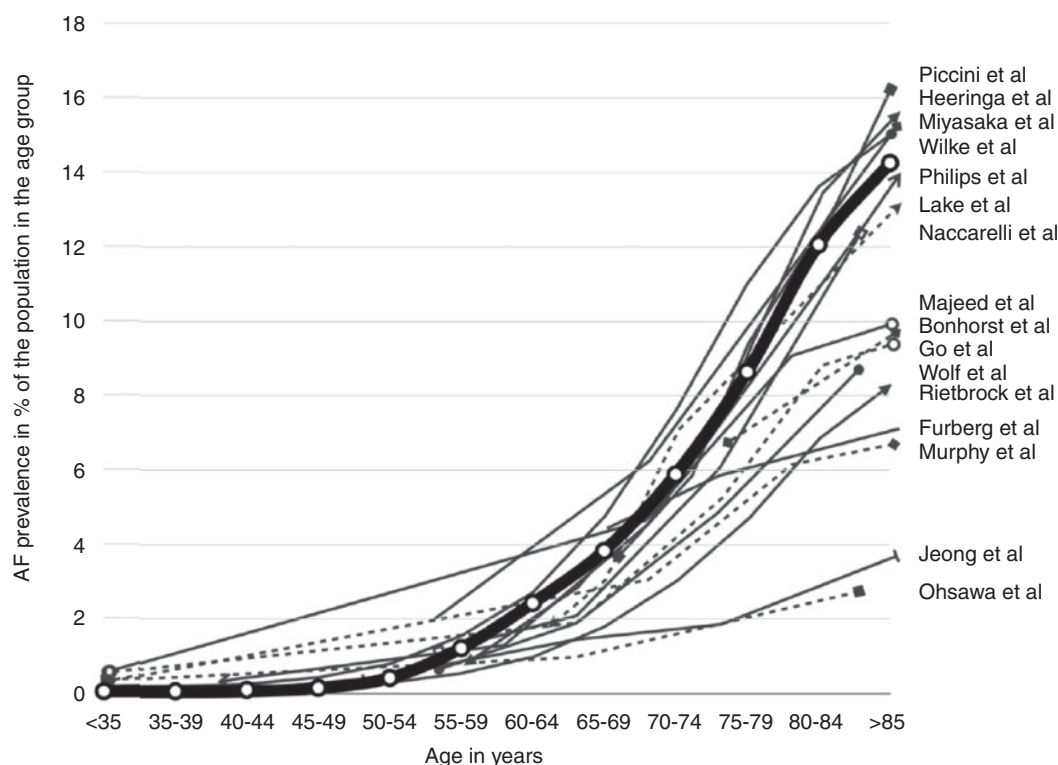


Figure 1 A depiction of the atrial fibrillation prevalence distribution found by each study published to date.¹⁵¹ This depiction uses the sex-specific average rates of AF prevalence, grouped by age. The thick line represents average AF prevalence rates by age group, as derived from a pooled analysis of the individual studies weighted by sample size. (Adapted from Andrade et al. *Circ Res* 2014.) AF, atrial fibrillation.

the world with AF of which 20.9 million were men and 12.6 million were women.¹⁴⁶ During the past 20 years, the age-adjusted prevalence rates of AF increased for both men and women and similarly the corresponding incidence rates have increased.^{146–150} Age is a major risk factor for the development of AF and in persons younger than 55 years a prevalence of AF around 0.5% is seen whereas in persons older than 85 years AF prevalence is around 15% (Figure 1).¹⁴⁴ A stepwise increase in AF prevalence with increasing age has been found in several studies.^{152,153} Studies in a multi-ethnic cohort from the United States has shown large variation in AF prevalence among various race-ethnicity groups in which AF associated hospitalizations were lower in Hispanics, Chinese, and Black Americans compared to White Americans.¹⁵³ The predominant contributor to the increasing AF prevalence is our aging populations, more widespread use and availability of screening tools, and improved treatment for various heart diseases that enhance longevity.

Among AF patients, those aged younger than 65 years are in general healthier than those older than 65 years.¹⁵⁴ Life time risks of AF in 55-year-old subjects without a history of AF have been found to be 20–24% in the Rotterdam study¹⁵⁵ but considerably higher at 37% in the Framingham study.¹³⁴ The lifetime risk of AF in Asians older than 20 years (1 in 6 for men and 1 in 7 for women; i.e. 14–17%) was lower than the risk reported from Western countries.¹⁵⁶

The incidence rates, prevalence, and lifetime risk of AF are higher for men than women. Despite this, the absolute number of women with AF exceeds the total number of men with AF because women live longer than men.¹⁴⁴ Women have their first episode of AF about 5 years later than men and less commonly have lone AF.¹⁴⁴ In general, women with AF are more likely to have hypertension or valvular heart disease compared to men.¹⁴⁴ Women often present with atypical symptoms related to AF (Figure 2). On the other hand, compared to men, women are less likely to have asymptomatic AF, they have a higher symptom burden, they have higher average heart rate during AF and more often longer lasting episodes of AF.¹⁴⁴ These factors contribute to the observation that women are more likely to contact their physician due to AF-related symptoms compared to men.

Conflicting results exist with respect to risk of stroke secondary to AF and its prognosis in women compared to men.^{157–159} There does not seem to be a gender difference with respect to development of dementia secondary to AF, although women have higher rates of dementia than men in general.^{145,157}

Since both AF and stroke are highly associated with age and stroke may occur as a complication of AF it seems reasonable to consider screening for this arrhythmia in elderly populations. Several studies are ongoing and expected to be finalized within the next couple of years. These studies are expected to guide us with respect to cost-effectiveness of these screening strategies.

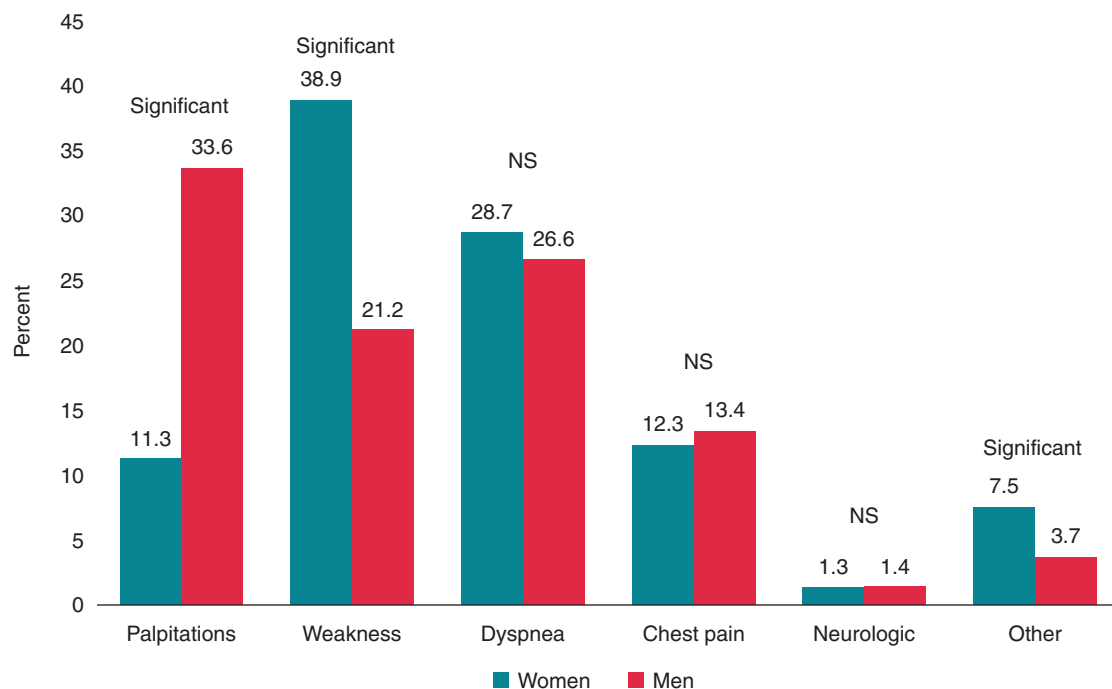








Figure 2 Sex differences in symptoms related to atrial fibrillation¹⁴⁴ (Adapted from Andrade et al. *Can J Cardiol* 2018).

Patients with heart failure

Investigations needed to assess risk for AF in patients with heart failure	Class	References
A careful evaluation of clinical characteristics known to be associated with increased risk for AF should be performed.		¹⁶⁰
Frequent interrogation or remote monitoring of stored arrhythmia episodes in device implanted HF patients should be performed in order to diagnose AF and allow its early management.		¹⁶¹
Echocardiography is useful in identifying cardiac characteristics associated with a higher risk for AF.		¹⁶²
Cardiac MRI may be considered in identifying degree of atrial fibrosis and scar.		¹⁶³
Use of biomarkers may be considered for identifying individuals with increased risk of future AF and for identifying individuals with high degree of atrial fibrosis.		^{107,164,165}
Searching for common genetic variants associated with AF risk by genetic molecular analysis has not been found to be useful in a routine clinical setting.		¹⁶⁶

Due to common risk factors like age, hypertension, diabetes, obesity, and sleep apnoea, AF and HF are intricately linked and share common pathophysiologic mechanisms. Atrial fibrillation occurs in more than half of individuals with HF and presence of both carries greater mortality risk compared with those without either condition.¹⁶⁷

In the particular case of cancer treatment, HF is also a common consequence of cardiotoxicity associated with some chemotherapeutic agents, including anthracyclines, human epidermal growth factor receptor 2 (HER2), and proteasome inhibitors. In this setting, isolated cases of AF have been reported. Even if the exact mechanism

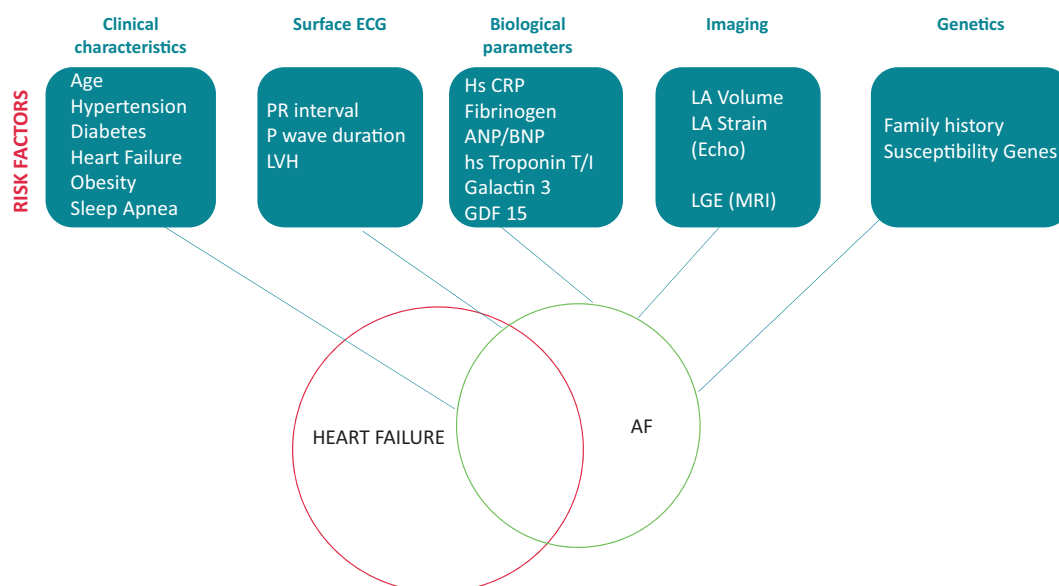


Figure 3 Investigations and associated risk factors useful to predict the development and progression of AF in HF patients. AF, atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiogram; HF, heart failure; LA, left atrium; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging.

of these arrhythmias induced by such drugs remains largely unknown, it seems plausible that the negative effect on the cardiac systolic function also plays a central role.¹⁶⁸

Given the deleterious effects of AF in HF patients, significant interest has been directed to risk factors predicting the development and progression of this arrhythmia (Figure 3).

Clinical risk factors

Older age and male gender are associated with a higher risk of developing AF.¹⁶⁰ Diabetes confers a 1.4- to 1.6-fold higher risk for AF.¹⁶⁰ Because of its high prevalence in the general population, hypertension is responsible for more AF in the population (14%) than any other risk factor.¹⁶⁰ Obesity and sleep apnoea are independent risk factors for AF.¹⁶⁹ AF incidence also increases in case of renal or thyroid dysfunction.^{170,171}

With regard to HF and the type of underlying heart disease, prevalence of AF increases significantly with the severity of HF symptomatology. Among the valvular diseases, the left-sided valve stenoses have the highest prevalence rates of AF. In addition, the presence of CAD or hypertrophic cardiomyopathy is a significant risk factor for incidence and progression of AF.¹⁷² Finally, in congenital heart disease patients, substantial AF rates appear decades before their onset in the general population.¹⁷³

Electrocardiography

Electrocardiogram-derived variables, such as the PR interval, ECG-based left ventricular hypertrophy (LVH), P wave indices like P wave duration, area, and terminal force have been used in various AF prediction models but their additive value over other clinical risk factors is minimal.¹⁷⁴ Short duration Holter monitoring is not useful for AF detection in asymptomatic patients. Longer duration monitoring with

external or implantable loop recorders may help when paroxysmal AF is suspected. In addition, frequent interrogation or remote monitoring of Holter memories in device implanted HF patients is mandatory in order to diagnose AF and allow its early management.¹⁶¹

Biomarkers

Markers of inflammation (high-sensitivity CRP, fibrinogen), atrial overload (atrial and B-type natriuretic peptides), myocardial ischaemia (high-sensitivity troponin T and I), cardiac fibrosis (galectin-3), and others (soluble ST2, growth differentiation factor-15), have been studied to predict AF incidence.¹⁶⁵ Of these, only natriuretic peptides have consistently demonstrated added predictive value beyond information on clinical variables.^{164,165}

Imaging

Many echocardiographic variables have been associated with a significantly higher AF recurrence rate. Possibly, left atrial volume is superior to left atrial diameter in predicting progression to persistent AF. Speckle left atrial strain and stiffness index can also predict the maintenance of sinus rhythm after cardioversion for AF.¹⁶²



Concerning MRI, the amount of left atrial enhancement quantified on MRI with LGE may be helpful to predict progression of AF,¹⁶³ but the reproducibility of such findings remains controversial.

Genetics

A family history of AF in a first-degree relative independently increases AF risk two-fold.¹⁷⁵ Recent research has identified several common genetic variants associated with the risk of AF.¹³⁶ Further studies are required to evaluate whether genetic information improves our ability to predict AF on top of clinical variables.

Risk assessment of AF in patients with HF can be carried out at first by considering the clinical features, comorbidities, and underlying aetiologies. It can be further refined by more sophisticated investigations.

Patients with obesity, hypertension, diabetes, sleep apnoea, or structural heart disease

Patients with obesity, hypertension, diabetes, sleep apnoea, or structural heart disease	Class	References
Clinical risk factors should be assessed to help identify incident AF and its complications.		176
Clinical risk scores may be useful to identify risk for incident AF.		177–179

The assessment of underlying AF in people at higher risk for AF can be considered from opportunistic perspective, or the consideration of clinical risk prediction tools.¹⁸⁰ Many patients with common conditions that may predispose to AF, such as obesity, sleep apnoea, hypertension, or SHD should or would be attending specialist clinics for their assessment and/or follow-up. Hence, an opportunistic strategy of pulse palpation and clinical assessment (e.g. symptoms) followed by appropriate ECG monitoring to confirm AF would be an appropriate and cost effective method for screening.¹⁸¹ In general, clinical scores have been less useful as most only have modest predictive value for identifying the population at risk; ultimately, these patients would also require their AF documented. A strategy of using risk scores to target high-risk patients for more intense screening efforts merits consideration.

The systematic review by Allan *et al.*¹⁷⁶ found that in relation to the relative risk of incident AF:

- For every 1–10 kg/m² increase in body mass index (BMI), or BMI ≥25–30 kg/m², all 19 reports showed significant direct associations (from 1.04 [1.02–1.05] to 2.24 [1.41–3.58]).
- For every 10–22 mmHg increase in systolic blood pressure, or systolic blood pressure ≥160 mmHg, most reports showed significant direct associations (from 1.14 [1.05–1.25] to 2.63 [1.83–3.78]).
- For diabetes mellitus (type unspecified), eight reports showed a direct but non-significant (from 1.02 to 1.49) and six reports showed significant direct associations (from 1.17 [1.16–1.19] to 1.80 [1.30–2.60]).

Many of these conditions are present concomitantly. Also, obesity and hypertension are commonly associated with sleep apnoea, which is another risk for incident AF.



Obesity has been associated with incident AF,¹⁸² but clinical trial data have a suggestion of an ‘obesity paradox’ whereby overweight AF patients tended to have improved outcomes; however, the relationship between obesity and outcomes from real-world observational cohorts are less clear.^{183–185} In a systematic review of trial and real-world evidence, there was suggestion of an obesity paradox in AF patients, particularly for all-cause and cardiovascular death outcomes.¹⁸⁴ An obesity paradox was also evident for stroke/systemic embolic event outcomes in the non-vitamin K antagonist oral anticoagulant (NOAC) trials, with a treatment effect favouring NOACs over warfarin for both efficacy and safety that was significant only for normal weight patients. Nonetheless, proactive management of obesity is part of the lifestyle advice for patients with AF.

On a population basis, hypertension is the most common aetiological factor for AF, and contributes to its complications. Indeed, AF can be regarded as a manifestation of hypertension target organ damage. The optimal blood pressure targets in AF patients have been described, being 120–129/<80 mmHg.¹⁸⁶ Also, longer hypertension duration is associated with the increased risk of ischaemic stroke; however, this long-term effect of hypertension duration can be attenuated by long-term strict SBP control throughout the entire duration of hypertension.¹⁸⁷

Poor diabetes control is associated with incident AF. In the diabetic AF patient, longer disease duration is related to a higher risk of stroke/thromboembolism in AF, but not with a higher risk of anticoagulant-related bleeding.¹⁸⁸ These risks were similar for Type 1 and Type 2 diabetes.¹⁸⁹ Evidence of other target organ damage such as diabetic retinopathy increased risk, although it did not add to the predictive value of risk assessment using the CHA₂DS₂-VASc score.¹⁹⁰ Indeed, the ATRIA study also confirmed that duration of diabetes is a more important predictor of ischaemic stroke than glycaemic control in patients who have diabetes and AF.¹⁹¹

Unsurprisingly SHD is a potent risk factor for incident AF, as well as its complications, such as stroke and HF.^{177,192} Systolic HF is one of the components of the simple C2HEST score [Chronic obstructive pulmonary disease and CAD [1 point each]; hypertension [1 point]; elderly [age ≥75 years, 2 points]; systolic HF [2 points]; thyroid disease [hyperthyroidism, 1 point]] which has been derived and validated in a large cohort of AF patients.¹⁷⁷ This score could potentially be considered to target the high-risk patients that may be suited for more intense screening for incident AF, e.g. post-stroke where the C2HEST score was superior to the other scores such as the Framingham score.¹⁷⁸ The risks of AF with associated valvular heart disease are well recognized, as recently discussed in an EHRA position document.¹⁹³ In terms of HF, there is a link between AF complications and HF, whether HF with a reduced EF (HFrEF) or HF with a preserved EF (HFpEF).¹⁹⁴ In the CHA₂DS₂-VASc score, the ‘C’ component refers to recent decompensated HF, irrespective of the EF, or the presence of moderate-severe systolic dysfunction whether asymptomatic or not.⁷ Of note, the CHA₂DS₂-VASc score is predictive of stroke in HF, whether or not AF is present.¹⁹⁵

Patients who have undergone cardiac surgery

Patients who have undergone cardiac surgery	Class	References
Heart rhythm monitoring for 4–7 days is recommended for detection of post-operative AF.		196–198
Patients with post-operative AF may undergo follow-up rhythm monitoring to assess for the presence of symptomatic and asymptomatic arrhythmias.		196–199

Post-operative AF remains the most common complication following cardiac surgery and its incidence ranges between 20–50% across numerous studies.¹⁹⁶ This risk increases from isolated CABG surgery, to valvular surgery, and in turn to concomitant CABG/valvular surgery.






Risk factors for developing AF may be divided into procedural- and patient-related factors. Procedural-related risk factors include type of surgery, mitral valve surgery, use of intra-aortic balloon pump, longer cardiopulmonary bypass and aortic clamp times, and perioperative issues such as inflammation, infection, fluid overload, inotropic use, atrial ischaemia, hypokalaemia, and hypomagnesaemia. Patient-related risk factors include advanced age, history of AF, history of HF, renal failure, hypertension, chronic obstructive pulmonary disease, post-operative withdrawal or absence of beta-blocker, or angiotensin-converting enzyme inhibitor (ACE inhibitor) therapy.^{197,200} Left atrial remodelling predisposes to post-cardiac surgery AF, with risk factors such as enlarged left atrial size, diastolic dysfunction, LVH, obesity, obstructive sleep apnoea, and the CHADS₂ and CHA₂DS₂-VASc score further predisposing to post-operative AF.^{197,201,202}

The majority of post-cardiac surgical AF occurs within the first 4 post-operative days, and is most common on the 2nd post-operative day, while recurrences are most common on the 3rd post-operative day.^{197,203} In another study of CABG patients, 94% of post-operative AF occurred by the 7th post-operative day.¹⁹⁸ Hence rhythm monitoring such as inpatient telemetry or ECG for post-operative AF should focus on this time frame.

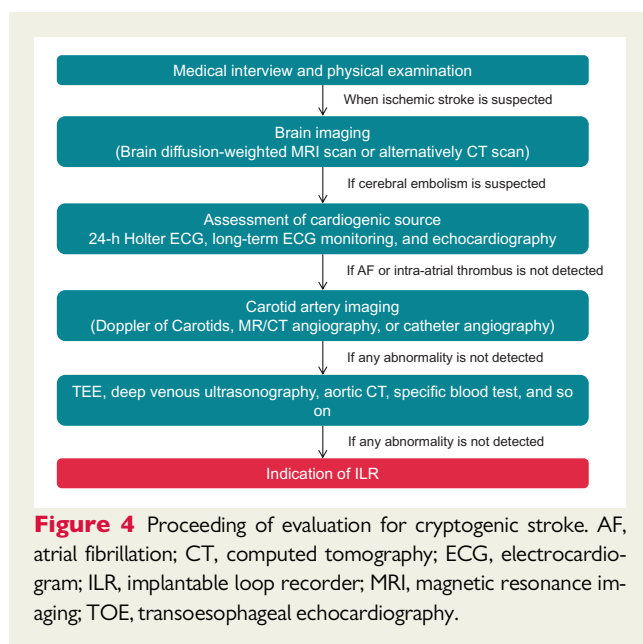
While post-cardiac surgical AF likely occurs as a result of the interaction between acute perioperative triggers and the underlying atrial and cardiac substrate, its occurrence identifies a subset of patients associated with long-term morbidity and mortality. In a study of patients who underwent CABG, post-operative AF conferred an eight-fold increased risk of future AF and doubled cardiovascular mortality on long-term follow-up.¹⁹⁹ Follow-up rhythm monitoring, for example with ECG or Holter monitoring is advisable in this subset of patients particularly in the setting of symptom development. There is emerging data on the use of implantable cardiac monitors for long-term monitoring of this subset of patients. While implantable cardiac monitors allow continuous long-term monitoring for arrhythmias

and asymptomatic arrhythmias, the risk–benefit ratio is balanced by the arrhythmia detection rate beyond the immediate post-operative period and level of invasiveness of the monitoring device. Its routine use will depend on further results from prospective medium to long-term studies.

Patients with cryptogenic stroke

Patients with cryptogenic stroke	Class	References
Patients should initially undergo brain diffusion-weighted MRI imaging for the diagnosis of cryptogenic stroke.		204,205
AF is more likely to be detected after cryptogenic stroke with more intense investigation with longer and more sophisticated monitoring.		205–207
Long-term ECG monitoring techniques, such as trans-telephonic ECG monitoring or cardiac event recorders or ILR can increase yield of AF diagnosis after cryptogenic stroke in selected patients.		205,206
The use of an ILR should be considered for detecting AF in selected patients who are at higher risk of AF development, including the elderly, patients with cardiovascular risk factors or comorbidities.		80,207
TOE may lead to the reclassification of cryptogenic stroke because many cases are embolic and due to a cardiogenic source, mainly AF.		205,206

Cryptogenic stroke is defined as ischaemic stroke of undetermined aetiology.²⁰⁸ The diagnosis of cryptogenic stroke is generally made by exclusion. Although cryptogenic stroke includes few potential causes, such as paradoxical embolism through a patent foramen ovale, atrial septal aneurysm, and aortic arch atheroma, the majority of cases are thought to be caused by cardio-embolism due to undetected paroxysmal AF.²⁰⁵ For the diagnosis of cryptogenic stroke or a suspected transient ischaemic attack (TIA), patients should initially undergo brain imaging. Diffusion-weighted MRI is more recommended than any other MRI sequence or CT as brain imaging, except when contraindicated.^{204,205} Advances in cardiac imaging techniques such as transoesophageal echocardiography (TOE) have prompted the reassessment of cryptogenic stroke because most cases are thought to be embolic due to a cardiogenic source, mainly AF.





Transoesophageal echocardiography can easily detect a thrombus of the left atrial appendage, particularly with contrast enhancement, which cannot be detected using conventional transthoracic echocardiography. Transthoracic echocardiography with contrast could be useful to detect a left ventricular thrombus (Figure 4).

The detection of permanent or persistent AF is relatively easy, whereas that of paroxysmal AF is more difficult. Current guidelines recommend the use of ECG monitoring among patients with ischaemic stroke including cryptogenic stroke and TIA for whom transient (paroxysmal) AF is suspected and no other causes of stroke are identified.^{205,206} First, 24-h Holter ECG is performed to detect the AF burden. If undetected, other long-term ECG monitoring techniques such as trans-telephonic ECG monitoring or cardiac event recorders (a symptom event monitor or a ILR) may be attempted as alternative methods. A meta-analysis indicated that a longer duration of ECG monitoring is associated with an increased detection of new AF when examining monitoring time as a continuous variable. Studies with monitoring lasting ≤ 72 h detected new AF in 5.1% of cases, whereas monitoring lasting ≥ 7 days detected AF in 15% of cases.²⁰⁹ The proportion of new diagnosis of AF was increased to 29.1% with 3-months extended monitoring. Recently, smartphone-based ECG recording systems have been developed and conferred acceptable sensitivity and specificity of detecting AF¹⁹¹ (see Wearables/direct to consumer section).

The use of an ILR is indicated for detecting the presence of AF or arrhythmia burden that might cause ischaemic stroke in selected patients, for example those who are at higher risk of AF development including elderly, patients with cardiovascular risk factors or comorbidities. An ILR is a useful tool for detecting arrhythmias. In the CRYSTAL AF study, AF was newly detected in 8.9% of patients with an ILR by the 6th month compared with 1.4% among those receiving conventional ambulatory ECG monitoring, increasing further to 12.4% by 12 months compared with 2.0% in conventional monitoring.⁸⁰ A similar outcome was observed in the EMBRACE trial, in

which AF was newly detected in 16.1% of patients who received 30-day ILR compared with 3.2% who received ambulatory 24-h monitoring.²¹⁰ A systematic review indicated that AF was newly detected in nearly one-quarter of patients with stroke or TIA by sequentially combining cardiac monitoring methods: 7.7% in phase 1 (emergency room), 5.1% in phase 2 (in-hospital), 10.7% in phase 3 (first ambulatory period), and 16.9% in phase 4 (second ambulatory period consisting of trans-telephonic ECG monitoring, cardiac event recorders, and ILR), and 23.7% in the overall detection after all phases of sequential ECG monitoring.²⁰⁷ Thus, if we 'look harder, look longer and look in more sophisticated ways' we are more likely to detect AF. It is possible that if we use clinical risk stratification (e.g. the C2HEST score) to identify patients post-stroke at high risk of incident AF, targeted intensive monitoring can be applied.²¹¹

How to assess high risk of atrial fibrillation in professional athletes

Atrial fibrillation in athletes	Class	References
In athletes who participate long term in endurance exercises with symptoms of arrhythmia screening for AF is recommended.		²¹²
Risk assessment for AF risk in athletes may include the duration and intensity of exercise as a potential modifiable risk factor.		^{213,214}

Atrial fibrillation risk in athletes—general

Paroxysmal or persistent AF is common in athletes and may be autonomically mediated or triggered by other supraventricular tachycardias.²¹⁵ AF is the primary arrhythmia observed in middle-aged athletes.²¹⁶ AF in athletes tends to be paroxysmal, vagally mediated, and highly symptomatic.²¹³ The mechanism of increased AF risk at either end of the physical activity spectrum likely includes autonomic, structural, inflammatory, and fibrotic changes to the heart. For example, increased vagal tone, which is often observed in the endurance athlete, has been shown to result in a short atrial refractory period, and thus initiates AF.²¹⁷

Atrial fibrillation risk in athletes—exercise paradox




Recent studies have observed a U-shaped risk relationship of physical activity to AF. At one end of the spectrum, a large observational study^{218,219} of people showed that those at the lowest levels of physical fitness had a 5-fold increased risk of AF.²²⁰ Increasing the physical activity of sedentary patients could help reduce the risk or burden of AF. Long-term endurance training, as well as a sedentary lifestyle,²²¹ increase chronic systemic inflammation, which in turn could also facilitate AF.¹⁰⁶ For example, one randomized study demonstrated that just 12 weeks of moderate-intensity physical activity decreased the AF burden by 41%.²²² Of the physically inactive with AF, the obese

might benefit the most from moderate levels of physical activity.²²⁰ In contrast, a meta-analysis of 655 endurance athletes also demonstrated a five-fold increased risk of AF.²¹² Of these studies, increased AF risk was generally only observed with the highest levels of physical activity that was maintained over a prolonged period of time.^{213,214} One uniform explanation for the exercise paradox is that both long-term endurance training and a sedentary lifestyle increase chronic systemic inflammation.

Atrial fibrillation risk in athletes—structural cardiac changes

Most studies have shown structural changes in endurance athletes, which have resulted in the term athlete's heart. These changes include dilatation of all four heart chambers, increase in left ventricular mass, and mild right ventricular hypertrophy.²²³ Studies show that moderate physical activity might reduce inflammatory markers.^{224–226} Extreme levels of exercise are a known cause of cardiac fibrosis, particularly in hinge point locations of the heart, such as the right ventricle; however, the significance of MRI-detected fibrosis remains controversial.²²⁷ Athletes who experience higher levels of fibrosis also have higher levels of coronary calcium.²²⁸ In turn, fibrosis is a well-established risk factor of AF.¹⁶³ In one study, the fibrotic changes caused by vigorous exercise were reversed after an 8-week period of physical activity cessation.²²⁹ Among young elite athletes, age, years of competition, and echocardiographically measured parameters, including left atrial anterior–posterior diameter and atrial strain, were associated with higher AF risk.^{230,231} Although increasing physical activity might reduce AF in sedentary patients, decreasing physical activity levels in elite endurance athletes may also reduce AF.²¹⁵ Currently, the role of deconditioning to lower AF risk in elite athletes for primary or secondary prevention of arrhythmia requires prospective evaluation.

Patients with inherited rhythm disease (long QT syndrome/short QT syndrome/catecholaminergic polymorphic ventricular tachyarrhythmia/Brugada syndrome)

Patients with inherited rhythm disease	Class	References
Patients with certain inherited arrhythmia syndromes are at higher risk for AF and benefit from symptom-driven and periodic surveillance.		123
Evaluation should include non-invasive symptom-driven surveillance for patients at risk for AF and periodic non-invasive surveillance for asymptomatic patients.		232–234
EPS to determine atrial AF substrate or susceptibility is not useful.		123

Some patients with primary electrical sudden death syndromes have an increased AF association, including Brugada Syndrome, LQTS, SQT, and catecholaminergic polymorphic ventricular tachycardia (CPVT). These patients are at risk for arrhythmia symptoms from AF and are vulnerable to AF consequences such as pro-arrhythmia and inappropriate ICD shocks.

Brugada Syndrome is characterized by ST-segment elevation in the precordial ECG leads and increased risk of SCD due to VF.²³⁵ Brugada Syndrome is associated with a higher incidence of SVTs, and AF is the most common SVT in these patients.^{236,237} AF susceptibility has been described with patients harbouring mutations in SCN5A, CACNA1C and patients without an identified genotype,^{234,238} suggesting a lack of genetic AF specific risk but AF may be more prevalent with more advanced disease.^{239,240} Importantly, AF events can be pro-arrhythmic for Brugada Syndrome patients^{123,241} and contribute to the high inappropriate ICD shock rates for Brugada Syndrome patients.²⁴¹

Long QT syndrome is a genetically heterogeneous syndrome associated with mutations in 17 different genes with some unique phenotypic characteristics based on genotype and electrically results in prolonged repolarization and risk for fatal ventricular arrhythmia torsade de pointes. While generally, prolonged repolarization inhibits AF initiation and this is the mechanism for Vaughn–Williams Class III anti-arrhythmic drugs, rare patients with LQTS have also been noted to have AF.^{242,243} This has been limited to single case reports and unverified, 1.7% of patients in a LQTS cohort, which is a higher prevalence than the general population.^{133,244} Not surprisingly, some genes associated with AF in LQTS have overlap with familial AF: LQT1 (KCNQ1), LQT2 (KCNH2), LQT3 (SCN5a), and LQT7 (KCNJ2). However, for potassium channels, in LQTS the genetic defect results in ‘loss of function’ in contrast to a ‘gain of function’ in familial AF.^{245,246} It is less clear how prolonged repolarization results in AF susceptibility but it may involve similar mechanisms to torsade de pointes²⁴⁷ or perhaps dispersion of repolarization and induction of early afterdepolarizations.^{248,249}






From an electrical substrate standpoint, it is easier to understand why SQTs and CPVT are associated with AF. Short QT syndrome is a rare disorder caused by a gain of function of potassium channels encoded by KCNQ1, KCNH2, and KCNJ2, causing a shortening of the action potential and manifests in the atrium by a decreased atrial refractory period and electrical substrate for AF.^{250–252} CPVT is an autosomal dominant disorder associated with polymorphic VT and bidirectional VT due to cellular calcium overload caused by mutations in calcium handling genes.^{253–255} A reciprocal condition can exist in the atria of patients with CPVT with AF susceptibility and has been shown to be more prevalent in patients with more dysfunctional ryanodine receptor2 channels.²⁵⁶ It is also unclear how clinically significant AF is for CPVT patients. However, the failure to recognize and treat AF can result in inappropriate shocks, pro-arrhythmia, and death.^{232,233}

These issues highlight the need for AF recognition, ICD programming to reduce the risk of inappropriate shocks, and preventative treatment. Because of the small cohort sizes and lack of systematic studies, it is difficult to prospectively estimate AF risk. Invasive EP studies evaluating atrial refractory periods, conduction time, and AF inducibility have been inconclusive^{236,237} and either not systematically

evaluated in large populations or are contraindicated (LQTS and CPVT).¹²³ We support vigilant non-invasive surveillance in these conditions. For patients with ICD, close follow-up is needed to decipher and to adjudicate if atrial arrhythmias are present and proactively increase the rate cut-off for VF detection and turn SVT discriminators on, if available. Patients without ICD, but suggestive symptoms, should undergo ambulatory monitoring and asymptomatic patients should have surveillance monitoring done every 1–2 years. Treatment is not the focus of this article, but it should be recognized that many AADs can worsen the electrical substrate for inherited arrhythmia patients (i.e. LQTS, Brugada Syndrome) and care should be taken when choosing antiarrhythmic drugs.

How to assess risk for adverse outcomes in patients with atrial fibrillation

Risk assessment for stroke/transient ischaemic attack/cognitive decline



Risk assessment for stroke/TIA/Cognitive decline	Class	References
A risk factor-based approach is recommended for stroke risk assessment in patients with AF.		8,257
Cognitive assessment should be performed in AF patients where there is suspicion of cognitive impairment.		258,259
Assessment of cognitive function may be multifaceted, and cognitive impairment screening by available tools is just one component.		258
Risk reduction of cognitive dysfunction and its comorbidities in AF may include risk assessment for vascular disease and/or Alzheimer's disease.		258,260
General health measures may reduce the concomitant risks of AF and stroke, with a putative benefit on cognitive function.		1,2

Patients with AF have increased mortality and morbidity compared with non-AF patients and may experience significant adverse events. Stroke and thrombo-embolic events are well known complications that can be avoided by oral anticoagulation. Since the risk of individual patient differs significantly, an individual risk assessment is necessary.



Several stroke risk scores, including ABC-stroke (age, biomarker, clinical history), ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), GARFIELD (Global Anticoagulant Registry in the FIELD), and Qstroke have been proposed as support tools for the decision on oral anticoagulation.^{261–264} However, the one currently most widely applied and recommended by international guidelines is the CHA₂DS₂-VASc risk scheme. According to CHA₂DS₂-VASc, patients with score of ≥ 1 in a male or ≥ 2 in a female should be considered for stroke prevention strategies.^{265–268} Nevertheless, it has to be kept in mind that no stroke risk scheme has perfect predictive accuracy.

Another major adverse effect of AF is impairment of cognitive function.^{258,259} Multiple risk factors for dementia have been identified in the general population, including modifiable and non-modifiable ones.²⁶⁹ Apart from these AF-non-specific risk factors, AF may lead to cognitive impairment by multiple mechanisms. These include apparent stroke, silent stroke but also other mechanisms that are independent of thromboembolism.²⁷⁰ A detailed description of the association between AF and cognitive impairment and possible preventive mechanisms has been provided recently in an expert consensus document.²⁵⁸ In terms of prevention of cognitive impairment in AF patients, there is evidence that early and effective use of oral anticoagulation in patients with stroke risk factors reduces the rate of cognitive decline and currently, this represents the most important preventive strategy. Consequently, the main risk assessment for cognitive impairment in AF patients is the assessment of stroke risk factors, preferably by use of the CHA₂DS₂-VASc risk scheme that can guide the decision on oral anticoagulation. When cognitive impairment is suspected, brief screening tools such as General Practitioner Assessment of Cognition (GPCOG), Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MOCA), and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) may be applicable.²⁵⁸ In addition, more comprehensive assessments may be done after appropriate referral to a psychiatrist, geriatrician, or neurologist.²⁵⁸

Risk assessment for stroke/transient ischaemic attack status post-left atrial appendage occlusion/ligation

Risk assessment for stroke/TIA after LAA occlusion/ligation	Class	References
TOE after 6 weeks and if necessary after 1 year is useful for detecting peri-device residual flow, incomplete appendage ligation, or device-related thrombus to identify patients at higher risk of stroke.		271,272
Clinical features such as previous TIA/stroke, persistent AF, low LVEF, vascular disease, and early		273,274

Continued

Continued		
Risk assessment for stroke/TIA after LAA occlusion/ligation	Class	References
discontinuation of anticoagulation may be helpful to guide decisions regarding imaging for device related thrombus.		
Multi-detector CT and cardiac CT angiography have been found to be equivalent to TOE to detect peri-device flow.		275,276
After surgical occlusion or exclusion of the left atrial appendage, imaging may be useful to look for a residual appendage and its function or a residual leak after ligation to guide decisions regarding anticoagulation.		277,278,535



Left atrial appendage (LAA) occlusion/ligation using one of several devices or surgical techniques has been developed as an alternative to anticoagulation in high-risk patients with non-valvular AF.^{279–281} The maximum experience has been with the Watchman device (Boston Scientific), which has been found to be non-inferior to warfarin in patients who are still candidates for short-term warfarin treatment.^{282–284} Results of comparison between LAA occlusion/ligation and NOACs are awaited. Current guidelines recommend use of LAA occlusion as a possible strategy in patients having contraindications to long-term anticoagulation.²⁶¹

The residual risk of stroke/TIA following LAA occlusion/ligation can be related to procedural or patient related risk factors. Among the procedure related factors, peri-device leak, and device-related thrombus are important factors for thrombo-embolic events in short and medium term after the procedure. Stroke risk is significantly elevated in patients in whom LAA ligation fails after surgical²⁸⁵ or percutaneous approaches.²⁸⁶

Post-procedure surveillance is therefore important to assess long-term risk of stroke and need for continued anticoagulation. These may be detected on TOE immediately or after few weeks/months.^{271,272} Multidetector CT and cardiac CT angiography have been compared with TOE and found to be an effective alternative technique to detect peri-device flow.^{275,276} Device-related thrombus is seen in 3–7% of patients after LAA closure, and leads to a 3–4 fold higher risk of stroke.^{273,274} Factors predicting device-related thrombus are previous TIA/stroke, persistent AF, low LVEF, vascular disease, and early discontinuation of anticoagulation.^{273,274}

If surgical LAA ligation fails or is incomplete, stroke rates are significantly increased. Similarly, with percutaneous closure devices, residual LAA leaks were associated with increased risk of thrombo-embolism in excess of that associated with baseline risk factors or echocardiogram findings.²⁸⁵

Risk for heart failure incidence and progression

Risk for heart failure incidence and prognosis	Class	References
Screening for AF in patients with HF should be performed because of the increased risk of adverse cardiovascular outcomes in combination more than the risk conveyed by either disease state alone.		287,288
Interval use of echocardiography and arrhythmia directed monitoring for development of AF-induced cardiomyopathy and risk assessment over time should be part of standard follow-up for patients with AF.		289,290


Atrial fibrillation and HF are conditions that coexist in many patients, and sometimes it will be difficult to establish if HF was the cause of AF or AF caused HF (tachycardia-induced cardiomyopathy).^{287,291} In the Framingham study, 41% of patients with AF and HF developed HF first, 38% developed AF first, and in the remaining 21%, AF and HF occurred at the same time.²⁸⁸ AF is associated with a three-fold increased risk of incident HF.²⁹² In trials of patients with chronic systolic heart failure, the prevalence of AF was 4% in patients with Class I symptoms, 10–27% in patients with Class II–III symptoms, and 50% for those with Class IV HF symptoms.²⁹⁰ Additionally, aging and the structural and neurohormonal changes in HF make the development and progression of AF much more likely. The risks of developing an AF-induced cardiomyopathy appear to be related to the ventricular rate during AF and the duration of AF. However, the precise incidence of tachycardia-induced cardiomyopathy with AF, in patients with and without SHD is unknown.

The mechanisms and pathophysiology of AF and HF share several risk factors and common pathophysiologic processes. Hypertension, smoking, obesity, diabetes, renal impairment, sleep apnoea, and CAD are all associated with an increased risk of developing both HF and AF, and each condition increases morbidity and mortality when associated with the other. All types of HF (HfPEF or HFrEF) are associated with an increase prevalence of AF.^{293,294} There are no studies examining the role of monitoring to detect AF in asymptomatic patients with HF or the management of AF if detected. For patients with cardiac implantable electronic devices, remote monitoring is a tool for determining AF burden and is part of routine device follow-up. In patients with HF, the risk of AF is increased by several mechanisms, remodelling of atrial structure and increased fibrosis, ectopy promoted by atrial stretch, increased spontaneous firing in the pulmonary veins

and alterations in calcium current handling in the atrial muscle and sarcoplasmic reticulum calcium content.²⁸⁹

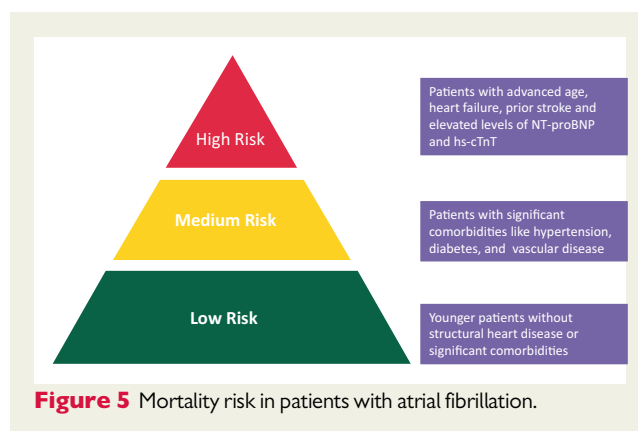
The loss of atrial systole in AF impairs LV filling and can result in left ventricular dilatation, decrease in myocardial blood flow and increase in LV wall stress and end-diastolic pressure. Atrial fibrillation can decrease cardiac output by 25% particularly in patients with diastolic dysfunction. The mechanisms for reduction in cardiac output include loss of atrial contribution to ventricular filling, increased mitral regurgitation and decreased left ventricular filling time. The irregular and rapid ventricular contraction in AF can lead to LV dysfunction in an unknown percentage of patients and in some patients a tachycardia-induced cardiomyopathy results.²⁹⁰ The irregular ventricular response also compromises ventricular performance through changes in calcium handling and reduced expression of Serca and phospholamban phosphorylation. Management can vary widely according to presentation and should be individualized since treatments shown to be effective in one or other condition alone, may give rise to safety or efficacy issues in an individual patient. Several recent trials have suggested a preferential role for primary catheter ablation of AF in select AF patients with HF compared to medical therapy alone.^{295–297} Treatment of AF by either rate or rhythm control may reverse the cardiomyopathy and improve clinical HF substantially in selected patients.

Risk for death in atrial fibrillation patients

Risk for death in AF patients (including risk for SCD)	Class	References
Clinical characteristics of the patient including presence of advanced age, cognitive dysfunction or dementia, diabetes mellitus, hypertension, prior stroke, vascular disease, and HF should be used as important risk markers of higher mortality in patients with AF.		298,299

Atrial fibrillation is associated with 1.5- to 2-fold higher risk of all-cause mortality which may result from stroke, HF, or SCD.²⁶¹ Of the mortality associated with AF, only 1 in 10 deaths are stroke, and >7 out of 10 are cardiovascular.³⁰⁰ A multipronged strategy incorporating stroke prevention, better symptom control, and cardiovascular risk optimization is associated with improved outcomes, including a reduction in mortality.^{3,4} Females with AF have slightly higher mortality compared to male patients. Ethnic or racial differences exist in mortality risk, with one study showing highest risk in African Americans among all racial/ethnic groups.³⁰¹ Also, presence of comorbidities increases the risk compared with 'lone' AF. Advanced age, renal failure, pulmonary disease, and HF have been found to be most important risk factors for higher mortality in AF (Figure 5).^{298,299}

Numerous risk scores have been designed to assess the mortality risk in AF. The CHA₂DS₂-VASc score was designed to assess stroke



risk, but given it is a cluster of common risk factors for cardiovascular mortality also predicts mortality risk.³⁰² More complex clinical risk scores designed to predict mortality, such as an integrated GARFIELD-AF risk tool, statistically improves mortality prediction, being superior to the CHA₂DS₂-VASc score.³⁰³ All clinical risk scores only have modest predictive value (c-indexes 0.6–0.7) but can always be statistically improved by the inclusion of cardiac biomarkers, such as NT-proBNP and hs-TnT. Both biomarkers (and others) have been found to be independently associated with increased midterm mortality in AF patients presenting to emergency room.³⁰⁴ Indeed, risk scores incorporating biomarkers have been proposed, such as the ABC-death risk score, which utilizes age, biomarkers, and clinical history. The ABC-death score achieved a c-index of 0.74 [95% confidence interval (CI) 0.72–0.76], while the CHA₂DS₂-VASc score achieved a c-index of 0.58 (95% CI 0.56–0.61).³⁰⁵ However, the clinical usefulness of any risk-prediction score for mortality has not been established, and further validation studies are needed. Indeed, many risk factors or biomarkers are based on measurements done at baseline, and follow-up events occur many years later. Cardiovascular risk is not static but changing with increasing age and incident risk factor(s), thus repeat risk re-assessment is more appropriate given that a change in risk scores is more highly predictive of adverse outcomes.



Importantly, many biomarkers are non-specific, more likely reflecting a patient with significant comorbidities and significant underlying heart disease, and are predictive of various endpoints apart from death, including stroke, heart failure, etc.^{306,307} Indeed, biomarker-based scores like ABC-death were derived from a highly selected clinical trial cohort which was anticoagulated, and values were determined at study entry (baseline). Many biomarkers also have a diurnal variation and inter/intra laboratory variability and are predictive of non-cardiovascular outcomes. Real-world studies investigating the usefulness of sequential addition of biomarkers have shown limited value over conventional clinical risk scores.^{10,308,309} Thus, statistically significant improved prediction should not be confused with clinically improved risk prediction. A balance is therefore needed between (statistically) improved risk prediction and simplicity or practicality for everyday clinical use in busy clinical settings. In summary, any novel biomarker (or biomarker-based scores) would need to be validated in large non-anticoagulated cohorts. This is the starting point of risk stratification with the newly diagnosed AF patient in any patient care pathway, and be simple, practical and adequately validated to

account for the dynamic nature of risk factors and changes in drug therapies (including the use of antithrombotic drugs) over time.

Stroke resulting from AF has significant medium-term mortality, which can be as high as 30.5% at 1 year.³¹⁰ An 8-point GPS-GF score utilizing variables including Glasgow Coma Scale, pneumonia, midline shift on brain images, blood glucose, and female sex has been developed and was found useful to predict 30-day mortality in patients with AF-related stroke.³¹¹

Spontaneous AF is associated with an increased risk of SCD in patients with Wolff–Parkinson–White (WPW) syndrome, HCM, and channelopathies such as Brugada syndrome.²⁶¹ Several recent studies on HF and LVH and those on the general population have reported that AF is linked to an increased risk of SCD.^{312–314} Mechanisms for SCD due to AF are well understood for WPW syndrome or HCM, but are unclear regarding other cardiac disorders. A meta-analysis demonstrated a significant association between AF and SCD in the general population as well as in patients with CAD, congestive HF, HCM, Brugada syndrome, and implanted rhythm devices.³¹⁵ In a nationwide cohort study from Taiwan, 352 656 patients were identified. Among AF patients, age ≥75 years, congestive heart failure, hypertension, diabetes mellitus, previous stroke/TIA, vascular diseases, chronic kidney disease, and chronic obstructive pulmonary disease were important risk factors for SCD or ventricular arrhythmias.³¹⁶ A recent study suggested that optimal pharmacological treatment, in addition to anticoagulant therapy, can reduce SCD rates in patients with AF.³¹⁷ Since pharmacological rhythm control has so far been relatively ineffective in preventing SCD in AF patients with low LVEF,³¹⁸ catheter ablation may be more appropriate for improving prognosis in patients with AF.²⁹⁶ To assess the risk of SCD in patients with AF, recognizing the presence of CAD, HF, LVH/HCM, pre-excitation, Brugada syndrome, and implanted rhythm devices is crucial. Examinations including 12-lead ECG, echocardiography, and other imaging modalities such as cardiac MRI are useful for detecting various cardiac disorders. Electrophysiological testing is useful for identifying risks in patients with WPW syndrome and paroxysmal AF.

Risk of adverse outcomes in patients treated with catheter ablation

Risk of adverse outcomes in patients treated with catheter ablation	Class	References
Patients that undergo an AF ablation should be monitored closely in the first 30 days after the procedure due to a higher risk of neurological, gastrointestinal, cardiovascular, vascular and peripheral complications.		319–324
Wolff–Parkinson–White syndrome patients following radiofrequency ablation may benefit from additional follow-up due to a persistent elevated risk of developing AF compared to the general population.		295,325

Radiofrequency (RF) ablation has emerged as a main therapeutic option for treatment of AF patients since 1998 after the observation that AF mostly initiates from arrhythmogenic triggers in muscular sleeves in the pulmonary veins.³²⁶ There is abundant evidence that AF ablation is an effective method for AF suppression leading to significant reduction of AF episodes and burden accompanied by substantial improvement in symptoms and quality of life if performed in symptomatic patients. For this reason, AF ablation is mainly recommended by current guidelines as a method for symptom improvement in symptomatic AF patients.²⁶¹

Post-ablation atrial fibrillation recurrence

Post-ablation AF recurrence is one of the most important and frequent adverse outcomes, which occurs in 30–50% of cases.^{327,328} In fact, although the acute success rate of AF catheter ablation seems high, achieving a durable treatment efficacy has remained a main challenge.^{261,328} Different factors including female gender, older age, traditional cardiac risk factors, left ventricular dysfunction, increased epicardial adipose tissue, myocardial fibrosis, and atrial enlargement have been proposed as possible predictors of post-ablation AF recurrence.^{329–331} Moreover, diverse AF recurrence risk-prediction scores, including APPLE, ALARMEc, ATLAS, BASE-AF2, CAAP-AF, DR-FLASH, and MB-LATER have been introduced; however, their integration into the daily clinical practice needs further support by healthcare systems.^{332–341}

Other adverse outcomes

Apart from AF recurrence, according to the available real-world data, around 5–15% of patients undergoing AF catheter ablation experience complications, mainly during the index hospitalization and early in the post-procedure course.^{319–324} A variety of complications, including neurological, gastrointestinal, cardiovascular, vascular and peripheral, as well as pulmonary complications have been reported to occur after ablation procedures.^{319–324,342–346} Although different modifiable factors such as metabolic syndrome, hypertension, alcohol consumption, sleep apnoea, and obesity have been proposed to be related with arrhythmia-free survival after catheter ablation,^{347–350} their impact on the ablation adverse outcomes is not clear yet, and requires further investigations.

Mortality and morbidity

The impact of the ablation on hard clinical endpoints is much less evident. Previous findings from observational studies indicated a positive effect of the procedure on mortality and morbidity.³⁵¹ These, however, were not confirmed in the recent large randomized Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA) that had as primary endpoint a composite of death, disabling stroke, serious bleeding, or cardiac arrest.²⁹⁵ In contrast, positive effects on hard clinical endpoints including mortality have been reported in patients with HF. In the CASTLE-AF trial, patients with impaired LVEF <35% and previous ICD implantation who were treated with ablation therapy had a lower rate of death from any cause or hospitalization for worsening HF compared to patients undergoing medical treatment.²⁹⁶

Stroke

Regarding the impact of AF ablation on stroke and in particular the validity of stroke risk schemes for stroke risk stratification after ablation, observational data suggest a reduced stroke risk after AF ablation and a possibly safe termination of anticoagulation, at least in selected patients.^{352,353} Conclusive evidence is expected from ongoing randomized trials as the Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial (OCEAN) (NCT02168829) and the Prevention of Silent Cerebral Thromboembolism by Oral Anticoagulation with Dabigatran After Pulmonary Vein Isolation for Atrial Fibrillation (ODIn-AF) trial (NCT02067182). Until now, one randomized trial showed that ablation therapy for AF in patients with impaired LVEF was associated with significantly lower rate of death from any cause and worsening HF.²⁷⁴ Subgroup recommendations may change after the completion of trials studying the effect of ablation on stroke and the need for anticoagulation. Particularly in HF patients, it remains to be seen in which subgroups of patients the data indicating mortality reduction after AF ablation are applicable.

Catheter ablation in Wolff–Parkinson–White patients

Careful attention must be given in WPW patients who underwent RF ablation, as it was demonstrated that they had an increased risk of AF at follow-up when compared to general population, though an increased risk of death was not reported.^{296,325}

Risk of adverse outcomes in patients treated with surgical Maze

The surgical Cox–Maze operation was introduced in 1987 to treat patients with refractory AF.³⁵⁴ This surgical approach carries more risk of complications than the catheter ablation procedure, and is suitable for selected patients only. In this setting, we can observe three different case-scenarios.

Atrial fibrillation surgery

A simplification of the Cox–Maze procedure was proposed by replacing the ‘cut and sew’ lesions by different ablation devices and minimally invasive access.³⁵⁵ In the recent years, bipolar RF clamping devices guided on a beating heart, by thoracoscopic epicardial approaches have been introduced.^{277,356} This evolution has allowed the implementation of this surgery for stand-alone persistent and long-standing persistent AF ablation, after an ineffective antiarrhythmic drug treatment or a previous endocardial ablation failure with a IIa (Level of Evidence B) indication.²⁷⁸ On another hand, this invasive approach carries some potential risks that need to be anticipated and discussed. Ideally, this step should involve an arrhythmia team in order to discuss the risk–benefit balance of the procedure on a case by case basis.³⁵⁷

Surgical Maze in patients with concomitant heart surgery

An AF surgical ablation procedure is reasonable for selected patients with AF undergoing cardiac surgery for other indications.²⁶¹ In patients that may receive a concomitant Maze procedure, a shared decision-making strategy should be used with an AF heart team to make the best decision available for the patient and their heart

condition.³⁵⁷ Mortality or major morbidity was not affected by concomitant AF surgery [adjusted odds ratio (OR) 1.00; 95% CI 0.83–1.20], but pacemaker implantation was more frequent (adjusted OR 1.26; 95% CI 1.07–1.49).³⁵⁸ Stiff LA syndrome was also reported after surgical Maze procedure, presenting with dyspnoea, pulmonary hypertension, and elevated left ventricular end-diastolic pressure attributed to reduced LA compliance.³⁵⁹

Predictors of AF recurrence after surgery include left atrial dilatation, older age, over 10-year history of AF, and non-paroxysmal AF.^{360–364}

Stand-alone surgical Maze

A stand-alone AF surgical ablation procedure may be reasonable for selected patients with highly symptomatic AF not well managed with other approaches (e.g. after a failed catheter ablation, longstanding AF, dilated left atrium).³⁶⁵ After Cox–Maze IV stand-alone procedure, overall operator mortality was 1–1.8%, overall complication rate was 10%, 8% required pacemaker placement, and 12-month freedom from atrial tachyarrhythmias was 89% (78% without antiarrhythmic drugs).^{366,367}

Left atrial appendage exclusion or removal during surgical Maze

The prospective randomized trial comparing the efficacy and safety of LAA exclusion or removal with surgical Maze procedure is lacking. However, epicardial LAA Atriclip occlusion showed a high rate of complete left atrial appendage occlusion and reduces the incidence of stroke in patients with AF undergoing cardiac surgery.²⁸¹ After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.²⁶¹ If surgical LAA ligation fails or is incomplete, stroke rates are significantly increased compared to patients with complete closure.²⁸⁵

How to assess risk for ventricular tachyarrhythmia in specific populations



Patients with ischaemic heart disease

Ventricular tachyarrhythmia/ventricular fibrillation events are closely related to the risk of SCD in patients with ICM. For this reason, the risk of VT/VF is commonly used as a surrogate for the risk of SCD. In addition, in ICM, myocardial ischaemia is the most common trigger for VF and SCD.

For primary prevention, our current approach to SCD risk stratification relies mainly on the evaluation of LVEF: values below 30–35% allow the identification of ICD candidates, who are at highest relative risk of SCD. On the other hand, patients with a LVEF >35% account for the highest absolute number of SCDs.³⁶⁸ For this reason, many researchers emphasize that EF is an inadequate marker for detecting patients who are at high risk for SCD despite having a normal or sub-normal EF. It seems also to have very limited value to identify amongst patients with a low LVEF those who will benefit the most from an ICD. In other words, many patients with EF ≤35% are


unnecessarily implanted with an ICD for primary prevention, while some others, having a EF >35% and a high risk of VT/VF, are not protected. In this setting, new markers are needed to optimize screening and patient selection for ICD implantation. For secondary prevention, SCD risk is significantly higher, and risk stratification is certainly more standardized.^{61,74}

Secondary prevention of ventricular tachyarrhythmia/ventricular fibrillation in patients with ICM

Secondary prevention of VT/VF in patients with ICM	Class	References
ICM substrate and ischaemic triggers for VT/VF must be evaluated when appropriate (coronary angiogram, functional ischaemic evaluation by nuclear scan, stress-echocardiography, or MRI).		54,70,71
Cardiac MRI with a LGE can be considered in order to evaluate arrhythmogenic substrate including myocardial scarring to include in risk assessment, and guide a possible VT ablation procedure. This investigation should be preferably performed before ICD implantation to avoid artefacts due to the presence of an implanted device.		369


For more than 20 years, patients with a history of sustained VT/VF have been recognized to be at high risk of recurrence.³⁷⁰ Nowadays, these patients are given a Class I (Level of Evidence A) indication for ICD implantation.⁷⁰ For this reason, the practical usefulness of VT/VF recurrence risk assessment is questionable, as additional testing is likely not going to influence decision pathways (i.e. catheter ablation or antiarrhythmic drug therapy as an alternative to ICD implantation), and patient outcomes in a secondary prevention setting.

Primary prevention of ventricular tachyarrhythmia/ventricular fibrillation in patients with ICM and a left ventricular ejection fraction ≤35%

Primary prevention of VT/VF in patients with ICM and LVEF ≤ 35%	Class	References
ICM substrate and ischaemic triggers for VT/VF must be evaluated when appropriate (coronary angiogram, functional ischaemic evaluation by nuclear scan, stress-echocardiography or MRI).		54,70,71
Cardiac MRI with a LGE can be considered in order to evaluate arrhythmogenic		369


Continued

Continued

Primary prevention of VT/VF in patients with ICM and LVEF ≤ 35%	Class	References
substrate including myocardial scarring to include in risk assessment and guide a possible VT ablation procedure. This investigation should be preferably performed before ICD implantation to avoid artefacts due to the presence of an implanted device.		



Patients presenting with ICM, in NYHA Class II–III, with EF ≤35% after 3 months of optimized heart failure pharmacological treatment, are given a Class I/A indication for ICD implantation for the primary prevention of SCD.⁷⁰ Nonetheless, it is widely recognized that only a small subgroup of these patients will present with VT/VF during follow-up, and consequently will benefit from the device. A better risk stratification of these patients would be crucial to help identify those who would indeed benefit from an ICD. Most of the numerous investigations assessed in this setting, like programmed ventricular stimulation (PVS), heart rate variability (HRV), late ventricular potentials (LVP), baroreflex sensitivity, QT interval dispersion, T-wave alternans, and heart rate turbulence have been largely abandoned because none of them have influenced routine clinical practice.^{46,73,371,372} However, some of these explorations, like T-wave alternans, have shown some value for SCD prediction in ICM patients.⁴² It is still uncertain whether biochemical markers as B-type natriuretic peptide and N-terminal pro-BNP will prove useful in assessing risk for VT/VF. Cardiac MRI with LGE should also help to improve VT/VF and SCD risk stratification by analysing cardiac structure and myocardial scarring.³⁷⁵ Finally, a recent randomized trial suggests that assessment for hibernating myocardium performed routinely is of no use to decrease the risk of SCD.⁶⁸

Primary prevention of ventricular tachyarrhythmia/ventricular fibrillation in patients with ICM and left ventricular ejection fraction 35%

Primary prevention of VT/VF in patients with ICM and LVEF > 35%	Class	References
ICM substrate and ischaemic triggers for VT/VF must be evaluated when appropriate (coronary angiogram, functional ischaemic evaluation by nuclear scan, stress-echocardiography or MRI).		54,70,71
EPS and non-sustained VT evaluation could be considered to		311,373,374

Continued

Continued



Primary prevention of VT/VF in patients with ICM and LVEF > 35%	Class	References
improve VT/VF risk stratification in patients with relatively preserved LVEF, particularly in the convalescent phase (first 2 months) after an acute coronary syndrome.		
Heart rate variability (HRV), LVP, baroreflex sensitivity, QT-interval dispersion, T-wave alternans and heart rate turbulence have not been evaluated adequately in this population for generalized use.		73,371,372

This group of patients should be the priority for VT/VF risk assessment: in absolute numbers, it represents by far the highest number of those at risk of VT/VF and SCD.³⁶⁸ In addition, these patients are currently non-protected, as they are not targeted for ICD implantation in guidelines, due to their LVEF value.⁷⁰ In this setting, MRI with LGE could be an option to better understand the diagnosis, prediction, and treatment of VT/VF.³⁶⁹ This investigation could possibly help improve VT/VF and SCD risk stratification by analysing cardiac structure and myocardial scarring, particularly when EF is relatively preserved. In this setting, a large prospective trial documenting that treatment guided by MRI-based risk stratification improves outcomes in this patient group is still very much expected.³⁷⁵

Otherwise, the MUSTT Trial suggested the value of EPS for improving the SCD risk stratification, in the subgroup of ICM patients with a residual EF comprised between 30 and 40%.³⁷⁶

In addition, other non-invasive investigations like tissue Doppler Imaging (TDI) seem also to be of potential value in predicting VT/VF in ICM. Late diastolic velocity assessed by TDI, particularly when detected in the inferior myocardial wall, seems to be a sensitive marker of future VT/VF.³⁷³ Finally, it is well known that non-sustained ventricular tachycardia (NSVT) is a marker of increased risk of VT/VF and arrhythmic death. During the convalescent phase after an acute coronary syndrome, NSVT seems to be associated with an increased risk of cardiovascular death, most marked within the first 2 months after detection.³⁷⁴ The use of such investigations could help to detect those patients at higher risk of VT/VF, more particularly during the early phase after an acute coronary event. Specific measures like prolonged monitoring or use of wearable cardiac defibrillator could be undertaken on an individual patient-case basis. However, more solid data are needed to support such recommendations broadly.

Patients with non-ischaemic heart failure

Patients with non-ischaemic heart failure	Class	References
MRI may be considered for further risk stratification of sudden death in patients with non-ICM who do not otherwise meet an indication for ICD implantation.		377
EPS may be considered for further risk stratification of sudden death in selected patients with non-ICM who do not otherwise meet an indication for ICD implantation.		377

Patients with non-ischaemic HF represent a broad and diverse group of patients including those with progressive and infiltrative forms of cardiomyopathies. For this reason, the risk of developing VT in non-ischaemic HF is difficult to accurately predict in this group of patients. Subsequent sections in this document will address specific conditions that have unique risk profiles including inflammatory cardiomyopathies, congenital heart disease, ACM, and Chagas' disease.


Prior investigations into identification of the risk of developing VT in non-ICM focused on the risk of SCD and the role of the implanted defibrillator for primary prevention. The DANISH trial⁶¹ reported no survival benefit from prophylactic ICD implantation in the overall cohort. Implantable cardioverter-defibrillator reduced SCD to half, and subgroup analysis showed that in patients younger than 68 years, survival was prolonged with an ICD. Although pooled analysis of the five primary prevention trials (DEFINITE, SCD-HeFT, CAT, AMIOVIRT, COMPANION, and DANISH; $n = 2970$) revealed that ICD therapy was superior to medical therapy in patients with non-ICM with decreased cardiac function, these trials were judged globally negative.³⁷⁸

In a limited number of studies outside of these clinical trials, the role of EPS or non-invasive programmed stimulation has revealed inconsistent results.³⁷⁷ More recently, the role of cardiac MRI for definition of scar and potential substrate has emerged as a powerful risk stratification tool in observational studies.^{49,379,380} Genetic testing is also useful in patients with decreased cardiac function with conduction disturbance (i.e. LMNA mutations).

In summary, non-ischaemic HF includes a diverse group of patients with reduced ventricular function due to cardiomyopathies from different aetiologies, and at high risk for VT. Reduced cardiac function remains a powerful predictor of VT and appropriate ICD therapy in these patients as a primary prevention. Cardiac MRI and EP testing shows promise in some subsets. Further characterization based on

the type of cardiomyopathy leading to HF shows the most promise for accurate assessment of VT risk.

Patients with inflammatory cardiomyopathies

Patients with inflammatory cardiomyopathies	Class	References
In patients with non-ischaemic heart disease who present with ventricular arrhythmias, use of cardiac MRI or cardiac PET can help delineate aetiology of non-ICM, initiate aetiology-driven treatment, and evaluate prognosis.		52,53,379

Inflammatory cardiomyopathies encompass a broad spectrum of disorders characterized by myocardial inflammation as the primary cause of cardiac dysfunction. This includes viral myocarditis (commonest cause), cardiac sarcoidosis, giant cell myocarditis, autoimmune myocarditis associated with underlying connective tissue diseases, eosinophilic cardiomyopathies, and Chagas disease (addressed in a separate chapter).

In patients who present with ventricular arrhythmias and diagnosed with non-ICM, the incidence of inflammatory cardiomyopathy may be as high as 50%.³⁸¹ Therefore, it is important to consider inflammatory cardiomyopathies as an underlying cause, given that these conditions may benefit from specific aetiology-driven treatments. Infectious causes of myocarditis include viral (e.g. parvovirus B19 and human herpes virus 6 genomes that predominate in inflammatory cardiomyopathies, other cardiotropic viruses include enteroviruses, adenoviruses, hepatitis C, and human immunodeficiency viruses) and uncommonly bacterial and other causes depending on the geographical area and immunosuppression status. Myocarditis associated with connective tissue and autoimmune diseases encompass systemic lupus erythematosus, scleroderma, rheumatoid arthritis, dermatomyositis, polymyositis, cardiac sarcoidosis and giant cell myocarditis. Drug reactions may also cause hypersensitivity myocarditis.^{381,382} In cases of an established cause of inflammatory cardiomyopathy, the focus should be on treating the underlying inflammatory condition. In the case of cardiac sarcoidosis, retrospective series have shown that specific treatment with immunosuppressive therapy can increase VT free survival.⁵²


Cardiac MRI scan is the gold standard for diagnosing myocarditis and inflammatory cardiomyopathies. Oedema, hyperaemia, and LGE form the diagnosis of acute myocarditis. Further diagnostic information is gleaned from T1 and T2 mapping techniques. Although no specific LGE pattern on MRI is diagnostic of cardiac sarcoidosis, LGE is most often observed in basal segments, particularly of the septum and lateral wall, and usually in the mid-myocardium and epicardium of the myocardium^{383–385}

The presence of LGE is significantly associated with increased risk of adverse cardiac events. The presence of LGE on cardiac MRI was associated with increased risk of ventricular arrhythmias and death by greater than 20 fold in patients with EF >35% and extracardiac sarcoidosis compared to sarcoid patients without evidence of LGE on MRI, and the burden of LGE was associated with higher rates of death/VT.³⁸⁶ In a meta-analysis of 155 patients with systemic sarcoidosis who underwent cardiac MRI for work-up of cardiac sarcoidosis, the presence of LGE was associated with hazard ratio of 31.6 for death, aborted SCD, or appropriate ICD discharge and provided superior prognostic information as to compared to other clinical and functional characteristics, including LVEF.⁵¹

In addition, the distribution of LGE confers important prognostic information, with mid-wall anteroseptal LGE representing a more malignant form compared to a sub-epicardial inferolateral wall LGE pattern.^{387,388} Inflammatory biomarkers, such as C-reactive protein, are typically lower in this group with septal LGE, but biomarkers of myocardial damage such as troponin are typically higher, suggestive of a subset with less inflammation but greater myocardial injury. F-fluorodeoxyglucose (FDG)-PET is advantageous for detecting active inflammation in cardiac sarcoidosis, and a mismatch of FDG and perfusion and involvement of the right ventricle predicts adverse cardiac events and ventricular arrhythmias, respectively.⁵³ Endomyocardial biopsy is performed in cases where a histological diagnosis is required to confirm cardiac sarcoidosis or giant cell myocarditis, with its yield enhanced by electrogram guidance. Active viral genomes may also be identified by biopsy, which can differ significantly from peripheral serological tests.^{382,389}





Little data exist on how to assess risk of VT/VF in inflammatory cardiomyopathies. Besides EF, which is used for all non-ischaemic aetiologies, no randomized studies have evaluated other parameters or even EF as a predictor of VT in different inflammatory cardiomyopathies. In particular, certain inflammatory cardiomyopathies may carry higher risk than others (sarcoidosis vs. viral myocarditis). Risk of ICD therapy may be as high as 15% per year in biopsy proven cardiac sarcoidosis patients.³⁹⁰ Although randomized data on use of higher EF in these patient populations is lacking, given risk of VT noted in retrospective studies, use of MRI and cardiac PET to evaluate aetiology of non-ischaemic heart disease is warranted, and treatment of inflammation to reduce risk of VT is advised. Furthermore, cardiac PET and MRI can be used to assess for recurrent inflammation or progression of disease on treatment.

Patients with congenital heart disease

Risk for ventricular arrhythmias in patients with congenital heart disease	Class	References
In the paediatric patient with CHD, ventricular overload, surgical scars and patches or baffles, ventricular dysfunction, and previous conduction defects are recognized risk factors for VT.		391–393

Continued

Continued

Risk for ventricular arrhythmias in patients with congenital heart disease	Class	References
In adult patients with CHD, older age at surgery, poor haemodynamic status, and prolonged QRS represent the most common risk factors for ventricular arrhythmias.		^{392–394}
In adult patients with CHD, VTs are mainly observed after correction of tetralogy of Fallot (TOF) and left ventricular outflow tract defects.		^{394–396}
In patients with TOF, residual haemodynamic lesions and ventricular dysfunction represent the most important risk factors for VT or SCD.		^{394–396}
In patients with TOF, frequent PVCs, QRS >180 ms, palliative systemic to pulmonary shunts, syncope, atrial tachycardia, decreased LVEF, dilated right ventricle, severe pulmonary stenosis or regurgitation, are risk factors for sustained VT.		^{394–396}



Ventricular arrhythmias in patients with congenital heart disease (CHD) may be observed in two different groups: the paediatric age group and adults with repaired congenital defects group.³⁹⁷ In the paediatric age, life-threatening VT is rare both prior to and after surgery. Ventricular tachyarrhythmia is seen in only 1.8% of children undergoing an EPS,³⁹¹ is usually associated with structurally normal heart and most frequently comes from the right outflow tract and left outflow tract and sinuses of Valsalva.

In paediatric patients with CHD, the haemodynamic and electrophysiologic factors related to each disease state and associated therapeutic interventions play an important role in the development of VT, with ventricular overload, surgical scars and patches, baffles and conducts, ventricular dysfunction, and previous conduction defects among the most relevant.³⁹² In the early post-operative stage, Van Hare *et al.* reported only 3 patients with VT out of 580 undergoing paediatric surgery and the most important risk factor was the surgical procedure.³⁹¹ Sustained VT may arise in the setting of myocardial ischaemia or infarction and may be facilitated by disruption of the ventricular myocardium caused by scar due to ventriculotomy, fibrotic tissue, or ventricular dilatation.³⁹³

In adult patients with CHD, VTs are mainly observed after correction of tetralogy of Fallot (TOF) and left ventricular outflow tract defects but may also arise in other defects as transposition of the great arteries with atrial switch, univentricular hearts, double-outlet RV, and ventricular septal defects. Older age at surgery, poor haemodynamic status, and prolongation of the QRS represent the most common risk factors. In patients with TOF, the correlation of residual haemodynamic lesions and right ventricular dysfunction with risk of VT or SCD has been extensively established.^{394,395} Potentially

treasurable residual haemodynamic problems, pulmonary hypertension, elevated end-diastolic pressures, and reduced ventricular function should be treated as part of the arrhythmia management. Particularly in this group, frequent PVCs, QRS 180 ms or more, palliative systemic to pulmonary shunts, syncope, atrial tachycardia, decreased LVEF, dilated right ventricle, severe pulmonary stenosis or regurgitation are risk factors for sustained VT, and inducible sustained VT correlates with increased risk of SCD.^{396,398} EPS might be considered for risk assessment of VT/VF in this group of patients with high-risk clinical characteristics and frequent ventricular arrhythmias.³²⁷

Patients with inherited arrhythmia diseases (inherited channelopathies and inherited structural diseases including arrhythmogenic right ventricular cardiomyopathy)

Risk for ventricular arrhythmias in patients with inherited arrhythmia diseases	Class	References
Patients with primary inherited arrhythmia syndromes and cardiomyopathies should undergo risk stratification that integrates clinical presentation, family history, and non-invasive diagnostic testing.		³⁹⁹
Select patients with primary inherited arrhythmia syndromes and cardiomyopathies may benefit from electrophysiologic testing to refine non-invasive risk stratification.		⁵³⁶

Patients with inherited arrhythmia disease are without doubt at increased risk for ventricular arrhythmias, including SCD. The extent to which this is pertinent and predictable is different for the various conditions.

The main primary inherited arrhythmia syndromes, i.e. the 'channelopathies' are LQTS, Brugada syndrome and CPVT.⁴⁰⁰ Patients that are symptomatic (syncope, cardiac arrest) at the time of presentation are at highest risk, with arrhythmic syncope representing a sentinel sign of risk, and resuscitated cardiac arrest reflecting the highest risk cohort.⁹⁷ Despite major social impact on perceived risk, family history is not of major importance in all three diseases.

In LQTS, clearly defined disease-specific risk factors are the extent of resting QT prolongation, documentation of arrhythmias and gene and even mutation specific associated risk.⁴⁰¹ In CPVT, the extent of the arrhythmic response of an exercise test predicts events, including breakthrough symptoms on therapy.⁴⁰² It follows that risk assessment requires a baseline ECG and an exercise test in both conditions, with potential value of ambulatory monitoring. Assessment should






include asymptomatic patients often identified during family screening or after incidental unrelated medical evaluation.

In Brugada syndrome, there is uncontested agreement that symptomatic patients (arrhythmic syncope, cardiac arrest) are at high risk for SCD, requiring aggressive therapy with an ICD in most circumstances. Risk stratification in asymptomatic individuals with a spontaneous type 1 ECG is much less clear, involving a variety of ECG characteristics and potential value of programmed electrical stimulation (PES).^{403,404} ECG parameters that have been associated with increased risk include QRS fragmentation, early repolarization, Brugada type changes in non-anterior precordial leads and a positive signal-averaged ECG. Programmed electrical stimulation with a non-aggressive stimulation protocol may be of importance, although the risk of an inducible patient is only marginally different from a non-inducible patient.⁷⁷ In LQTS, CPVT, and Early Repolarization syndrome, PES is of no importance. The presence of a SCN5a mutation may contribute to risk in Brugada syndrome.⁴⁰⁵ Early repolarization syndrome, short-coupled idiopathic VF (SCIVF), and SQTS are uncommon causes of cardiac arrest and sudden death. Though the early repolarization pattern conveys a small increase in risk, the only patients where the risk is substantive to consider intervention are those with prior cardiac arrest or syncope with a positive family history. There are no validated risk models in SQTS and SCIVF.

In the cardiomyopathies, i.e. the secondary inherited arrhythmia syndromes, risk stratification is also disease specific. In hypertrophic cardiomyopathy (HCM) septal thickness, the hallmark of the disease is an important contributor to risk. Other risk factors include left atrial dimension, left ventricular outflow tract gradient (all echocardiographic parameters), the presence of ventricular arrhythmias on ambulatory monitoring (Holter) or documentation otherwise, symptoms (i.e. unexplained syncope, palpitations associated with near syncope), demographic factors (age in particular), and family history. All these factors are included in the ESC risk score calculator,⁴⁰⁶ which is readily available in an online tool (<http://www.doc2do.com/hcm/webHCM.html>), and applied after standard imaging, exercise testing and ambulatory monitoring. Validation of the ESC risk calculator is not compelling, and consideration of imaging and exercise blood pressure response parameters have also been used in borderline cases. In inherited, i.e. non-ischaemic, dilated cardiomyopathy (DCM), the genetic background is very important, with LMNA (Lamin A/C) and PLN (Phospholamban) leading to highly arrhythmic substrates.^{123,407,408} Of course, reduced LVEF and the presence of ventricular arrhythmias during ambulatory monitoring are important risk factors as well. In arrhythmogenic right ventricular cardiomyopathy (ARVC or ACM), symptomatic arrhythmic events identify the patient at highest risk, and major risk factors include age, male sex, unexplained syncope, non-sustained VT, number of anterior precordial leads with T wave inversion, and severe right or left ventricular dysfunction.⁴⁰⁹ Hence, as for the other cardiomyopathies, echocardiographic imaging, and Holter monitoring is required for risk assessment. In all cardiomyopathies, MRI is becoming increasingly important, in particular to show the presence of fibrosis (HCM, DCM, ACM) and assess left and right ventricular function. Genetic testing should be considered in any patient with a phenotype suggesting an inherited cardiomyopathy and in DCM with a suggestive family history or onset at an early age that is otherwise unexplained (i.e. not myocarditis, sarcoidosis etc.). Genetic testing is largely for diagnosis,

and only informs risk when a high-risk form of cardiomyopathy is diagnosed, such as PLN or LMNA.

Risk stratification in patients with ACM, specified for arrhythmogenic right ventricular cardiomyopathy

Risk stratification of ventricular arrhythmias in ARVC	Class	References
In patients with ARVC, history of aborted sudden death, sustained ventricular arrhythmias, and severe right and/or left ventricular dysfunction identify a high risk of cardiac death.		410,411
In patients with ARVC, advice to not perform high-level or endurance exercise should be given.		412,413
Clinical factors including age, male sex, unexplained syncope, non-sustained VT, number of anterior precordial leads with T wave inversion, and genetic mutation status can be used for prognostic stratification of patients with ARVC.		410,411
In patients with confirmed ARVC, regular Holter monitoring and imaging for assessment of ventricular function may be useful.		412,413
A detailed history of exercise intensity and duration may be helpful in patients with ARVC as exercise level may represent a modified risk factor of adverse cardiovascular events and disease progression.		414

In arrhythmogenic right ventricular cardiomyopathy (ARVC or ACM), the most important features characterized as the high arrhythmic risk include the electric instability (i.e. sustained ventricular arrhythmia [VA]), genotype-positive, extent of structural involvement, cardiac syncope, the presence of multiple mutations, and the history of competitive or endurance exercise.^{410,411} In patients without prior VA, an available online prediction model, derived from the largest cohort of ARVC patients, using readily available clinical parameters was devised to estimate the risk of VA and to guide the decisions of ICD implantation as primary prevention (www.arvcrisk.com).⁴¹⁵ There is a dose-dependent relationship between endurance exercise and the disease onset and progression in confirmed ARVC patients. Exercise restriction is recommended to prevent disease progression and SCD in confirmed ARVC patients with ICD⁴¹² and genotype-positive relatives.⁴¹³ In general, high-level or endurance exercise is not recommended in confirmed ARVC patients or at risk. Ambulatory ECG monitoring is crucial to detect the PVCs burden or the presence of non-sustained VT, which also provide prognostic




information in ARVC.⁴¹⁴ All positive criteria of signal-averaged ECG non-invasively identifies the slow conduction of myocardium and has been proven for risk stratification in patients with suspicion or confirmed ARVC.⁴¹⁶

Echocardiography and cardiac MRI provide accurate measurements of right ventricular global and regional dysfunction and right ventricular volume and regional/global ventricular function, as the important variable for assessment of right and left ventricular disease. The Task Force Criteria did not include cardiac MRI measures of right ventricular myocardial fat or LGE in order to risk stratify the ARVC.⁴¹⁷ In summary, abnormal cardiac MRI was an independent predictor of clinical events with a cumulative effect of the abnormalities including morphology, wall motion, and fat/fibrosis in ARVC patients.⁴¹⁶

An EPS may provide help distinguish ARVC from idiopathic right ventricular outflow tract (RVOT) VT. Additionally, positive inducibility on program ventricular simulation is not a perfect surrogate marker neither for ARVC diagnosis, nor the decision of ICD implantation.^{410,411} EPS may be beneficial to identify patients that may benefit from ablation. In this setting, EPS with high-dose isoproterenol may help differentiate patients with idiopathic VT or ventricular premature beats from those with ARVC.⁴¹⁸ The positive inducibility of EPS can predict any ICD therapy, including VF, and can be an important parameter for risk stratification in patients with ARVC.

ARVC is considered to have desmosome dysfunction. Genetic causes of isolated or predominantly RV arrhythmia and structural abnormalities are most commonly associated with desmosomal gene variants. Positive genetic test contributes up to 50% of the diagnosis of ARVC, however, in confirmed ARVC patients, limited evidence of clinical actionable risk stratification or use of management of disease. Several gene variants have been reported in patients with left ventricular or biventricular arrhythmia. Left ventricular dysfunction is most often present in patients with ARVC with pathogenic variants in Lamin A/C, or variants in the PLN and TMEM43 genes, and followed by variants in DSP, DSG2/DSC2.^{123,399,419,420}

Patients with Chagas's disease

Patients with Chagas' disease	Class	References
The Rassi score is useful in assessing risk of death in Chagas' disease patients.		523,524
In patients with syncope and a BBB, an invasive EPS is useful in assessing risk of sustained ventricular arrhythmias.		525,526
When available, cardiac MRI with LGE should be considered to evaluate for arrhythmogenic substrate as part of a risk stratification strategy in those patients with cardiomyopathy.		527–530

Chagas disease is an infectious disease affecting 10 million people around the world and 100 million more are at risk of this infection. Due to migration, it is estimated 750 000 infected carriers live in the USA or Europe.^{531,532} VA, especially sustained VT is closely related to high mortality, sudden death (SCD) happening in 17–50% of chronically ill patients.⁵³³ Based on the identification of different risk factors, Rassi *et al.* developed a mortality risk score (Table 3).⁵²³ Patients with HF, NYHA Class III/IV and NSVT on Holter and patients in NYHA Class I/II, with left ventricular dysfunction and NSVT on Holter are at the highest risk of death and should be regarded as candidates for aggressive therapeutic management.

Conversely, patients with an abnormal ECG (right or left bundle branch conduction disorders) but in NYHA Class I/II HF without left ventricular dysfunction or NSVT on Holter are at lower risk of death. These patients should be followed up annually or biannually. Between these two extremes, some patients are at intermediate risk and their treatment strategies should be individualized.

Sustained VT has been reported as the main cause of syncope in patients with non-documented recurrent syncope and bundle branch block (BBB). In these cases, an EPS has been recommended for diagnosis elucidation.⁵²⁵ A finding of scar by LGE by cardiac MRI in patients with Chagas disease is considered a strong predictor of a combination of sustained VT and death.⁵³⁴

Table 3 Rassi score

Risk factor	Points		
NYHA Classes III or IV	5		
Cardiomegaly (chest radiograph)	5		
Segmental or global wall motion abnormality (2D echocardiogram)	3		
Non-sustained ventricular tachycardia (24-h Holter)	3		
Low QRS voltage (ECG)	2		
Male sex	2		
Total points	Total mortality (%)	Risk	
	5 years	10 years	
0–6	2	10	Low
7–11	18	44	Intermediate
12–20	63	84	High

How to assess risk for adverse outcomes in patients with ventricular tachyarrhythmia

Risk for appropriate and inappropriate implantable cardioverter-defibrillator therapies

ICD therapies are associated with an increase in mortality.^{370,422–424} A single ICD shock is associated with a two- to five-fold increase in mortality, and progressive heart failure has been reported the most

common cause of mortality among these patients.^{425–427} ICD therapies are classified as appropriate, inappropriate, avoidable, and phantom.^{370,428,429} Approximately 12–17% of patients receive inappropriate ICD shocks.^{422,425–427} Both appropriate and inappropriate shocks are associated with an increase in mortality and can significantly lower quality of life. Thus, identifying predictors of ICD therapies may improve quality of life and long-term outcomes in patients with ICDs.

Appropriate shock predictors

A previous episode of sustained VT correlates with high rate of appropriate shocks.^{430–433} A higher risk of appropriate therapy was seen in a secondary prevention ICD group when compared with a primary prevention ICD group at 5-year follow-up, while the rate of inappropriate therapy was comparable.⁴³⁴ Several studies have shown male sex as an independent risk factor for appropriate ICD therapies.⁴³⁵ Women are 30–50% less likely to receive an appropriate shock,^{436–439} and this difference is more pronounced among CRT-D recipients.^{440–442} However, most of studies have shown similar mortality rates in both genders after ICD implantation.^{435–442} AF is common in patients with left ventricular dysfunction; the prevalence can increase up to 50%. Worsening AF subtype increases the risk for both appropriate shocks and overall mortality.^{443–446}





Other risk factors implicated to increase the risk of appropriate shocks are diabetes,^{443,447} elevated baseline NT-proBNP and BNP,⁴⁴⁸ NSVT,^{445,449} left atrial diameter,^{443,449} and impaired renal function.⁴⁵⁰ Data from SCD-HeFT and MADIT II trials have found a higher NYHA class, a lower LVEF, lack of use of beta-blocker therapy and single-chamber ICD as significant independent predictors for appropriate ICD shocks.⁴⁵¹ Data from the Danish ICD Registry showed that LVEF <25% predicted an increased risks of both appropriate and inappropriate therapies.⁴⁵²

Inappropriate shock predictors

The presence of supraventricular tachycardias, in particular AF, has been reported as the most common risk factor for inappropriate ICD shocks.^{426,444,445} Another risk factor associated with inappropriate shock is younger age.^{448,450,451} Inappropriate shocks secondary to AF/atrial flutter are associated with increased mortality while inappropriate shocks related to sinus tachycardia or non-arrhythmic events like noise, artefact, and oversensing have shown similar survival as compared to those who do not receive a shock.⁴⁵³ Studies have failed to establish the superiority of dual-chamber ICD over the single chamber in reducing inappropriate shocks.^{454,455} The Danish ICD Registry showed a two-fold increase in the risk of inappropriate shocks associated with a dual-chamber ICD.⁴⁵⁶ Device technologies and programming, i.e. prolonged detection time, high rate programming, and better discrimination algorithms have markedly reduced the risk of inappropriate therapies.^{370,456,457}

Risk for heart failure incidence and progression

Tachycardia-induced cardiomyopathy is a reversible cause of HF and impaired left ventricular function. Ventricular rhythms causing tachycardia-induced cardiomyopathy include VT, fascicular tachycardia, PVCs, and even persistent rapid DDD pacing. Left ventricular

Risk for heart failure incidence and progression	Class	References
Periodic monitoring of PVC burden (every 6 months) and LVEF and dimensions are useful in patients with frequent, asymptomatic PVCs and a normal LVEF and dimensions.		458
PVC burden exceeding 20% is associated with a higher risk of PVC-related cardiomyopathy.		459–461
PVC burden lower than 10% is associated with a lower risk of PVC-related cardiomyopathy.		462,463
In patients with PVC-related cardiomyopathy, absence of LGE on cardiac MRI may be used to identify patients with a favourable prognosis of left ventricular systolic function recovery.		464–466

systolic function improves or normalizes and symptoms resolve, when tachycardia is corrected or controlled with medication or pharmacologic or non-pharmacologic rhythm control strategies.

Sustained monomorphic VT less commonly causes tachycardia-induced cardiomyopathy as compared to supraventricular tachycardias, since sustained VT is most often associated with some form of structural heart disease. When VT does lead to tachycardia-induced cardiomyopathy, it is by definition idiopathic and most commonly originates from the RVOT, left ventricular outflow tract, or coronary cusps. If these arrhythmias become persistent or high burden, they may cause reversible left ventricular dysfunction.⁴⁶⁷

A single centre series reported that 11% of patients who presented with frequent PVCs also had sustained monomorphic VT and 7% of those patients had tachycardia-induced cardiomyopathy. The presence of repetitive monomorphic VT was a significant predictor of tachycardia-induced cardiomyopathy development, particularly when it was the predominant arrhythmia on 24-h Holter monitoring.⁴⁶¹

PVCs are very common and usually do not require treatment in the absence of symptoms. However, in the clinical setting of troublesome symptoms, or when PVCs trigger polymorphic VT or cause cardiomyopathy, proper treatment is critical. The concept of PVC-induced cardiomyopathy was first proposed by Duffee et al.,⁴⁶⁰ who observed a small group of patients with cardiomyopathy recover normal left ventricular function after pharmacological suppression of frequent PVCs.

Baman et al.⁴⁵⁹ reported on 174 consecutive patients referred for PVC ablation, 54 of whom had depressed left ventricular function. The authors concluded that although PVC-related cardiomyopathy may occur in patients with less PVCs, “in the presence of a PVC burden ≥24%, it may be helpful to suppress the PVCs by catheter ablation or drug therapy to avoid the development of cardiomyopathy.” However, Aki Lee et al., demonstrated a high rate of resolution of




frequent PVCs among untreated patients with normal left ventricular function and minimal symptoms. A strategy of active surveillance is appropriate for the majority of patients with frequent idiopathic PVCs in association with preserved LVEF, owing to the low risk of developing left ventricular systolic dysfunction and the high rate of spontaneous resolution. Periodic monitoring of PVC burden and LVEF and dimensions can be useful in patients with frequent, asymptomatic PVCs and a normal LVEF and dimensions.⁴⁵⁸

It has become clear that comparative effectiveness trials are needed to understand what the best treatment approach is for patients with frequent PVCs and cardiomyopathy. A pilot multicentre study (PAPS: Prospective Assessment of PVC Suppression in Cardiomyopathy) is ongoing to better understand the prevalence of frequent PVCs and CM, and prove the feasibility of a large-scale randomized clinical trial (not yet published).⁴⁶⁸

Several circumstances have been associated with PVC-induced cardiomyopathy, including the PVC burden, asymptomatic status, duration of a high PVC burden, PVC QRS width >150 ms, interpolated PVCs, epicardial origin, and male gender. However, no prospective longitudinal assessments have been conducted that definitively prove their causal relation to PVC-induced cardiomyopathy.⁴⁶⁹

The diagnosis of tachycardia-induced cardiomyopathy or PVC-related cardiomyopathy can be challenging and the role of imaging modalities in the characterization of myocardial tissue as part of the diagnostic workup is limited.⁴⁶⁴ Cardiac MRI with LGE can accurately identify the presence and extent of myocardial scar and has become a first-line non-invasive imaging modality for the aetiological assessment of primary cardiomyopathies and/or left ventricular systolic dysfunction, and could identify early stage of the structural heart disease.

Risk for death in ventricular tachyarrhythmia patients



Risk for death in VT patients (including risk for SCD)	Class	References
Risk for SCD should be judged in each patient on a case-by-case basis and risk considered as a continuous variable rather than a dichotomized variable (high or low risk may change).		71,470,471
Individual risk assessment needs to be dynamic as the type and severity of risks can change over time (repeated measurements need to be made over time).		472
Risk assessment may include consideration of mode of death as the relative risk of non-sudden, non-cardiac death, sudden cardiac death, and non-sudden cardiac death is influenced by ageing and worsening cardiomyopathy and cardiovascular risk factors.		369,473,474

Risk prediction of death in VT patients has used numerous non-invasive and invasive markers including: clinical markers, mode of initial clinical presentation (e.g. sustained stable monomorphic VT, ventricular flutter, or VF), biomarkers, ECG abnormalities (e.g. left bundle branch block), heart rate variability, signal-averaged ECG, ambulatory ECG-based frequency domain T wave, microvolt level-T wave alternans, heart rate turbulence, heart rate deceleration, QT dispersion, cardiac autonomic function, echocardiographic evaluation of LVEF, left ventricular diameter, left ventricular mechanical dispersion by tissue Doppler, strain and velocity parameters to evaluate regional LV function, exercise testing to evaluate functional status, MRI to measure scar burden, and EPS to assess for inducibility of VT. Most of these tests and markers were applied to patients at risk of SCD and not patients who already have VT. Thus, their use for predicting death in a patient with VT is unknown.

The main sources of information about risk for SCD in patients with VT are from two studies from the era prior to widespread ICD use,^{475,476} the control groups (patients who did not receive ICDs) in the primary prevention ICD studies (MUSTT, MADIT, MADIT II, SCD-HeFT, DANISH, DEFINITE, CABage-PATCH, IRIS, DINAMIT) as well as analysis of large data samples from registries since ICD approval from Europe, Canada, and the USA.^{70,477} These data have been extensively reviewed to better characterize which variables predict the development of SCD and death in high-risk patients. Data from secondary prevention studies (AVID, CIDS, CASH) provide additional information about risk of death in patients who have had VT. Another source of information is the International VT Ablation Center Collaborative Study Group which analysed a large group of patients with VT (approximately 2000 patients from 12 international sites) undergoing catheter ablation.⁴⁷⁸ Finally, a third useful source of data is the Seattle Heart Failure model developed by Wayne Levy and his colleagues who analysed data from a large sample of heart failure patients to predict risk of death and SCD as well as create a model for predicting benefit from ICD therapy.⁴⁷⁹ This model has been prospectively validated among five additional study cohorts of almost 10 000 heart failure patients. It is important to recognize that the causes of death can change over time. For example, the risk of death in a patient with post-MI VT may be largely due to mechanical problems (VSD, mitral regurgitation, heart failure) in the first several weeks to months after MI and then 3–6 months later the risk of arrhythmic death may be much higher due to matured scar-mediated substrate.

Based on these studies, the risk factors for death in VT patients include increasing NYHA class, old age, female gender, electrical storm, frailty, diabetes mellitus, AF, chronic kidney disease, chronic obstructive lung disease, peripheral arterial disease, advanced HF, non-ICM, lower EF, multiple different VT morphologies, use of haemodynamic support devices during VT ablation, and poor functional status. These risk factors can be divided into risk factors related to non-cardiac disease (e.g. renal function, diabetes, COPD, peripheral arterial disease) which are powerful and determine mortality, and cardiac risk factors (ischaemic vs. non-ischaemic aetiology, multiple morphologies of VT, EF, and functional status). There was an interaction between variables, such as higher rates of both VT recurrence and mortality, which was observed in patients with lower EF and worse NYHA failure status.^{478,479}

Risk of adverse outcomes in patients treated with catheter ablation

Risk of adverse outcomes in patients treated with catheter ablation	Class	References
The aetiology and severity of cardiomyopathy and inducibility of arrhythmias after VT ablation are useful in determining risk of recurrence of VT after catheter ablation.		480
Risk scores in combination with procedural characteristics may be useful for assessing adverse outcomes associated with catheter ablation of VT.		481–483

Risk of death or acute haemodynamic compromise in patients who undergo catheter ablation of ventricular arrhythmias is driven by patient-specific factors (comorbidities), procedural factors, and presentation of the patient. In a large retrospective multicentre registry, factors such as low EF, chronic kidney disease, VT storm, and unmapable VTs were associated with early mortality.⁴⁸⁴ As mentioned above, male sex is associated with occurrence of VT/VF and ICD shocks.⁴⁸⁵ As procedural factors are often difficult to determine prior to the procedure, various risk scores have been developed to assess risk of acute haemodynamic compromise and/or death in patients undergoing catheter ablation of VT. Of these, a modified version of the Seattle HF Model and PAINESD score have been used in single centre and multicentre retrospective studies to evaluate risk of acute haemodynamic compromise or death post-procedure.^{481,482,484} The Seattle HF Model incorporates, amongst other variables, age, EF, blood pressure, weight, gender, HF medications, blood electrolyte, and haemoglobin levels as well as NYHA to predict mortality. A modified version of this model which incorporates VT storm and ICD shocks was recently reported to be potentially more useful in predicting 6 months survival in patients who undergo VT ablation.⁴⁸³ The PAINESD score incorporates pulmonary disease, age, presence of ICM, NYHA, EF, VT storm, and diabetes and assigns a score between 3 and 6 to each of these patient characteristics. In retrospective studies, patients with a PAINESD score greater than 15 had a 24% risk of acute haemodynamic compromise and a significantly higher risk of mortality.^{482,484} Use of these risk scores can be important in discussion of risks and benefits in patients undergoing catheter ablation and may help determine need for haemodynamic support during the procedure. However, larger multicentre prospective studies are required. It is important to note that patients with lower EF and NYHA Class IV HF may still benefit from successful catheter ablation of VT, and freedom from VT after successful ablation is associated with improved mortality.^{478,486}

With regard to VT recurrence, in addition to patient related comorbidities, large single centre and multicentre studies have shown that the risk of VT recurrence is driven by the underlying aetiology, particularly in patients with non-ischaemic heart disease, even after adjusting for other patient comorbidities.^{487–489} In particular, patients with Lamin A/C cardiomyopathy, hypertrophic cardiomyopathy, cardiac sarcoidosis, and valvular cardiomyopathy appear to be at higher risk for VT recurrence after catheter ablation as compared to idiopathic DCM.^{480,487} In addition, location of scar seems to determine risk of VT recurrence post-catheter ablation.⁴⁹⁰ In this regard, endocardial ablation alone may be insufficient in many non-ischaemic cardiomyopathies. In arrhythmogenic right ventricular cardiomyopathy, epicardial presence of scar can serve as the substrate for VT and combined endo-epicardial mapping and ablation or adjuvant epicardial ablation after endocardial ablation is often required.^{491–494} Cardiac MRI with LGE can be used in assessment of scar location and may be beneficial in diagnosis and peri-procedural planning of VT ablation.⁴⁹⁵

Retrospective studies have shown that inducibility of VT at the end of ablation is associated with adverse outcomes, even after adjusting for other patient comorbidities. Non-inducibility of VT in ICM patients was shown to be associated with improved arrhythmia-free survival rates and all-cause mortality,^{496,497} even after adjusting for other comorbidities. In addition, inducible clinical VT during non-invasive programmed electrical ventricular stimulation (PES) is associated with decreased 1-year VT free survival as compared with those who are not inducible (<30% vs. >80%)⁴⁹⁸



Patients who were non-inducible during non-invasive PES after ablation had a VT recurrence rate of only 9% at 1 year of follow-up when both acute (at the end of the procedure) and late (at 6 days post-procedure) programmed stimulation were negative.⁴⁹⁹ Therefore, PES may be used to guide redo ablation and address ICD programming.

Finally, although catheter ablation is generally performed after the occurrence of ICD therapies, two clinical trials reported the value of catheter ablation prior to or in conjunction with ICD implantation. The Prophylactic Catheter Ablation for Prevention of Defibrillator Therapy clinical trial randomized patients with spontaneous ventricular tachycardia or fibrillation and history of myocardial infarction to ICD or ICD and catheter ablation. In this trial, 30-day mortality was zero along with a significant reduction in ICD therapies from 31% to 9% between the control (ICD) and intervention arms (ICD + catheter ablation).⁵⁰⁰ The Catheter Ablation of Stable Ventricular Tachycardia before Defibrillator Implantation in Patients with Coronary Heart Disease (VTACH) trial randomized patients with history of myocardial infarction and stable VT to catheter ablation followed by ICD implantation vs. ICD implantation alone and showed that catheter ablation reduced occurrence of VT or VF by 18% at 2 years of follow-up. These data imply that in patients who receive ICD for secondary prevention and have ischaemic heart disease, catheter ablation can be considered earlier, at the time of ICD implantation, to reduce future ICD therapies and prior to potential presentation with VT storm.⁵⁰¹ The impact of early ablation (at the time of ICD implantation) on mortality was the subject of the BERLIN-VT clinical trial, early results of which have indicated a lack of a difference in death or hospitalization for VT/VF in the deferred group (ablation after occurrence of third appropriate shock) vs. those who underwent prophylactic ablation at the time of ICD implantation.⁵⁰² It is

important to note that in these studies, patients had a history of VT or VF. In patients with ischaemic heart disease undergoing ICD implantation for primary prevention of sudden cardiac death, prophylactic substrate modification of scar by catheter ablation requires further investigation. In the Substrate Modification Study, patients randomized to ICD implantation plus VT ablation had similar time to VT recurrence as those who underwent ICD implantation only. However, catheter ablation at the time of ICD implantation was associated with a greater than 50% reduction in total number of ICD therapies throughout the follow-up period.⁵⁰³

How to assess risk for adverse outcome in patients with other specific cardiac conditions

Patients with ventricular premature contractions

Patients with ventricular premature contractions	Class	References
An evaluation of cardiac function and screening for heart failure symptoms should be considered in patients with frequent ventricular ectopy (>10 000 PVCs within 24 h or >10% over a more extended timeframe).		⁵⁰⁴
An evaluation of cardiac function and screening for heart failure symptoms may be considered in patients with frequent multiform PVCs, PVCs with a QRS duration > 150 ms or PVCs with a coupling interval of <450 ms.		^{505,506}

Frequent PVCs can lead to cardiomyopathy and HF, and are associated with increased mortality.⁵⁰⁴ In addition, in some patients with an inherited ACM, PVCs may be the initial clinical manifestation that leads to this diagnosis. An initial case series describing four patients who had reversal of cardiomyopathy after amiodarone successfully suppressed a high PVC burden has resulted in the recognition for the potential reversibility of this condition.⁴⁶⁰ However, only a minority of patients with PVCs will develop symptoms or adverse sequelae. The factors that can potentially predict development of HF and increased risk of adverse outcomes include PVC frequency as well as characteristics of the PVC morphology and timing of the PVC coupling interval.

Premature ventricular complex frequency

In a large cohort of patients, increased PVC frequency was associated with reduced LV function, a higher incidence of heart failure, and a

higher risk of death. Specifically, compared to the lowest quartile of PVC frequency (<0.002%), the highest quartile (0.123% to 17.7%) in this cohort of patients with a structurally normal heart at baseline had a 31% increased risk of death over a follow-up of >13 years.⁵⁰⁴ Other studies correlating frequency with PVC-induced cardiomyopathy suggested a threshold effect observed at >20%, though there is no accepted cut-off that appears to be protective.^{459,505} In a study of 239 consecutive patients with apparently normal hearts, a PVC burden of >20 000 in 24 h was associated with a reduced LVEF, whereas >10 000 but <20 000 showed LV dilation with preserved LVEF.⁵⁰⁷

Premature ventricular complex morphology

In addition to PVC burden, the morphological features of the PVC have been evaluated. The width of the PVC QRS complex, perhaps reflective of dyssynchrony, has been associated with increased risk of developing PVC-induced cardiomyopathy.^{505,506} In these retrospective studies, patients with a PVC duration of >150 ms appeared to require a lower burden for development of a cardiomyopathy. A PVC duration of >153 ms in patients with a > 10% burden, was associated with an 82% sensitivity and 75% specificity for subsequent development of a cardiomyopathy. The presence of multiform PVCs has also been associated with the development of new onset heart failure.⁵⁰⁸






Premature ventricular complex coupling interval

One mechanism of PVC-induced cardiomyopathy may be due to ineffective mechanical contraction leading to adverse remodelling, possibly related to the timing of the PVC. However, there are only a few small studies evaluating this. In a retrospective cohort study of 510 patients, a PVC coupling interval of <450 ms was associated with a reduced LVEF.⁵⁰⁹ Another smaller study of 70 patients did not show any association, though its power was limited.⁵¹⁰ Another study specifically identified the presence of interpolated PVCs regardless of coupling interval as associated with reduced LVEF.⁵¹¹ A short PVC coupling interval may also be an important determinant of VF, especially in patients with genetic or acquired early or abnormal repolarization.^{42,512,513}

While the promise of effective treatment for reversing the potential adverse cardiac effects of frequent PVCs remains a possibility, it remains unclear whether such patients can easily be identified. Most cardiologists accept the dose–response relationship of PVC burden and reduced cardiac function, although the precise threshold for this effect remains unknown. There also is the potential for other factors aside from frequency alone, such as PVC QRS duration and coupling intervals, to influence adverse events associated with frequent PVCs.

Patients with supraventricular tachyarrhythmia such as Wolff–Parkinson–White syndrome and focal atrial tachycardia

Patients with WPW may experience dramatic adverse events including SCD due to VF.⁵¹⁶ The estimate for the frequency of SCD ranges up to 4% with more recent studies reporting a rate of 2%.⁵¹⁴ Alarming, in approximately half of the patients SCD is the first clinical manifestation of the syndrome rendering appropriate risk stratification essential.⁵¹⁵

Patients with supraventricular tachyarrhythmia such as WPW syndrome and focal atrial tachycardia	Class	References
EPS, with the use of isoprenaline, is recommended to risk stratify individuals with asymptomatic pre-excitation who have high-risk occupations/hobbies, and those who participate in competitive athletics.		514-516
EPS should be considered for risk stratification in asymptomatic pre-excitation patients without high-risk occupations or those who are not competitive athletes.		514,516,517
Non-invasive screening with exercise testing, drug testing, and ambulatory monitoring may be considered for risk stratification in asymptomatic pre-excitation patients without high-risk occupations or those who are not competitive athletes.		514,516,517
High-risk features to consider at EPS with or without catecholamine challenge are accessory pathways with an antegrade refractory period ≤ 250 ms, shortest pre-excited RR interval during AF ≤ 250 ms, inducible atrioventricular re-entrant tachycardia, and multiple accessory pathways.		514,518,519
Observation without treatment may be reasonable in asymptomatic WPW patients who are considered to be at low risk following EPS, abrupt loss of pre-excitation during exercise testing, or due to intermittent pre-excitation on a resting ECG or during ambulatory monitoring.		514,516

Risk assessment strategies have been recently reviewed in the 2019 ESC Guidelines for the management of patients with supraventricular tachycardia.⁵²⁰ Main risk factors for the development of malignant arrhythmias and SCD in patients with pre-excitation are: (i) a short anterograde refractory period of the accessory pathway with the optimal cut-off reported to be at 250 ms and (ii) inducible atrioventricular reentrant tachycardia triggering pre-excited AF. A short pre-excited RR interval during AF ≤ 250 ms and the presence of multiple accessory pathways have been also reported as risk markers. For these reasons, EPS is recommended for risk stratification in subjects with asymptomatic ventricular pre-excitation who either have high-risk occupations or are competitive athletes. In patients without high-risk occupations or those who are not competitive athletes, EPS should be considered for risk stratification of patients with

asymptomatic pre-excitation that can derive a prognostic benefit from prophylactic catheter ablation of the accessory pathway.⁵²⁰ Permanent Junctional Reciprocating Tachycardia (PJRT) re-presents a rare form of atrioventricular reciprocating tachycardia using a concealed accessory pathway. The incessant behaviour of PJRT may result in tachycardia-induced cardiomyopathy that usually resolves after successful treatment by RF catheter ablation.

Non-invasive testing may also be helpful. Non-invasive findings that identify a pathway not capable of maintaining rapid conduction during AF include intermittent loss of conduction over the accessory pathway on the resting ECG or during ambulatory monitoring, and abrupt loss of pre-excitation during exercise testing.^{518,519}

Focal atrial tachycardias are characterized by regular atrial activation from atrial areas with centrifugal spread and can be classified as sustained or non-sustained. Sustained focal atria tachycardia in the adult population is usually associated with a benign prognosis, although tachycardia-mediated cardiomyopathy has been reported in up to 10% of patients referred for ablation of incessant SVT.⁵²¹ Non-sustained atrial tachycardia is frequently found on Holter recordings and often does not require treatment; however, we should consider that patients with a high premature atrial complex burden ($>500/24$ h) are at increased risk for developing of AF and be educated on the symptoms of AF.⁵²²

Summary

In clinical practice and for scientific purposes, cardiologists and primary care physicians perform risk assessment in patients with cardiac diseases or conditions with high risk of developing such.

The European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS) set down this expert consensus statement task force to summarize the consensus regarding risk assessment in cardiac arrhythmias. Objectives were to raise awareness of using the right risk assessment tool for a given outcome in a given population, and to provide physicians with practical proposals that may lead to rational and evidence-based risk assessment and improvement of patient care in this regard. A large variety of methods are used for risk assessment and choosing the best methods and tools hereof in a given situation is not simple. Even though parameters and test results found associated with increased risk of one outcome (e.g. death) may also be associated with higher risk of other adverse outcomes, specific risk assessment strategies should be used only for the purposes for which they are validated.

The work of this task force is summarized in a row of consensus statement tables.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: J.C.N.: Personal research funding from Novo-Nordisk Foundation: Research in arrhythmia and device therapy (2018). Y.-J.L.: None declared. M.J.d.O.F.: Direct personal payment from Boehringer-Ingelheim: Dabigatran (2018) and Daiichi Sankyo: Edoxaban (2018). A.S.S.: None declared. A.A.: None declared. S.B.:

Direct personal payment from Medtronic: Arrhythmias (ablation) (2018); Microport: Arrhythmias (ICD) (2018); Boston Scientific: Arrhythmias (S-ICD) (2018); Zoll Medical: WCD (2018). N.D.: Research funding from Abbott, Biotronik, Medtronic, Boston Scientific: Electrophysiology, arrhythmias (2018). D.D.T.: None declared. L.L.E.: Direct personal payment from Up to Date: Chapter on Cellular Arrhythmia Mechanisms (2018). K.E.: Direct personal payment from Biosense Webster: Research Grants, Consultant (2018); Biotronik: Speaker, Consultant (2018); Medtronic: Speaker, Consultant, Honoraria (2018); Boston Science: Speaker, Consultant, Honoraria (2018). Payment to department or institution from Abbott: Honoraria, Consulting (2018). Research funding from Biosense Webster: Ablation (2018); Medtronic: Device Research (2018); Boston Scientific: Research ablation and devices (2018). C.H.: Direct personal payment from Johnson & Johnson: Biosense Webster (2018). T.I.: Direct personal payment from Boehringer-Ingelheim: Honoraria (2018); Daiichi Sankyo: Honoraria (2018); Bayer Healthcare: Honoraria (2018); Bristol Myers Squibb: Honoraria (2018). A.J.: Direct personal payment from Abbott: CIED (2018); Medtronic: CIED (2018); Abbott Laboratories: Drugs (2018); Employment with Fortis Escorts Heart Institute, New Delhi (2018). E.K.: Research funding from Boehringer-Ingelheim: anticoagulation (2018); General Electric: electrocardiographic analysis (2018); Member of the Heart Rhythm Society, the American College of Cardiology, and the American Heart Association. A.K.: Direct personal payment from Medtronic: CIED (2018); Research funding from Medtronic: Sudden death (2018); President, Canadian Cardiovascular Society Secretary Treasurer, Heart Rhythm Society (2018). K.K.: Direct personal payment from Bayer: anticoagulation (2018); Daiichi Sankyo: anticoagulation (2018); Pfizer: anticoagulation (2018); Bristol Myers Squibb: anticoagulation (2018); Boston Scientific: Pacemaker/ICD (2018); Biotronik: Pacemaker/ICD (2018); Medtronic: Pacemaker/ICD (2018); Payment from Boston Scientific: pacemaker/ICD (2018) and Medtronic: pacemaker/ICD (2018). V.K.: Direct personal payment from Biotronik: Home Monitoring (2018) and Zoll Medical: Women Initiative (2018); Payment from Duke Clinical Research Institute: CRT (2018); Research funding from Biotronik: CRT (2018); Boston Scientific: S-ICD (2018); Zoll Medical: WCD (2018). H.S.L.: Research funding from St Jude Medical: Research Support to Hospital (2018). G.L.: Payment to department or institution from Daiichi-Sankyo: Anticoagulation (2018); Bayer/Janssen: Anticoagulation (2018); Verseen: Anticoagulation development (2018); Boehringer Ingelheim: Anticoagulation; Registries; Steering Committees (2018); Pfizer: Anticoagulation; Registries (2018); BMS: Antithrombotic therapy (2018); Research funding from Boehringer-Ingelheim: AF registries [unrestricted educational grant] (2018); BMS/Pfizer: AF registries [unrestricted educational grant] (2018); Daiichi-Sankyo: Systematic reviews [unrestricted educational grant] (2018); Shares in private limited company (a legal separate entity in UK), but no salary/dividends/income/personal remuneration received (2018). S.N.T.: Direct personal payment from Biosense Webster: Electrophysiology (2018); Cook Medical: lead extraction (2018); Abbott: Pacing and Defibrillation. (2018). H.-N.P.: Secretary General, Asian Pacific Heart Rhythm Society, (2019-Present) Director of Policy and Insurance, Korean Heart Rhythm Society, (2017-Present) (2018); Director of Cardiac Intervention and Electrophysiology Laboratory, Severance Cardiovascular Hospital, (2014-Present)

Outside Cooperation Committee Chair, Severance Cardiovascular Hospital, (2017-Present) (2018). G.R.D.: Direct personal payment from Medtronic: Cryoballoon ablation proctoring (2018); Pfizer: Oral Anticoagulation (2018); Bayer Schering Pharma: Oral Anticoagulation (2018). W.S.: Direct personal payment from Boston Scientific: Catheter Ablation (2018); St Jude Medical: Catheter Ablation (2018); Biosense Webster: Catheter Ablation (2018); Research funding from Biosense Webster: Catheter Ablation (2018). A.S.: Direct personal payment from Abbott: Consultancy, Speaker Fees (2018); Bayer: Consultancy, Speaker Fees (2018); Boehringer-Ingelheim: Consultancy, Speaker Fees (2018); Boston Scientific: Consultancy, Speaker Fees (2018); Medtronic: Consultancy, Speaker Fees (2018); Novartis: Consultancy, Speaker Fees (2018); Pfizer: Consultancy, Speaker Fees (2018). J.H.S.: Direct personal payment from Medtronic: ICDs and pacemakers (2018); Research funding from Gilead: Antiarrhythmic medication (2018) and Medtronic: ICDs and pacemakers (2018); Consultant for Insurance company (2018). D.V.: Direct personal payment from St Jude Medical: Implantable Loop Recorder (2018). M.V.: None declared. A.W.: Payment to department or institution from Audentes (in 2017): gene therapy (2018); Coordinator of the European Reference Network (on rare cardiac diseases, GUARD-Heart) (2018). T.J.B.: Research funding from Boehringer-Ingelheim: Research Grant - Cognitive Atrial Fibrillation Trial (2018) and Boston Scientific: Research Grant - PLUG MRI trial (2018).

ESC Scientific Document Group: A.E.B.: Direct personal payment from Boston Scientific: Implantable Defibrillators (2018); Royalties from Wiley Blackwell: Cardiac Arrhythmia (2018). G.C.: None Declared. T.-F.C.: None Declared. L.E.: Direct Personal Payment From Abbott: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Boehringer-Ingelheim: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Boston Scientific: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Daiichi Sankyo: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Medtronic: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Biotronik: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Bayer Healthcare: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Bristol Myers Squibb: Speaker Fees, Honoraria, Consultancy, Advisory Board Fees, Investigator, Committee Member (2018); Research Funding From Deutsche Forschungsgemeinschaft (2018) And German Cardiac Society (2018). H.E.: Direct personal payment from Boston Scientific: Honoraria fee (2018) and German Cardiac Society: Honoraria fee (2018). A.M.G.: Direct personal payment from Medtronic: Implantable Devices (2018); American Heart Association, Associate Editor Circulation Arrhythmias and Electrophysiology (2018). R.I.: None declared. J.K.: Direct personal payment from EPIX: ablation catheter (2018); Biosense Webster: catheters, mapping system (2018); Bayer: drugs (2018); Boehringer-Ingelheim: drugs (2018); Daiichi Sankyo: drugs (2018); Pfizer: drugs (2018); Bayer Healthcare: drugs (2018); MSD: drugs (2018); Boston Scientific: pacemakers, ICDs (2018); Biotronik: pacemakers, ICDs, catheters (2018); Liva nova (Sorin): pacemakers, ICDs, catheters (2018); Medtronic:

pacemakers, ICDs, catheters, mapping system (2018); St Jude Medical (Abbott): pacemakers, ICDs, catheters, mapping system (2018). P.M.: Direct personal payment from Boston Scientific: EP (2018). J.D.M.: Direct personal payment from Boston Scientific: Electrophysiology (2018); Biosense Webster: Electrophysiology (2018); Vytronus, Inc: Electrophysiology (2018). G.-B.N.: None declared. B.O.: Direct personal payment from Lundbeck: Droxidopa (2018); Respironics: phrenic nerve stimulator (2018); Boehringer-Ingelheim: Pradaxa (2018). L.F.P.M.: None declared. M.Pi.: Direct personal payment from Daiichi Sankyo: Edoxaban (2018) and Bayer: Rivaroxaban (2018). M.Pr.: None declared. W.S.T.: Direct personal payment from Biotronik: CRM (2018); Abbott: CRM and Electrophysiology (2018); Boston Scientific: CRM and Electrophysiology (2018); Medtronic: CRM and Electrophysiology (2018); Biosense Webster: Electrophysiology mapping and ablation (2018); Electrophysiology Mapping and Ablation (2018); Payment to department or institution from Biosense Webster: Catheter Ablation (2018) and Abbott: Catheter Ablation and CRM (2018); Research funding from Abbott: Catheter Ablation (2018) and Boston Scientific: CRM (2018). P.S.: Direct personal payment from Abbott: Ablation (2018); Biosense Webster: Ablation (2018); Boehringer-Ingelheim: NOAC (2018); Daiichi Sankyo: NOAC (2018); Bayer Healthcare: NOAC (2018); Bristol Myers Squibb: NOAC (2018); Payment to department or institution from Abbott: Innovation (2018); Biosense Webster: Innovation (2018) J.S.: None declared. A.V.: None declared. T.D.: Direct personal payment from Herzklinik Bad Neustadt: Catheter ablation (2018); Research Funding from Herzklinik Bad Neustadt: Infrared Thermography Probe (2018).

References

- Benhorin J, Bodenheimer M, Brown M, Case R, Dwyer EM Jr, Eberly S et al. Improving clinical practice guidelines for practicing cardiologists. *Am J Cardiol* 2015;**115**:1773–6.
- Lip G. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol* 2017;**14**:627–8.
- Proietti M, Romiti GF, Olshansky B, Lane DA, Lip G. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) pathway. *Am J Med* 2018;**131**:1359–66 e6.
- Pastori D, Pignatelli P, Menichelli D, Violi F, Lip G. Integrated care management of patients with atrial fibrillation and risk of cardiovascular events: the ABC (Atrial fibrillation Better Care) pathway in the ATHERO-AF study cohort. *Mayo Clin Proc* 2019;**94**:1261–7.
- Pastori D, Farcomeni A, Pignatelli P, Violi F, Lip GY. ABC (Atrial fibrillation Better Care) pathway and healthcare costs in atrial fibrillation: the ATHERO-AF study. *Am J Med* 2019;**132**:856–61.
- Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS et al. Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple ABC (Atrial Fibrillation Better Care) pathway for integrated care management: a nationwide cohort study. *Thromb Haemost* 2019;**19**:1695–703.
- Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost* 2017;**117**:1230–9.
- Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost* 2018;**118**:2171–87.
- Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest* 2018;**154**:1121–201.
- Rivera-Caravaca JM, Marin F, Vilchez JA, Galvez J, Esteve-Pastor MA, Vicente V et al. Refining stroke and bleeding prediction in atrial fibrillation by adding consecutive biomarkers to clinical risk scores. *Stroke* 2019;**50**:1372–9.
- Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS et al. Dynamic changes of CHA2DS2-VASc score and the risk of ischaemic stroke in Asian patients with atrial fibrillation: a nationwide cohort study. *Thromb Haemost* 2018;**118**:1296–304.
- Chao TF, Liao JN, Tuan TC, Lin YJ, Chang SL, Lo LW et al. Incident comorbidities in patients with atrial fibrillation initially with a CHA2DS2-VASc score of 0 (males) or 1 (females): implications for reassessment of stroke risk in initially 'low-risk' patients. *Thromb Haemost* 2019;**119**:1162–170.
- Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW et al. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:122–32.
- Apostolakis S, Lane DA, Buller H, Lip GY. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. *Thromb Haemost* 2013;**110**:1074–9.
- Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF et al. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. *Thromb Haemost* 2018;**118**:768–77.
- Ferrante di Ruffano L, Hyde CJ, McCaffery KJ, Bossuyt PM, Deeks JJ. Assessing the value of diagnostic tests: a framework for designing and evaluating trials. *BMJ* 2012;**344**:e686.
- Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *Circulation* 2008;**118**:1497–518.
- Verrier RL, Klingenhoven T, Malik M, El-Sherif N, Exner DV, Hohnloser SH et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility—consensus guideline by International Society for Holter and Noninvasive Electrocardiology. *J Am Coll Cardiol* 2011;**58**:1309–24.
- Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;**93**:1043–65.
- De Bacquer D, Willekens J, De Backer G. Long-term prognostic value of p-wave characteristics for the development of atrial fibrillation in subjects aged 55 to 74 years at baseline. *Am J Cardiol* 2007;**100**:850–4.
- Cheng M, Lu X, Huang J, Zhang S, Gu D. Electrocardiographic PR prolongation and atrial fibrillation risk: a meta-analysis of prospective cohort studies. *J Cardiovasc Electrophysiol* 2015;**26**:36–41.
- Magnani JW, Johnson VM, Sullivan LM, Gorodeski EZ, Schnabel RB, Lubitz SA et al. P-wave duration and risk of longitudinal atrial fibrillation in persons ≥ 60 years old (from the Framingham Heart Study). *Am J Cardiol* 2011;**107**:917–21 e1.
- Nielsen JB, Kuhl JT, Pietersen A, Graff C, Lind B, Struijk JJ et al. P-wave duration and the risk of atrial fibrillation: results from the Copenhagen ECG Study. *Heart Rhythm* 2015;**12**:1887–95.
- Nikolaïdou T, Ghosh JM, Clark AL. Outcomes related to first-degree atrioventricular block and therapeutic implications in patients with heart failure. *JACC Clin Electrophysiol* 2016;**2**:181–92.
- Buxton AE, Josephson ME. The role of P wave duration as a predictor of post-operative atrial arrhythmias. *Chest* 1981;**80**:68–73.
- Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr, Nazarian S et al. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. *Stroke* 2014;**45**:2786–8.
- Nikolaïdou T, Pellicori P, Zhang J, Kazmi S, Goode KM, Cleland JG et al. Prevalence, predictors, and prognostic implications of PR interval prolongation in patients with heart failure. *Clin Res Cardiol* 2018;**107**:108–19.
- Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA et al. Prognostic significance of prolonged PR interval in the general population. *Eur Heart J* 2014;**35**:123–9.
- Andrade JG, Roy D, Wyse DG, Dorian P, Talajic M, Leduc H et al. ECG features associated with adverse cardiovascular outcomes in patients with atrial fibrillation: a combined AFFIRM and AF-CHF analysis. *J Cardiovasc Electrophysiol* 2016;**27**:404–13.
- Januszkievicz L, Vegh E, Borgquist R, Bose A, Sharma A, Orencole M et al. Prognostic implication of baseline PR interval in cardiac resynchronization therapy recipients. *Heart Rhythm* 2015;**12**:2256–62.
- Rickard J, Karim M, Baranowski B, Cantillon D, Spragg D, Tang WHW et al. Effect of PR interval prolongation on long-term outcomes in patients with left bundle branch block vs non-left bundle branch block morphologies undergoing cardiac resynchronization therapy. *Heart Rhythm* 2017;**14**:1523–8.
- Das MK, Zipes DP. Fragmented QRS: a predictor of mortality and sudden cardiac death. *Heart Rhythm* 2009;**6**(3 Suppl):S8–14.
- Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ et al.; Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization

- and interpretation of the electrocardiogram: Part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society; endorsed by the International Society for Computerized Electrocardiology. *Circulation* 2009;**119**:e241–50.
34. Elming H, Holm E, Jun L, Torp-Pedersen C, Køber L, Kircshoff M *et al*. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. *Eur Heart J* 1998;**19**:1391–400.
 35. Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR, Study A. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *J Am Coll Cardiol* 2004;**43**:565–71.
 36. Chiang TM, Hau YW, Lim CW. Ventricular tachyarrhythmias prediction methods and its prognostic features: a review. *Int J Comput Digital Syst* 2019;**8**: 351–65.
 37. Prenner SB, Shah SJ, Goldberger JJ, Sauer AJ. Repolarization heterogeneity: beyond the QT interval. *J Am Heart Assoc* 2016;**5**:1–10.
 38. Porta-Sanchez A, Spillane DR, Harris L, Xue J, Dorsey P, Care M *et al*. T-wave morphology analysis in congenital long QT syndrome discriminates patients from healthy individuals. *JACC Clin Electrophysiol* 2017;**3**:374–81.
 39. Hermans BJM, Bennis FC, Vink AS, Kooopsen T, Lyon A, Wilde AAM *et al*. Improving long-QT syndrome diagnosis by a polynomial-based T-wave morphology characterization. *Heart Rhythm* 2020. pii: S1547-5271(20)30001-1.
 40. Panikath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R *et al*. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol* 2011;**4**: 441–7.
 41. Malik M, Huikuri H, Lombardi F, Schmidt G, Zabel M; on behalf of e-Rhythm Study Group of EHRA. Conundrum of the Tpeak-Tend interval. *J Cardiovasc Electrophysiol* 2018;**29**:767–70.
 42. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L *et al*. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;**358**:2016–23.
 43. Wu SH, Lin XX, Cheng YJ, Qiang CC, Zhang J. Early repolarization pattern and risk for arrhythmia death: a meta-analysis. *J Am Coll Cardiol* 2013;**61**:645–50.
 44. Aagaard P, Baranowski B, Aziz P, Phelan D. Early repolarization in athletes: a review. *Circ Arrhythm Electrophysiol* 2016;**9**:e003577.
 45. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. *Circulation* 1984;**69**:250–8.
 46. Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L *et al*. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. *Lancet* 1999;**353**:1390–6.
 47. Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G *et al*. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;**352**:2581–8.
 48. Gula LJ, Klein GJ, Hellkamp AS, Massel D, Krahn AD, Skanes AC *et al*. Ejection fraction assessment and survival: an analysis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Am Heart J* 2008;**156**:1196–200.
 49. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA *et al*. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC: Heart Fail* 2016;**5**:28–38.
 50. Coleman GC, Shaw PW, Balfour PC, Gonzalez JA, Kramer CM, Patel AR *et al*. Prognostic value of myocardial scarring on CMR in patients with cardiac sarcoidosis. *JACC: Cardiovasc Imaging* 2017;**10**:411–20.
 51. Greulich S, Deluigi CC, Gloekler S, Wahl A, Zürn C, Kramer U *et al*. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. *JACC: Cardiovasc Imaging* 2013;**6**:501–11.
 52. Naruse Y, Sekiguchi Y, Nogami A, Okada H, Yamauchi Y, Machino T *et al*. Systematic treatment approach to ventricular tachycardia in cardiac sarcoidosis. *Circ Arrhythm Electrophysiol* 2014;**7**:407–13.
 53. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL *et al*. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. *J Am Coll Cardiol* 2014;**63**:329–36.
 54. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H *et al*. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;**335**:1933–40.
 55. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS *et al*. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83.
 56. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R *et al*. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–37.
 57. Moss AJ, Greenberg H, Case RB, Zareba W, Hall WJ, Brown MW *et al*. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004;**110**:3760–5.
 58. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R *et al*. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol* 2006;**47**:1161–6.
 59. Gorgels AP, Gijssels C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest-the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *European Heart Journal* 2003;**24**:1204–9.
 60. Stevens SM, Reinier K, Chugh SS. Increased left ventricular mass as a predictor of sudden cardiac death: is it time to put it to the test? *Circ Arrhythm Electrophysiol* 2013;**6**:212–7.
 61. Køber L, Thune JJ, Nielsen JC, Haarbø J, Videbæk L, Korup E *et al*. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–30.
 62. Piers SR, Tao Q, van Huls van Taxis CF, Schalij MJ, van der Geest RJ, Zeppenfeld K. Contrast-enhanced MRI-derived scar patterns and associated ventricular tachycardias in nonischemic cardiomyopathy: implications for the ablation strategy. *Circ Arrhythm Electrophysiol* 2013;**6**:875–83.
 63. White JA, Fine NM, Gula L, Yee R, Skanes A, Klein G *et al*. Utility of cardiovascular magnetic resonance in identifying substrate for malignant ventricular arrhythmias. *Circ Cardiovasc Imaging* 2012;**5**:12–20.
 64. Gutman SJ, Costello BT, Papapostolou S, Voskoboinik A, Iles L, Ja J *et al*. Reduction in mortality from implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy patients is dependent on the presence of left ventricular scar. *Eur Heart J* 2019;**40**:542–50.
 65. Fallavollita JA, Heavey BM, Luisi AJ, Michalek SM, Baldwa S, Mashtare TL *et al*. Regional myocardial sympathetic denervation predicts the risk of sudden cardiac arrest in ischemic cardiomyopathy. *J Am Coll Cardiol* 2014;**63**:141–9.
 66. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;**341**:1882–90.
 67. Brembilla-Perrot B, Suty-Selton C, Beurrier D, Houriez P, Nippert M, de la Chaise AT *et al*. Differences in mechanisms and outcomes of syncope in patients with coronary disease or idiopathic left ventricular dysfunction as assessed by electrophysiologic testing. *J Am Coll Cardiol* 2004;**44**:594–601.
 68. Panza JA, Ellis AM, Al-Khalidi HR, Holly TA, Berman DS, Oh JK *et al*. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med* 2019;**381**:739–48.
 69. 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**:878–86.
 70. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J *et al*. 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). *Europace* 2015;**17**:1601–87.
 71. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB *et al*. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Circulation* 2018;**138**:e272–e391.
 72. 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**: 24–9.
 73. Buxton AE, Fisher JD, Josephson ME, Lee KL, Pryor DB, Prystowsky EN *et al*. Prevention of sudden death in patients with coronary artery disease: The Multicenter Unsustained Tachycardia Trial (MUSTT). *Prog Cardiovasc Dis* 1993;**36**:215–26.
 74. Hilfiker G, Schoenenberger AW, Erne P, Kobza R. Utility of electrophysiological studies to predict arrhythmic events. *World J Cardiol* 2015;**7**:344–50.
 75. Mankbadi M, Hassan S, McGee M, Jan B, Mangal S, Altier J *et al*. Brugada syndrome: the role of risk stratification in selecting patients for implantable cardioverter-defibrillator placement. *Cureus* 2018;**10**:e2799.
 76. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;**72**:1064–59.
 77. Sroubek J, Probst V, Mazzanti A, Delise P, Hevia JC, Ohkubo K *et al*. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: a pooled analysis. *Circulation* 2016;**133**:622–30.
 78. Solbiati M, Casazza G, Dipaola F, Barbic F, Caldato M, Montano N *et al*. The diagnostic yield of implantable loop recorders in unexplained syncope: A systematic review and meta-analysis. *Int J Cardiol* 2017;**231**:170–6.

79. Ibrahim OA, Drew D, Hayes CJ, McIntyre W, Seifer CM, Hopman W et al. Implantable loop recorders in the real world: a study of two Canadian centers. *J Interv Card Electrophysiol* 2017;**50**:179–85.
80. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–86.
81. Edvardsson N, Frykman V, van Mechelen R, Mitro P, Mohii-Oskarsson A, Pasquie JL et al.; PICTURE Study Investigators. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. *Europace* 2011;**13**:262–9.
82. Brignole M, Moya A, de Lange FJ, Deharo J, Yue AM, Greenwell EF, Phillips PC et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018;**39**:1883–948.
83. Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD et al. 2017 ACC/AHA/HRS Guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation* 2017;**136**:e60–e122.
84. Roberts PR, Zachariah D, Morgan JM, Yue AM, Greenwood EF, Phillips PC et al. Monitoring of arrhythmia and sudden death in a hemodialysis population: the CRASH-ILR Study. *PLoS One* 2017;**12**:e0188713.
85. Cheung CC, Krahn AD, Andrade JG. The emerging role of wearable technologies in detection of arrhythmia. *Can J Cardiol* 2018;**34**:1083–7.
86. Bumgarner JM, Lambert CT, Hussein AA, Cantillon DJ, Baranowski B, Wolski K et al. Smartwatch algorithm for automated detection of atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:2381–8.
87. Liu S. Number of Connected Wearable Devices Worldwide from 2016 to 2022. 2019 <https://www.statista.com/statistics/487291/global-connected-wearable-devices/> (1 February 2020, date last accessed).
88. Valiaho ES, Kuoppa P, Lipponen JA, Martikainen TJ, Jantti H, Rissanen TT et al. Wrist band photoplethysmography in detection of individual pulses in atrial fibrillation and algorithm-based detection of atrial fibrillation. *Europace* 2019;**21**:1031–8.
89. Brasier N, Raichle CJ, Dorr M, Becke A, Nohturfft V, Weber S et al. Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-centre, clinical validation study (DETECT AF PRO). *Europace* 2019;**21**:41–7.
90. Verbrugge FH, Proesmans T, Vijgen J, Mullens W, Rivero-Ayerza M, Van Herendaal H et al. Atrial fibrillation screening with photo-plethysmography through a smartphone camera. *Europace* 2019;**21**:1167–75.
91. Gillinov S, Etiwy M, Wang R, Blackburn G, Phelan D, Am G et al. Variable accuracy of wearable heart rate monitors during aerobic exercise. *Med Sci Sports Exerc* 2017;**49**:1697–703.
92. Wang R, Blackburn G, Desai M, Phelan D, Gillinov L, Houghtaling P et al. Accuracy of wrist-worn heart rate monitors. *JAMA Cardiol* 2017;**2**:104–6.
93. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019;**381**:1909–17.
94. Guo Y, Wang H, Zhang H, Liu T, Liang Z, Xia Y et al. Mobile photoplethysmographic technology to detect atrial fibrillation. *J Am Coll Cardiol* 2019;**74**:2365–75.
95. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Europace* 2011;**13**:1077–109.
96. Haugaa KH, Dan GA, Iliodromitis K, Lenarczyk R, Marinkis G, Osca J et al. Management of patients with ventricular arrhythmias and prevention of sudden cardiac death-translating guidelines into practice: results of the European Heart Rhythm Association survey. *Europace*: european pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the. *Eur Soc Cardiol* 2018;**20**:f249–53.
97. Anastasakis A, Papatheodorou E, Ritsatos K, Protonotarios N, Rentoumi V, Gatzoulis K et al. Sudden unexplained death in the young: epidemiology, aetiology and value of the clinically guided genetic screening. *Europace* 2018;**20**:472–80.
98. Pontecorvoli G, Figueras I, Carlosena A, Benito E, Prat-Gonzales S, Padeletti L et al. Use of delayed-enhancement magnetic resonance imaging for fibrosis detection in the atria: a review. *Europace* 2017;**19**:180–9.
99. Halliday BP, Cleland JGF, Goldberger JJ, Prasad SK. Personalizing risk stratification for sudden death in dilated cardiomyopathy: the past, present, and future. *Circulation* 2017;**136**:215–31.
100. Margulescu AD, Nunez-Garcia M, Alarcon F, Benito EM, Enomoto N, Cozzari J et al. Reproducibility and accuracy of late gadolinium enhancement cardiac magnetic resonance measurements for the detection of left atrial fibrosis in patients undergoing atrial fibrillation ablation procedures. *Europace* 2019;**21**:724–31.
101. Goetze JP, Mogelvang R, Maage L, Scharling H, Schnohr P, Sogaard P et al. Plasma pro-B-type natriuretic peptide in the general population: screening for left ventricular hypertrophy and systolic dysfunction. *Eur Heart J* 2006;**27**:3004–10.
102. Darkner S, Goetze JP, Chen X, Henningsen K, Pehrson S, Svendsen JH. Natriuretic peptides as markers of atrial fibrillation burden and recurrence (from the AMIO-CAT Trial). *Am J Cardiol* 2017;**120**:1309–15.
103. Sinner MF, Stepas KA, Moser CB, Krijthe BP, Aspelund T, Sotoodehnia N et al. B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies. *Europace* 2014;**16**:1426–33.
104. Kemp Gudmundsdottir K, Fredriksson T, Svennberg E, Al-Khalili F, Friberg L, Frykman V et al. Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study. *Europace* 2020;**22**:24–32.
105. Sepehri Shamloo A, Bollmann A, Dages N, Hindricks G, Arya A. Natriuretic peptides: biomarkers for atrial fibrillation management. *Clin Res Cardiol* 2020. doi:10.1007/s00392-020-01608-x.
106. Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *Eur Heart J* 2005;**26**:2083–92.
107. Nyrnes A, Njolstad I, Mathiesen EB, Wilsaard T, Hansen JB, Skjelbakken T et al. Inflammatory biomarkers as risk factors for future atrial fibrillation. An eleven-year follow-up of 6315 men and women: the Tromso study. *Genet Med* 2012;**9**:536–47 e2.
108. Henningsen KM, Therkelsen SK, Johansen JS, Bruunsgaard H, Svendsen JH. Plasma YKL-40, a new biomarker for atrial fibrillation? *Europace* 2009;**11**:1032–6.
109. Nattel S. Molecular and cellular mechanisms of atrial fibrosis in atrial fibrillation. *JACC Clin Electrophysiol* 2017;**3**:425–35.
110. Watanabe T, Takeishi Y, Hirono O, Itoh M, Matsui M, Nakamura K et al. C-reactive protein elevation predicts the occurrence of atrial structural remodeling in patients with paroxysmal atrial fibrillation. *Heart Vessels* 2005;**20**:45–9.
111. Henningsen KM, Nilsson B, Bruunsgaard H, Chen X, Pedersen BK, Svendsen JH. Prognostic impact of hs-CRP and IL-6 in patients undergoing radiofrequency catheter ablation for atrial fibrillation. *Scand Cardiovasc J* 2009;**43**:285–91.
112. Henningsen KM, Therkelsen SK, Bruunsgaard H, Krabbe KS, Pedersen BK, Svendsen JH. Prognostic impact of hs-CRP and IL-6 in patients with persistent atrial fibrillation treated with electrical cardioversion. *Scand J Clin Lab Invest* 2009;**69**:425–32.
113. Aronson D, Boulous M, Suleiman A, Bidoosi S, Agmon Y, Kapeliovich M et al. Relation of C-reactive protein and new-onset atrial fibrillation in patients with acute myocardial infarction. *Am J Cardiol* 2007;**100**:753–7.
114. Canpolat U, Aytemir K, Hazirolan T, Ozer N, Oto A. Serum YKL-40 as a marker of left atrial fibrosis assessed by delayed enhancement MRI in lone atrial fibrillation. *Pacing Clin Electrophysiol* 2015;**38**:1386–95.
115. Henningsen KM, Nilsson B, Johansen JS, Chen X, Pehrson S, Svendsen JH. Plasma YKL-40 is elevated in patients with recurrent atrial fibrillation after catheter ablation. *Inflamm Res* 2010;**59**:463–9.
116. Marott SCW, Benn M, Johansen JS, Jensen GB, Tybjaerg-Hansen A, Nordestgaard BG. YKL-40 levels and atrial fibrillation in the general population. *Int J Cardiol* 2013;**167**:1354–9.
117. Van Wagoner DR, Piccini JP, Albert CM, Anderson ME, Benjamin EJ, Brundel B et al. Progress toward the prevention and treatment of atrial fibrillation: a summary of the Heart Rhythm Society Research Forum on the Treatment and Prevention of Atrial Fibrillation, Washington, DC, December 9–10, 2013. *Heart Rhythm* 2015;**12**:e5–e29.
118. Fenger-Gron M, Overvad K, Tjønneland A, Frost L. Lean body mass is the predominant anthropometric risk factor for atrial fibrillation. *J Am Coll Cardiol* 2017;**69**:2488–97.
119. Sandhu RK, Conen D, Tedrow UB, Fitzgerald KC, Pradhan AD, Ridker PM et al. Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. *J Am Heart Assoc* 2014;**3**:e000916.
120. Frost L, Benjamin EJ, Fenger-Gron M, Pedersen A, Tjønneland A, Overvad K. Body fat, body fat distribution, lean body mass and atrial fibrillation and flutter. A Danish cohort study. *Obesity (Silver Spring)* 2014;**22**:1546–52.
121. Zhuang J, Lu Y, Tang K, Peng W, Xu Y. Influence of body mass index on recurrence and quality of life in atrial fibrillation patients after catheter ablation: a meta-analysis and systematic review. *Clin Cardiol* 2013;**36**:269–75.
122. Abed HS, Samuel CS, Lau DH, Kelly DJ, Royce SG, Alasady M et al. Obesity results in progressive atrial structural and electrical remodeling: implications for atrial fibrillation. *Heart Rhythm* 2013;**10**:90–100.
123. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and

- management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389–406.
124. Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amlie JP, Timothy K *et al*. The Jervell and Lange-Nielsen syndrome: natural history, molecular basis, and clinical outcome. *Circulation* 2006;**113**:783–90.
 125. Splawski I, Timothy KW, Sharpe LM, Decher N, Kumar P, Bloise R *et al*. Ca(V)_{1.2} calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* 2004;**119**:19–31.
 126. Barsheshet A, Goldenberg I, O-Uchi J, Moss AJ, Jons C, Shimizu W *et al*. Mutations in cytoplasmic loops of the KCNQ1 channel and the risk of life-threatening events: implications for mutation-specific response to beta-blocker therapy in type 1 long-QT syndrome. *Circulation* 2012;**125**:1988–96.
 127. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc D, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children: a 7-year follow up of 21 patients. *Circulation* 1995;**91**:1512–9.
 128. Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y *et al*. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart* 2003;**89**:66–70.
 129. van der Werf C, Nederend I, Hofman N, van Geloven N, Ebink C, Frohn-Mulder IM *et al*. Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives. *Circ Arrhythm Electrophysiol* 2012;**5**:748–56.
 130. Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J *et al*. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. *Heart Rhythm* 2010;**7**:33–46.
 131. Liu M, Yang KC, Dudley SC Jr. Cardiac sodium channel mutations: why so many phenotypes? *Nat Rev Cardiol* 2014;**11**:607–15.
 132. Eckhardt LL. Phenotype, genotype, and cellular physiology: need for clarity in characterization. *Heart Rhythm* 2012;**9**:1993–4.
 133. Weng LC, Lunetta KL, Muller-Nurasyid M, Smith AV, Theriault S, Weeke PE *et al*. Genetic interactions with age, sex, body mass index, and hypertension in relation to atrial fibrillation: the AFGen consortium. *Sci Rep* 2017;**7**:11303.
 134. Weng LC, Preis SR, Hulme OL, Larson MG, Choi SH, Wang B *et al*. Genetic predisposition, clinical risk factor burden, and lifetime risk of atrial fibrillation. *Circulation* 2018;**137**:1027–38.
 135. Ahlberg G, Refsgaard L, Lundegaard PR, Andreassen L, Ranthe MF, Linscheid N *et al*. Rare truncating variants in the sarcomeric protein titin associate with familial and early-onset atrial fibrillation. *Nat Commun* 2018;**9**:4316.
 136. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM *et al*. Multi-ethnic genome-wide association study for atrial fibrillation. *Nat Genet* 2018;**50**:1225–33.
 137. Hannun AY, Rajpurkar P, Haghighi M, Tison GH, Bourn C, Turakhia MP *et al*. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. *Nat Med* 2019;**25**:65–9.
 138. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ *et al*. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* 2019;**394**:861–7.
 139. Ebrahimzadeh E, Kalantari M, Joulani M, Shahraki RS, Fayaz F, Ahmadi F. Prediction of paroxysmal Atrial Fibrillation: a machine learning based approach using combined feature vector and mixture of expert classification on HRV signal. *Comput Methods Programs Biomed* 2018;**165**:53–67.
 140. Attia ZI, Kapa S, Lopez-Jimenez F, McKie PM, Ladewig DJ, Satam G *et al*. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat Med* 2019;**25**:70–4.
 141. Motwani M, Dey D, Berman DS, Germano G, Achenbach S, Al-Mallah MH *et al*. Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. *Eur Heart J* 2017;**38**:500–7.
 142. Narula S, Shameer K, Salem Omar AM, Dudley JT, Sengupta PP. Machine-learning algorithms to automate morphological and functional assessments in 2D echocardiography. *J Am Coll Cardiol* 2016;**68**:2287–95.
 143. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD *et al*. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–62.
 144. Andrade JG, Deyell MW, Lee AY, Macle L. Sex differences in atrial fibrillation. *Can J Cardiol* 2018;**34**:429–36.
 145. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. *Circ Res* 2017;**120**:1501–17.
 146. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ *et al*. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–47.
 147. Stefansdottir H, Aspelund T, Gudnason V, Arnar DO. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. *Europace* 2011;**13**:1110–7.
 148. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP *et al*. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;**114**:119–25.
 149. Kloosterman M, Crijns H, Mulder BA, Groeneweld HF, Van Veldhuisen DJ, Rienstra M *et al*. Sex-related differences in risk factors, outcome, and quality of life in patients with permanent atrial fibrillation: results from the RACE II study. *Europace* 2019. doi:10.1093/europace/euz300.
 150. Cheng X, Hu Q, Gao L, Liu J, Qin S, Zhang D. Sex-related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Europace* 2019;**21**:1509–18.
 151. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res* 2014;**114**:1453–68.
 152. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J *et al*. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. *Heart* 2007;**93**:606–12.
 153. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC Jr. *et al*. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: the Multi-Ethnic Study of Atherosclerosis. *Ann Epidemiol* 2015;**25**:71–6, 76.e1.
 154. Naderi S, Wang Y, Miller AL, Rodriguez F, Chung MK, Radford MJ *et al*. The impact of age on the epidemiology of atrial fibrillation hospitalizations. *Am J Med* 2014;**127**:158.e1–7.
 155. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;**27**:949–53.
 156. Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH *et al*. Lifetime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan nationwide AF cohort study. *Chest* 2018;**153**:453–66.
 157. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016;**13**:321–32.
 158. Friberg J, Scharling H, Gadsboll N, Truelsen T, Jensen GB; Copenhagen City Heart Study. Comparison of the impact of atrial fibrillation on the risk of stroke and cardiovascular death in women versus men (The Copenhagen City Heart Study). *Am J Cardiol* 2004;**94**:889–94.
 159. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB *et al*. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol* 2007;**49**:986–92.
 160. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2n–9n.
 161. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsis M *et al*. Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke prevention Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J* 2014;**35**:508–16.
 162. Shaikh AY, Maan A, Khan UA, Aurigemma GP, Hill JC, Kane JL *et al*. Speckle echocardiographic left atrial strain and stiffness index as predictors of maintenance of sinus rhythm after cardioversion for atrial fibrillation: a prospective study. *Cardiovasc Ultrasound* 2012;**10**:48.
 163. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F *et al*. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA* 2014;**311**:498–506.
 164. Skanes AC, Tang A. Atrial fibrillation and heart failure: untangling a modern Gordian knot. *Can J Cardiol* 2018;**34**:1437–48.
 165. Smith JG, Newton-Cheh C, Almgren P, Struck J, Morgenthaler NG, Bergmann A *et al*. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. *J Am Coll Cardiol* 2010;**56**:1712–9.
 166. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV *et al*. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet* 2012;**44**:670–5.
 167. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA *et al*. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;**133**:484–92.
 168. Buza V, Rajagopalan B, Curtis AB. Cancer treatment-induced arrhythmias: focus on chemotherapy and targeted therapies. *Circ Arrhythm Electrophysiol* 2017;**10**.

169. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;**49**:565–71.
170. Djousse L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. *Am J Cardiol* 2004;**93**:710–3.
171. Selmer C, Olesen JB, Hansen ML, Lindhardtsen J, Olsen AM, Madsen JC et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ* 2012;**345**:e7895.
172. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. *J Am Coll Cardiol* 1990;**15**:1279–85.
173. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;**285**:2370–5.
174. Magnani JW, Zhu L, Lopez F, Pencina MJ, Agarwal SK, Soliman EZ et al. P-wave indices and atrial fibrillation: cross-cohort assessments from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2015;**169**:53–61.e1.
175. Fox CS, Parise H, D'Agostino RB Sr, Lloyd-Jones DM, Vasan RS, Wang TJ et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA* 2004;**291**:2851–5.
176. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemostasis* 2017;**117**:837–50.
177. Li YG, Pastori D, Farcomeni A, Yang PS, Jang E, Joung B et al. A simple clinical risk score (C2HEST) for predicting incident atrial fibrillation in Asian subjects: derivation in 471,446 Chinese subjects, with internal validation and external application in 451,199 Korean subjects. *Chest* 2019;**155**:510–18.
178. Yan-Guang L, Bisson A, Bodin A et al. The C2HEST score and the prediction of incident atrial fibrillation in post-stroke subjects: a French nationwide study. *J Am Heart Assoc* 2019;**8**:e012546.
179. Hu WS, Hsieh MH, Lin CL. A novel atrial fibrillation prediction model for Chinese subjects: a nationwide cohort investigation of 682 237 study participants with random forest model. *Europace* 2019;**21**:1307–12.
180. Li Y, Pastori D, Guo Y, Wang Y, Lip G. Risk factors for new-onset atrial fibrillation: a focus on Asian populations. *Int J Cardiol* 2018;**261**:92–8.
181. Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess* 2005;**9**:iii-iv, ix-x, 1–74.
182. Long MJ, Jiang CQ, Lam TH, Xu L, Zhang WS, Lin JM et al. Atrial fibrillation and obesity among older Chinese: the Guangzhou Biobank Cohort Study. *Int J Cardiol* 2011;**148**:48–52.
183. Boriani G, Laroche C, Diemberger I, Fantecchi E, Meeder J, Kurpesa M et al. Overweight and obesity in patients with atrial fibrillation: sex differences in 1-year outcomes in the EORP-AF General Pilot Registry. *J Cardiovasc Electrophysiol* 2018;**29**:566–72.
184. Proietti M, Guiducci E, Cheli P, Lip GY. Is there an obesity paradox for outcomes in atrial fibrillation? A systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant trials. *Stroke* 2017;**48**:857–66.
185. Middeldorp ME, Pathak RK, Meredith M, Mehta AB, Elliott AD, Mahajan R et al. PREVENTion and regReSSive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *Europace* 2018;**20**:1929–35.
186. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY et al. Ideal blood pressure in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**72**:1233–45.
187. Kim TH, Yang PS, Yu HT, Jang E, Shin H, Kim HY et al. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. *Eur Heart J* 2019;**40**:809–19.
188. Overvad TF, Skjoth F, Lip GY, Lane DA, Albersen IE, Rasmussen LH et al. Duration of diabetes mellitus and risk of thromboembolism and bleeding in atrial fibrillation: nationwide cohort study. *Stroke* 2015;**46**:2168–74.
189. Fangel MV, Nielsen PB, Larsen TB, Christensen B, Overvad TF, Lip GYH et al. Type 1 versus type 2 diabetes and thromboembolic risk in patients with atrial fibrillation: a Danish nationwide cohort study. *Int J Cardiol* 2018;**268**:137–42.
190. Lip GY, Clementy N, Pierre B, Boyer M, Fauchier L. The impact of associated diabetic retinopathy on stroke and severe bleeding risk in diabetic patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2015;**147**:1103–10.
191. Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM et al. Effect of diabetes and glycemic control on ischemic stroke risk in AF patients: ATRIA study. *J Am Coll Cardiol* 2016;**67**:239–47.
192. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J* 2012;**76**:2289–304.
193. Lip GYH, Collet JP, de Caterina R, Fauchier L, Lane DA, Larsen TB et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace* 2017;**19**:1757–8.
194. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY et al. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley Atrial Fibrillation Project. *Eur J Heart Fail* 2012;**14**:295–301.
195. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA* 2015;**314**:1030–8.
196. Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME et al. Rate control versus rhythm control for atrial fibrillation after cardiac surgery. *N Engl J Med* 2016;**374**:1911–21.
197. Mathew J; Investigators of the Ischemia Research and Education Foundation; Multicenter Study of Perioperative Ischemia Research Group. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720–9.
198. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M et al. Predictors of atrial fibrillation after coronary artery surgery: current trends and impact on hospital resources. *Circulation* 1996;**94**:390–7.
199. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. *Eur J Cardio-Thorac Surg* 2010;**37**:1353–9.
200. Dobrev D, Aguilar M, Heijman J, Guichard J-B, Nattel S. Postoperative atrial fibrillation: mechanisms, manifestations and management. *Nat Rev Cardiol* 2019;1.
201. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol* 2008;**51**:793–801.
202. Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah AS, Habib RH. Obesity and risk of new-onset atrial fibrillation after cardiac surgery. *Circulation* 2005;**112**:3247–55.
203. Lowres N, Mulcahy G, Jin K, Gallagher R, Neubeck L, Freedman B. Incidence of postoperative atrial fibrillation recurrence in patients discharged in sinus rhythm after cardiac surgery: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg* 2018;**26**:504–11.
204. National Collaborating Centre for Chronic Conditions (UK). *Stroke: National Clinical Guideline for Diagnosis and Initial Management of Acute Stroke and Transient Ischaemic Attack (TIA)*. London, UK: Royal College of Physicians; 2008.
205. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors J, Demerschalk BM et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;**44**:870–947.
206. Steinberg JS, Varma N, Cygankiewicz I, Aziz P, Balsam P, Baranchuk A et al. 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry. *Heart Rhythm* 2017;**14**:e55–e96.
207. Sposato LA, Cipriano LE, Saposnik G, Vargas ER, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015;**14**:377–87.
208. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35–41.
209. Dussault C, Toeg H, Nathan M, Wang ZJ, Roux J-F, Secemsky E. Electrocardiographic monitoring for detecting atrial fibrillation after ischemic stroke or transient ischemic attack: systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2015;**8**:263–9.
210. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467–77.
211. Li YG, Bisson A, Bodin A, Herbert J, Grammatico-Guillon L, Joung B et al. C2 HEST Score and prediction of incident atrial fibrillation in poststroke patients: a French Nationwide Study. *J Am Heart Assoc* 2019;**8**:e012546.
212. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace* 2009;**11**:1156–9.
213. Heidebuchel H, Anne W, Willems R, Adriaenssens B, Van de Werf F, Ector H. Endurance sports is a risk factor for atrial fibrillation after ablation for atrial flutter. *Int J Cardiol* 2006;**107**:67–72.

214. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009;**103**:1572–7.
215. Hoogsteen J, Schep G, Van Hemel NM, Van Der Wall EE. Paroxysmal atrial fibrillation in male endurance athletes. A 9-year follow up. *Europace* 2004;**6**:222–8.
216. Swanson DR. Atrial fibrillation in athletes: implicit literature-based connections suggest that overtraining and subsequent inflammation may be a contributory mechanism. *Med Hypotheses* 2006;**66**:1085–92.
217. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation* 2002;**105**:2753–9.
218. McGann C, Akoum N, Patel A, Kholmovski E, Revelo P, Damal K et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. *Circ Arrhythm Electrophysiol* 2014;**7**:23–30.
219. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 1999;**10**:1525–33.
220. Qureshi WT, Alirhayim Z, Blaha MJ, Juraschek SP, Keteyian SJ, Brawner CA et al. Cardiorespiratory Fitness and risk of incident atrial fibrillation: results from the Henry Ford Exercise Testing (FIT) project. *Circulation* 2015;**131**:1827–34.
221. Allison MA, Jensky NE, Marshall SJ, Bertoni AG, Cushman M. Sedentary behavior and adiposity-associated inflammation: the Multi-Ethnic Study of Atherosclerosis. *Am J Preventive Med* 2012;**42**:8–13.
222. Malmo V, Nes BM, Amundsen BH, Tjonna AE, Stoylen A, Rossvoll O et al. Aerobic interval training reduces the burden of atrial fibrillation in the short term: a randomized trial. *Circulation* 2016;**133**:466–73.
223. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med* 1999;**130**:23–31.
224. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;**104**:2886–91.
225. Korantzopoulos P, Kolettis T, Siogas K, Goudevenos J. Atrial fibrillation and electrical remodeling: the potential role of inflammation and oxidative stress. *Med Sci Monit* 2003;**9**:Ra225–9.
226. Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. *Am J Cardiol* 2005;**95**:764–7.
227. Mont L, Elosua R, Brugada J. Endurance sport practice as a risk factor for atrial fibrillation and atrial flutter. *Europace* 2009;**11**:11–7.
228. Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M et al. on behalf of the Marathon Study Investigators and the Heinz Nixdorf Recall Study Investigators. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J* 2008;**29**:1903–10.
229. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC et al. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation* 2011;**123**:13–22.
230. Boraita A, Santos-Lozano A, Heras ME, Gonzalez-Amigo F, Lopez-Ortiz S, Villacastin JP et al. Incidence of atrial fibrillation in elite athletes. *JAMA Cardiol* 2018;**3**:1200.
231. Cuspidi C, Tadic M, Sala C, Gherbesi E, Grassi G, Mancia G. Left atrial function in elite athletes: a meta-analysis of two-dimensional speckle tracking echocardiographic studies. *Clin Cardiol* 2019;**42**:579–87.
232. Pizzale S, Gollob MH, Gow R, Birnie DH. Sudden death in a young man with catecholaminergic polymorphic ventricular tachycardia and paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;**19**:1319–21.
233. Miyake CY, Webster G, Czossek RJ, Kantoch MJ, Dubin AM, Avasarala K et al. Efficacy of implantable cardioverter defibrillators in young patients with catecholaminergic polymorphic ventricular tachycardia: success depends on substrate. *Circ Arrhythm Electrophysiol* 2013;**6**:579–87.
234. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D et al. Brugada syndrome: report of the second consensus conference. *Heart Rhythm* 2005;**2**:429–40.
235. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;**20**:1391–6.
236. Eckardt L, Kirchhof P, Loh P, Schulze-Bahr E, Johna R, Wichter T et al. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? *J Cardiovasc Electrophysiol* 2001;**12**:680–5.
237. Morita H, Kusano-Fukushima K, Nagase S, Fujimoto Y, Hisamatsu K, Fujio H et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol* 2002;**40**:1437–44.
238. Francis J, Antzelevitch C. Atrial fibrillation and Brugada syndrome. *J Am Coll Cardiol* 2008;**51**:1149–53.
239. Bordachar P, Reuter S, Garrigue S, Cai X, Hocini M, Jais P et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J* 2004;**25**:879–84.
240. Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. *Europace* 2007;**9**:947–50.
241. Sacher F, Probst V, Lesaka Y, Jacon P, Laborde J, Mizon-Gerard F et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. *Circulation* 2006;**114**:2317–24.
242. Johnson JN, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. *Heart Rhythm* 2008;**5**:704–9.
243. Knoche JW, Orland KM, January CT, Maginot KR. Atrial fibrillation and long QT syndrome presenting in a 12-year-old girl. *Case Rep Pediatr* 2012;**2012**:124838.
244. Sankaranarayanan R, Kirkwood G, Dibb K, Garratt CJ. Comparison of atrial fibrillation in the young versus that in the elderly: a review. *Cardiol Res Pract* 2013;**2013**:1–16.
245. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY et al. KCNQ1 gain-of-function mutation in familial atrial fibrillation. *Science* 2003;**299**:251–4.
246. Lieve KV, Verkerk AO, Podliesna S, van der Werf C, Tanck MW, Hofman N et al. Gain-of-function mutation in SCN5A causes ventricular arrhythmias and early onset atrial fibrillation. *Int J Cardiol* 2017;**236**:187–93.
247. Kirchhof P, Eckardt L, Franz MR, Monnig G, Loh P, Wedekind H et al. Prolonged atrial action potential durations and polymorphic atrial tachyarrhythmias in patients with long QT syndrome. *J Cardiovasc Electrophysiol* 2003;**14**:1027–33.
248. Maruyama M, Joung B, Tang L, Shinohara T, On YK, Han S et al. Diastolic intracellular calcium-membrane voltage coupling gain and postshock arrhythmias: role of Purkinje fibers and triggered activity. *Circ Res* 2010;**106**:399–408.
249. Morotti S, McCulloch AD, Bers DM, Edwards AG, Grandi E. Atrial-selective targeting of arrhythmogenic phase-3 early afterdepolarizations in human myocytes. *J Mol Cell Cardiol* 2016;**96**:63–71.
250. Brugada R, Hong K, Dumaine R, Cordeiro J, Gaita F, Borggrefe M et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 2004;**109**:30–5.
251. Hong K, Bjerregaard P, Gussak I, Brugada R. Short QT syndrome and atrial fibrillation caused by mutation in KCNH2. *J Cardiovasc Electrophysiol* 2005;**16**:394–6.
252. Priori SG, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. *Circ Res* 2005;**96**:800–7.
253. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise T et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001;**103**:196–200.
254. Postma AV, Denjoy I, Hoorntje TM, Lupoglazoff J-M D, Costa A, Sebillon P et al. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ Research* 2002;**91**:1–6.
255. Marsman RF, Barc J, Beekman L, Alders M, Dooijes D, van den Wijngaard A et al. A mutation in CALM1 encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence. *J Am Coll Cardiol* 2014;**63**:259–66.
256. Lieve KVV, Verhagen JMA, Wei J, Bos JM, van der Werf C, Roses INF et al. Linking the heart and the brain: neurodevelopmental disorders in patients with catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* 2019;**16**:220–8.
257. Lip GYH, Jensen M, Melgaard L, Skjoth F, Nielsen PB, Larsen TB. Stroke and bleeding risk scores in patients with atrial fibrillation and valvular heart disease: evaluating 'valvular heart disease' in a nationwide cohort study. *Europace* 2019;**21**:33–40.
258. Dagres N, Chao TF, Fenelon G, Aguinaga L, Benhayon D, Benjamin EJ et al.; ESC Scientific Document Group. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHS) expert consensus on arrhythmias and cognitive function: what is the best practice? *Europace* 2018;**20**:1399–421.
259. Krawczyk M, Fridman S, Cheng Y, Fang J, Saposnik G, Sposato LA. Atrial fibrillation diagnosed after stroke and dementia risk: cohort study of first-ever ischaemic stroke patients aged 65 or older. *Europace* 2019. doi: 10.1093/europace/euz237.
260. Andrieu S, Coley N, Lovestone S, Aisen PS, Vellas B. Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. *Lancet Neurol* 2015;**14**:926–44.
261. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
262. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. *BMJ* 2013;**346**:f2573–f2573.

263. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**:e000250.
264. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–90.
265. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–67.
266. Fauchier L, Clementy N, Bisson A, Ivanov F, Angoulvant D, Babuty D et al. Should atrial fibrillation patients with only 1 nongender-related CHA₂DS₂-VASc risk factor be anticoagulated? *Stroke* 2016;**47**:1831–6.
267. Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged ≥ 75 years with atrial fibrillation: the Loire Valley atrial fibrillation project. *Stroke* 2015;**46**:143–50.
268. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF et al. Age threshold for the use of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with atrial fibrillation: insights into the optimal assessment of age and incident comorbidities. *Eur Heart J* 2019;**40**:1504–14.
269. Sepelhi Shamlou A, Dagnes N, Mussigbrodt A, Stauber A, Kircher S, Richter S et al. Atrial fibrillation and cognitive impairment: new insights and future directions. *Heart Lung Circ* 2020;**29**:69–85.
270. Schwarz N, Kuniss M, Nedelmann M, Kaps M, Bachmann G, Neumann T et al. Neuropsychological decline after catheter ablation of atrial fibrillation. *Heart Rhythm* 2010;**7**:1761–7.
271. Saw J, Tzikas A, Shakir S, Gafoor S, Omran H, Nielsen-Kudsk JE et al. Incidence and clinical impact of device-associated thrombus and peri-device leak following left atrial appendage closure with the Amplatzer Cardiac Plug. *JACC Cardiovasc Interv* 2017;**10**:391–9.
272. Viles-Gonzalez JF, Kar S, Douglas P, Dukkipati S, Feldman T, Horton R et al. The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. *J Am Coll Cardiol* 2012;**59**:923–9.
273. Dukkipati SR, Kar S, Holmes DR, Doshi SK, Swarup V, Gibson DN et al. Device-related thrombus after left atrial appendage closure. *Circulation* 2018;**138**:874–85.
274. Fauchier L, Cinaud A, Brigadeau F, Lepillier A, Pierre B, Abbey S et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:1528–36.
275. Saw J, Fahmy P, DeJong P, Lempereur M, Spencer R, Tsang M et al. Cardiac CT angiography for device surveillance after endovascular left atrial appendage closure. *Eur Heart J Cardiovasc Imaging* 2015;**16**:1198–206.
276. Berte B, Jost CA, Maurer D, Fähr-Gunz A, Pillois X, Naegeli B et al. Long-term follow-up after left atrial appendage occlusion with comparison of transesophageal echocardiography vs. computed tomography to guide medical therapy and data about post-closure cardioversion. *J Cardiovasc Electrophysiol* 2017;**28**:1140–50.
277. Wolf RK, Schneeberger EW, Osterday R, Miller D, Merrill W, Flege JB Jr. et al. Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation. *J Thorac Cardiovasc Surg* 2005;**130**:797–802.
278. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L et al. 2017 HRS/EHRA/ECAS/APHS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace* 2018;**20**:157–208.
279. Schellinger PD, Tsigoulis G, Steiner T, Kohrmann M. Percutaneous left atrial appendage occlusion for the prevention of stroke in patients with atrial fibrillation: review and critical appraisal. *J Stroke* 2018;**20**:281–91.
280. Sharma SP, Park P, Lakkireddy D. Left atrial appendage occlusion: current status and prospective. *Korean Circ J* 2018;**48**:692–704.
281. Caliskan E, Sahin A, Yilmaz M, Seifert B, Hinzpeter R, Alkadi H et al. Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery. *Europace* 2018;**20**:e105–14.
282. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 2014;**312**:1988–98.
283. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;**64**:1–12.
284. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K et al. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J Am Coll Cardiol* 2017;**70**:2964–75.
285. Aryana A, Singh SK, Singh SM, Gearoid O'Neill P, Bowers MR, Allen SL et al. Association between incomplete surgical ligation of left atrial appendage and stroke and systemic embolization. *Heart Rhythm* 2015;**12**:1431–7.
286. Mohanty S, Gianni C, Trivedi C, Gadiyaram V, Della Rocca DG, MacDonald B et al. Risk of thromboembolic events after percutaneous left atrial appendage ligation in patients with atrial fibrillation: long-term results from a multicenter study. *Heart Rhythm* 2019.
287. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J* 2015;**36**:3250–7.
288. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920–5.
289. Denham NC, Pearman CM, Caldwell JL, Madders GW, Eisner DA, Trafford AW et al. Calcium in the pathophysiology of atrial fibrillation and heart failure. *Front Physiol* 2018;**9**.
290. Deedwania PC, Lardizabal JA. Atrial fibrillation in heart failure: a comprehensive review. *Am J Med* 2010;**123**:198–204.
291. Muller-Edenborn B, Minners J, Allgeier J, Burkhardt T, Lehrmann H, Ruile P et al. Rapid improvement in left ventricular function after sinus rhythm restoration in patients with idiopathic cardiomyopathy and atrial fibrillation. *Europace* 2019;**21**:871–8.
292. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;**113**:359–64.
293. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997–2004.
294. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;**203**:660–6.
295. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnsen TD, Poole JE et al.; for the CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1261.
296. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–27.
297. Mathew JS, Marzec LN, Kennedy KF, Jones PG, Varosy PD, Masoudi FA et al. Atrial fibrillation in heart failure US ambulatory cardiology practices and the potential for uptake of catheter ablation: an National Cardiovascular Data Registry (NCDR((R))) Research to Practice (R2P) Project. *J Am Heart Assoc* 2017;**6**:1–11.
298. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *The Lancet* 2016;**388**:1161–9.
299. Fauchier L, Samson A, Chaize G, Gaudin AF, Vainchtock A, Bailly C et al. Cause of death in patients with atrial fibrillation admitted to French hospitals in 2012: a nationwide database study. *Open Heart* 2015;**2**:e000290.
300. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL et al. Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: data from ROCKET AF. *J Am Heart Assoc* 2016;**7**:3. e00219.
301. Turagam MK, Velagapudi P, Visotcky A, Szabo A, Kocheril AG. African Americans have the highest risk of in-hospital mortality with atrial fibrillation related hospitalizations among all racial/ethnic groups: a nationwide analysis. *Int J Cardiol* 2012;**158**:165–6.
302. Jacobs V, May HT, Bair TL, Crandall BG, Cutler M, Day JD et al. The impact of risk score (CHA₂DS₂ versus CHA₂DS₂-VASc) on long-term outcomes after atrial fibrillation ablation. *Heart Rhythm* 2015;**12**:681–6.
303. Fox KAA, Lucas JE, Pieper KS, Bassand JP, Camm AJ, Fitzmaurice DA et al. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. *BMJ Open* 2017;**7**:e017157.
304. Niederdockl J, Simon A, Schnaubelt S, Schuetz N, Laggner R, Sulzgruber P et al. Cardiac biomarkers predict mortality in emergency patients presenting with atrial fibrillation. *Heart* 2019;**105**:482–8.
305. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW et al.; the ARISTOTLE and RE-LY Investigators. A biomarker-based risk score to predict death in patients with atrial fibrillation: the ABC (age, biomarkers, clinical history) death risk score. *Eur Heart J* 2018;**39**:477–85.
306. Esteve-Pastor MA, Roldan V, Rivera-Caravaca JM, Ramirez-Macias I, Lip GYH, Marin F. The use of biomarkers in clinical management guidelines: a critical appraisal. *Thromb Haemost* 2019.

307. Chang TY, Lip GYH, Chen SA, Chao TF. Importance of risk reassessment in patients with atrial fibrillation in guidelines: assessing risk as a dynamic process. *Can J Cardiol* 2019;**35**:611–8.
308. Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, Vicente V, Valdes M, Marin F et al. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. *Thromb Haemostasis* 2017;**117**:1848–58.
309. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH et al. Long-term stroke risk prediction in patients with atrial fibrillation: comparison of the ABC-stroke and CHA₂DS₂-VASc scores. *J Am Heart Assoc* 2017;**6**:1–9.
310. Kaarisalo MM, Immonen-Räihä P, Marttila RJ, Salomaa V, Kaarsalo E, Salmi K et al. Atrial fibrillation and stroke. Mortality and causes of death after the first acute ischemic stroke. *Stroke* 1997;**28**:311–5.
311. Gao H, Sun X, Li W, Gao Q, Zhang J, Zhang Y et al. Development and validation of a risk score to predict 30-day mortality in patients with atrial fibrillation-related stroke: GPS-GF score. *Neural Res* 2018;**40**:532–40.
312. Reinier K, Marijon E, Uy-Evanado A, Teodorescu C, Narayanan K, Chugh H et al. The association between atrial fibrillation and sudden cardiac death: the relevance of heart failure. *JACC Heart Fail* 2014;**2**:221–7.
313. Okin PM, Bang CN, Wachtell K, Hille DA, Kjeldsen SE, Dahlöf B et al. Relationship of sudden cardiac death to new-onset atrial fibrillation in hypertensive patients with left ventricular hypertrophy. *Circ Arrhythm Electrophysiol* 2013;**6**:243–51.
314. Chen LY, Sotoodehnia N, Bůžková P, Lopez FL, Yee LM, Heckbert SR et al. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. *JAMA Intern Med* 2013;**173**:29–35.
315. Rattanawong P, Upala S, Riangwiwat T, Jaruvongvanich V, Sanguankeo A, Vuthikraivit W et al. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. *J Interv Card Electrophysiol* 2018;**51**:91–104.
316. Chao TF, Liu CJ, Tuan TC, Chen SJ, Chen TJ, Lip GYH et al. Risk and prediction of sudden cardiac death and ventricular arrhythmias for patients with atrial fibrillation—a Nationwide Cohort Study. *Sci Rep* 2017;**7**:46445.
317. Eisen A, Ruff CT, Braunwald E, Nordio F, Corbalan R, Dalby A et al. Sudden cardiac death in patients with atrial fibrillation: insights from the ENGAGE AF-TIMI 48 trial. *J Am Heart Assoc* 2016;**5**:1–12.
318. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667–77.
319. Arbelo E, Brugada J, Hindricks G, Maggioni A, Tavazzi L, Vardas P et al.; on behalf of the Atrial Fibrillation Ablation Pilot Study Investigators. ESC-EURObservational Research Programme: the Atrial Fibrillation Ablation Pilot Study, conducted by the European Heart Rhythm Association. *Europace* 2012;**14**:1094–103.
320. Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P et al.; on behalf of the Atrial Fibrillation Ablation Pilot Study Investigators. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *Eur Heart J* 2014;**35**:1466–78.
321. Arbelo E, Brugada J, Blomstrom-Lundqvist C, Laroche C, Kautzner J, Pokushalov E et al.; on behalf of the ESC-EHRA Atrial Fibrillation Ablation Long-term Registry Investigators. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J* 2017;**38**:1303–16.
322. De Greef Y, Stroker E, Schwagten B, Kupics K, De Cocker J, Chierchia GB et al. Complications of pulmonary vein isolation in atrial fibrillation: predictors and comparison between four different ablation techniques: results from the Middelheim PVI-registry. *Europace* 2018;**20**:1279–86.
323. Steinbeck G, Sinner MF, Lutz M, Müller-Nurasyid M, Käbb S, Reinecke H. Incidence of complications related to catheter ablation of atrial fibrillation and atrial flutter: a nationwide in-hospital analysis of administrative data for Germany in 2014. *Eur Heart J* 2018;**39**:4020–9.
324. Fink T, Metzner A, Willems S, Eckardt L, Ince H, Brachmann J et al. Procedural success, safety and patients satisfaction after second ablation of atrial fibrillation in the elderly: results from the German Ablation Registry. *Clin Res Cardiol* 2019;**108**:1354–63.
325. Bunch TJ, May HT, Bair TL, Anderson JL, Crandall BG, Cutler MJ et al. Long-term natural history of adult Wolff-Parkinson-White syndrome patients treated with and without catheter ablation. *Circ Arrhythm Electrophysiol* 2015;**8**:1465–71.
326. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66.
327. Ebert M, Stegmann C, Kosiuk J, Dinov B, Richter S, Arya A et al. Predictors, management, and outcome of cardioversion failure early after atrial fibrillation ablation. *Europace* 2018;**20**:1428–34.
328. Deng H, Bai Y, Shantsila A, Fauchier L, Potpara TS, Lip GY. Clinical scores for outcomes of rhythm control or arrhythmia progression in patients with atrial fibrillation: a systematic review. *Clin Res Cardiol* 2017;**106**:813–23.
329. Degiovanni A, Boggio E, Prenna E, Sartori C, De Vecchi F, Marino PN; From the Novara Atrial Fibrillation (NAIF) Study Group. Association between left atrial phasic conduit function and early atrial fibrillation recurrence in patients undergoing electrical cardioversion. *Clin Res Cardiol* 2018;**107**:329–37.
330. Mujović N, Marinković M, Lip GY, Potpara TS. Predicting recurrent atrial fibrillation after catheter ablation. *Europace* 2018;**20**:f460–f461.
331. Sepehri Shamloo A, Dagues N, Dinov B, Sommer P, Husser-Bollmann D, Bollmann A et al. Is epicardial fat tissue associated with atrial fibrillation recurrence after ablation? A systematic review and meta-analysis. *Int J Cardiol Heart Vasc* 2019;**22**:132–8.
332. Mesquita J, Ferreira AM, Cavaco D, Moscoso Costa F, Carmo P, Marques H et al. Development and validation of a risk score for predicting atrial fibrillation recurrence after a first catheter ablation procedure—ATLAS score. *Europace* 2018;**20**:f428–35.
333. Winkle RA, Jarman JW, Mead RH, Engel G, Kong MH, Fleming W et al. Predicting atrial fibrillation ablation outcome: the CAAP-AF score. *Heart Rhythm* 2016;**13**:2119–25.
334. Canpolat U, Aytemir K, Yorgun H, Şahiner L, Kaya EB, Oto A. A proposal for a new scoring system in the prediction of catheter ablation outcomes: promising results from the Turkish Cryoablation Registry. *Int J Cardiol* 2013;**169**:201–6.
335. Oacute Jcik M, Berkowitsch A, Greiss H, Zaltsberg S, Pajitnev D. Repeated catheter ablation of atrial fibrillation. *Circ J* 2013;**77**:2271–9.
336. Kornej J, Buttner P, Sommer P, Dagues N, Dinov B, Schumacher K et al. Prediction of electro-anatomical substrate using APPLE score and biomarkers. *Europace* 2019;**21**:54–9.
337. Buttner P, Schumacher K, Dinov B, Zeynalova S, Sommer P, Bollmann A et al. Role of NT-proANP and NT-proBNP in patients with atrial fibrillation: association with atrial fibrillation progression phenotypes. *Heart Rhythm* 2018;**15**:1132–7.
338. Kornej J, Hindricks G, Shoemaker MB, Husser D, Arya A, Sommer P et al. The APPLE score: a novel and simple score for the prediction of rhythm outcomes after catheter ablation of atrial fibrillation. *Clin Res Cardiol* 2015;**104**:871–6.
339. Kornej J, Hindricks G, Arya A, Sommer P, Husser D, Bollmann A. The APPLE Score—a novel score for the prediction of rhythm outcomes after repeat catheter ablation of atrial fibrillation. *PLoS One* 2017;**12**:e0169933.
340. Kornej J, Schumacher K, Dinov B, Kosich F, Sommer P, Arya A et al. Prediction of electro-anatomical substrate and arrhythmia recurrences using APPLE, DR-FLASH and MB-LATER scores in patients with atrial fibrillation undergoing catheter ablation. *Sci Rep* 2018;**8**:12686.
341. Kosiuk J, Dinov B, Kornej J, Acou WJ, Schonbauer R, Fiedler L et al. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. *Heart Rhythm* 2015;**12**:2207–12.
342. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:32–8.
343. Lee G, Sparks PB, Morton JB, Kistler PM, Vohra JK, Medi C et al. Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural heart disease from a single center. *J Cardiovasc Electrophysiol* 2011;**22**:163–8.
344. Deshmukh A, Patel NJ, Pant S, Shah N, Chothani A, Mehta K et al. In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures. *Circulation* 2013;**128**:2104–12.
345. Tripathi B, Arora S, Kumar V, Abdelrahman M, Lahewala S, Dave M et al. Temporal trends of in-hospital complications associated with catheter ablation of atrial fibrillation in the United States: an update from Nationwide Inpatient Sample database (2011–2014). *J Cardiovasc Electrophysiol* 2018;**29**:715–24.
346. Voskoboinik A, Sparks PB, Morton JB, Lee G, Joseph SA, Hawson JJ et al. Low rates of major complications for radiofrequency ablation of atrial fibrillation maintained over 14 years: a single centre experience of 2750 consecutive cases. *Heart Lung Circ* 2018;**27**:976–83.
347. Shamloo AS, Dagues N, Arya A, Hindricks G. Atrial fibrillation: a review of modifiable risk factors and preventive strategies. *Rom J Intern Med* 2019;**57**:99–109.
348. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;**64**:2222–31.

349. Providencia R, Adragao P, de Asmundis C, Chun J, Chierchia G, Defaye P et al. Impact of body mass index on the outcomes of catheter ablation of atrial fibrillation: a European Observational Multicenter Study. *J Am Heart Assoc* 2019;**8**: e012253.
350. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S et al. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–8.
351. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. *J Am Coll Cardiol* 2003;**42**:185–97.
352. Mansour M, Heist EK, Agarwal R, Bunch TJ, Karst E, Ruskin JN et al. Stroke and cardiovascular events after ablation or antiarrhythmic drugs for treatment of patients with atrial fibrillation. *Am J Cardiol* 2018;**121**:1192–9.
353. Themistoclakis S, Corrado A, Marchlinski FE, Jais P, Zado E, Rossillo A et al. The risk of thromboembolism and need for oral anticoagulation after successful atrial fibrillation ablation. *J Am Coll Cardiol* 2010;**55**:735–43.
354. Cox JL, Ad N, Palazzo T, Fitzpatrick S, Suyderhoud JP, DeGroot KW et al. Current status of the Maze procedure for the treatment of atrial fibrillation. *Semin Thorac Cardiovasc Surg* 2000;**12**:15–9.
355. La Meir M, Gelsomino S, Luca F, Pison L, Colella A, Lorusso R et al. Minimal invasive surgery for atrial fibrillation: an updated review. *Europace* 2013;**15**: 170–82.
356. Gaynor SL, Diodato MD, Prasad SM, Ishii Y, Schuessler RB, Bailey MS et al. A prospective, single-center clinical trial of a modified Cox Maze procedure with bipolar radiofrequency ablation. *J Thorac Cardiovasc Surg* 2004;**128**:535–42.
357. Fumagalli S, Chen J, Dobeanu D, Madrid AH, Tiltz R, Dagues N. The role of the Arrhythmia Team, an integrated, multidisciplinary approach to treatment of patients with cardiac arrhythmias: results of the European Heart Rhythm Association survey. *Europace* 2016;**18**:623–7.
358. Gammie JS, Haddad M, Milford-Beland S, Welke KF, Ferguson TB Jr, O'Brien SM et al. Atrial fibrillation correction surgery: lessons from the Society of Thoracic Surgeons National Cardiac Database. *Ann Thorac Surg* 2008;**85**: 909–14.
359. Khurram IM, Maqbool F, Berger RD, Marine JE, Spragg DD, Ashikaga H et al. Association between left atrial stiffness index and atrial fibrillation recurrence in patients undergoing left atrial ablation. *Circ Arrhythm Electrophysiol* 2016;**9**:1–9.
360. Chen MC, Chang JP, Chang HW. Preoperative atrial size predicts the success of radiofrequency Maze procedure for permanent atrial fibrillation in patients undergoing concomitant valvular surgery. *Chest* 2004;**125**:2129–34.
361. Sunderland N, Maruthappu M, Nagendran M. What size of left atrium significantly impairs the success of Maze surgery for atrial fibrillation? *Interact Cardiovasc Thorac Surg* 2011;**13**:332–8.
362. Chaiyaroj S, Ngarmukos T, Lertsithichai P. Predictors of sinus rhythm after radiofrequency Maze and mitral valve surgery. *Asian Cardiovasc Thorac Ann* 2008;**16**:292–7.
363. Gillinov AM, Bhavani S, Blackstone EH, Rajeswaran J, Svensson LG, Navia JL et al. Surgery for permanent atrial fibrillation: impact of patient factors and lesion set. *Ann Thorac Surg* 2006;**82**:502–13; discussion 13–4.
364. Beukema WP, Sie HT, Misier AR, Delnoy PP, Wellens HJ, Elvan A. Predictive factors of sustained sinus rhythm and recurrent atrial fibrillation after a radiofrequency modified Maze procedure. *Eur J Cardio-Thorac Surg* 2008;**34**:771–5.
365. Boersma LV, Castella M, van Boven W, Berrueto A, Yilmaz A, Nadal M et al. Atrial fibrillation catheter ablation versus surgical ablation treatment (FAST): a 2-center randomized clinical trial. *Circulation* 2012;**125**:23–30.
366. Damiano RJ Jr, Schwartz FH, Bailey MS, Maniar HS, Munfakh NA, Moon MR et al. The Cox Maze IV procedure: predictors of late recurrence. *J Thorac Cardiovasc Surg* 2011;**141**:113–21.
367. Edgerton JR, McClelland JH, Duke D, Gerdtsch MW, Steinberg BM, Bronleewe SH et al. Minimally invasive surgical ablation of atrial fibrillation: six-month results. *J Thorac Cardiovasc Surg* 2009;**138**:109–13; discussion 14.
368. Myerburg RJ, Mitrani R, Interian A Jr, Castellanos A. Interpretation of outcomes of antiarrhythmic clinical trials: design features and population impact. *Circulation* 1998;**97**:1514–21.
369. Disertori M, Rigoni M, Pace N, Casolo G, Mase M, Gonzini L et al. Myocardial fibrosis assessment by LGE is a powerful predictor of ventricular tachyarrhythmias in ischemic and nonischemic LV dysfunction: a meta-analysis. *JACC Cardiovasc Imaging* 2016;**9**:1046–55.
370. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator study. *Eur Heart J* 2000;**21**:2071–8.
371. Disertori M, Mase M, Rigoni M, Nollo G, Ravelli F. Heart rate turbulence is a powerful predictor of cardiac death and ventricular arrhythmias in postmyocardial infarction and heart failure patients: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2016;**9**.
372. Morin DP, Zacks ES, Mauer AC, Ageno S, Janik M, Markowitz SM et al. Effect of bundle branch block on microvolt T-wave alternans and electrophysiologic testing in patients with ischemic cardiomyopathy. *Heart Rhythm* 2007;**4**:904–12.
373. Biering-Sorensen T, Olsen FJ, Storm K, Fritz-Hansen T, Olsen NT, Jons C et al. Prognostic value of tissue Doppler imaging for predicting ventricular arrhythmias and cardiovascular mortality in ischaemic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2016;**17**:722–31.
374. Bui AH, Cannon CP, Steg PG, Storey RF, Husted S, Guo J et al. Relationship between early and late nonsustained ventricular tachycardia and cardiovascular death in patients with acute coronary syndrome in the Platelet Inhibition and Patient Outcomes (PLATO) Trial. *Circ Arrhythm Electrophysiol* 2016;**9**:e002951.
375. Selvanayagam JB, Hartshorne T, Billot L, Grover S, Hillis GS, Jung W et al. Cardiovascular magnetic resonance-GUIDED management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): study protocol for a randomized controlled trial. *Ann Noninvasive Electrocardiol* 2017;**22**:e12420.
376. Prystowsky EN, Nisam S. Prophylactic implantable cardioverter defibrillator trials: MUSTT, MADIT, and beyond. Multicenter Unsustained Tachycardia Trial. Multicenter Automatic Defibrillator Implantation Trial. *Am J Cardiol* 2000;**86**: 1214–5. a5.
377. Goldberger JJ, Subacius H, Patel T, Cunnane R, Kadish AH. Sudden cardiac death risk stratification in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 2014;**63**:1879–89.
378. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA* 2004;**292**:2874–9.
379. Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M. Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: a systematic review and meta-analysis. *Circ Cardiovasc Imaging* 2014;**7**:250–8.
380. Marume K, Noguchi T, Tateishi E, Morita Y, Kamakura T, Ishibashi K et al. Mortality and sudden cardiac death risk stratification using the noninvasive combination of wide QRS Duration and late gadolinium enhancement in idiopathic dilated cardiomyopathy. *Circ Arrhythm Electrophysiol* 2018;**11**:e006233.
381. Tung R, Bauer B, Schelbert H, Lynch JP, Auerbach M, Gupta P et al. Incidence of abnormal positron emission tomography in patients with unexplained cardiomyopathy and ventricular arrhythmias: the potential role of occult inflammation in arrhythmogenesis. *Heart Rhythm* 2015;**12**:2488–98.
382. Heymans S, Eriksson U, Lehtonen J, Cooper LT Jr. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. *J Am Coll Cardiol* 2016;**68**:2348–64.
383. Betensky BP, Tschabrunn CM, Zado ES, Goldberg LR, Marchlinski FE, Garcia FC et al. Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators. *Heart Rhythm* 2012;**9**:884–91.
384. Smedema JP, Snoep G, van Kroonenburgh MP, van Geuns RJ, Dassen WR, Gorgels AP et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol* 2005;**45**:1683–90.
385. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation* 2009;**120**:1969–77.
386. Murtagh G, Laffin LJ, Beshai JF, Maffessanti F, Bonham CA, Patel AV et al. Prognosis of myocardial damage in sarcoidosis patients with preserved left ventricular ejection fraction: risk stratification using cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2016;**9**:e003738.
387. Aquaro GD, Perfetti M, Camastra G, Monti L, Dellegrattaglia S, Moro C et al. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. *J Am Coll Cardiol* 2017;**70**:1977–87.
388. Grani C, Eichhorn C, Biere L, Murthy VL, Agarwal V, Kaneko K et al. Prognostic value of cardiac magnetic resonance tissue characterization in risk stratifying patients with suspected myocarditis. *J Am Coll Cardiol* 2017;**70**:1964–76.
389. Mahfoud F, Gartner B, Kindermann M, Ukena C, Gadomski K, Klingel K et al. Virus serology in patients with suspected myocarditis: utility or futility? *Eur Heart J* 2011;**32**:897–903.
390. Ichinose A, Otani H, Oikawa M, Takase K, Saito H, Shimokawa H et al. MRI of cardiac sarcoidosis: basal and subepicardial localization of myocardial lesions and their effect on left ventricular function. *Am J Roentgenol* 2008;**191**:862–9.
391. Van Hare GF, Javitz H, Carmelli D, Saul JP, Tanel RE, Fischbach PS et al. Prospective assessment after pediatric cardiac ablation: demographics, medical profiles, and initial outcomes. *J Cardiovasc Electrophysiol* 2004;**15**:759–70.
392. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the

- American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Can J Cardiol* 2014;**30**:e1–63.
393. Brugada J, Blom N, Sarquella-Brugada G, Blomstrom-Lundqvist C, Deanfield J, Janousek J et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEP-Cardiac Arrhythmia Working Group joint consensus statement. *Europace* 2013;**15**:1337–82.
 394. Harrison DA, Harris L, Siu SC, MacLoughlin CJ, Connelly MS, Webb GD et al. Sustained ventricular tachycardia in adult patients late after repair of tetralogy of Fallot. *J Am Coll Cardiol* 1997;**30**:1368–73.
 395. Knauth AL, Gauvreau K, Powell AJ, Landzberg MJ, Walsh EP, Lock JE et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. *Heart* 2008;**94**:211–6.
 396. Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, MarçOn FOIS et al. Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study. *Circulation* 2004;**109**:1994–2000.
 397. Hernandez-Madrid A, Paul T, Abrams D, Aziz PF, Blom NA, Chen J et al. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPCC), and the European Society of Cardiology (ESC) Working Group on Grown-up Congenital heart disease, endorsed by HRS, PACES, APHRS, and SOLAEC. *Europace* 2018;**20**:1719–53.
 398. Vehmeijer JT, Koyak Z, Bokma JP, Budts W, Harris L, Mulder BJM et al. Sudden cardiac death in adults with congenital heart disease: does QRS-complex fragmentation discriminate in structurally abnormal hearts? *Europace* 2018;**20**:f122–f8.
 399. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C et al. 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 AEPCC in June 2013. *Heart Rhythm* 2013;**10**:1932–63.
 400. Roston TM, Yuchi Z, Kannankeril PJ, Hathaway J, Vinocur JM, Etheridge SP et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. *Europace* 2018;**20**:541–7.
 401. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J* 2013;**34**:3109–16.
 402. Hayashi M, Denjoy I, Extramiana F, Maltret A, Buisson NR, Lupoglazoff JM et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2009;**119**:2426–34.
 403. Adler A, Rosso R, Chorin E, Havakuk O, Antzelevitch C, Viskin S. Risk stratification in Brugada syndrome: clinical characteristics, electrocardiographic parameters, and auxiliary testing. *Heart Rhythm* 2016;**13**:299–310.
 404. Sieira J, Conte G, Ciconte G, Chierchia GB, Casado-Arroyo R, Baltogiannis G et al. A score model to predict risk of events in patients with Brugada Syndrome. *Eur Heart J* 2017;**38**:1756–63.
 405. Yamagata K, Horie M, Aiba T, Ogawa S, Aizawa Y, Ohe T et al. Genotype-phenotype correlation of SCN5A mutation for the clinical and electrocardiographic characteristics of probands with Brugada syndrome: a Japanese Multicenter Registry. *Circulation* 2017;**135**:2255–70.
 406. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–20.
 407. Priori SG, Document Reviewers, Wilde AA, Horie M, Cho Y, Behr ER, Berul C et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* 2013;**15**:1389–406.
 408. van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooij AJ et al. Risk factors for malignant ventricular arrhythmias in Lamin A/C mutation carriers: a European cohort study. *J Am Coll Cardiol* 2012;**59**:493–500.
 409. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med* 2017;**376**:61–72.
 410. Pedersen CT, Kay GN, Kalman J, Borggreffe M, Della-Bella P, Dickfeld T et al. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Europace* 2014;**16**:1257–83.
 411. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2017;**136**:2068–82.
 412. Wang W, Orgeron G, Tichnell C, Murray B, Crosson J, Monfredi O et al. Impact of exercise restriction on arrhythmic risk among patients with arrhythmogenic right ventricular cardiomyopathy. *J Am Heart Assoc* 2018;**7**.
 413. Savant AC, Te Riele AS, Tichnell C, Murray B, Bhonsale A, Tandri H et al. Safety of American Heart Association-recommended minimum exercise for desmosomal mutation carriers. *Heart Rhythm* 2016;**13**:199–207.
 414. Philips B, Madhavan S, James C, Tichnell C, Murray B, Needleman M et al. High prevalence of catecholamine-facilitated focal ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Arrhythm Electrophysiol* 2013;**6**:160–6.
 415. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Bohm M et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J* 2016;**37**:1850–8.
 416. Deac M, Alpendurada F, Fanaie F, Vimal R, Carpenter JP, Dawson A et al. Prognostic value of cardiovascular magnetic resonance in patients with suspected arrhythmogenic right ventricular cardiomyopathy. *Int J Cardiol* 2013;**168**:3514–21.
 417. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J* 2010;**31**:806–14.
 418. Denis A, Sacher F, Derval N, Martin R, Lim HS, Pambrun T et al. Arrhythmogenic response to isoproterenol testing vs. exercise testing in arrhythmogenic right ventricular cardiomyopathy patients. *Europace* 2018;**20**:f30–6.
 419. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JD et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J* 2015;**36**:847–55.
 420. Quarta G, Syrris P, Ashworth M, Jenkins S, Zuborne Alapi K, Morgan J et al. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2012;**33**:1128–36.
 421. Gali WL, Sarabanda AV, Baggio JM, Silva EF, Gomes GG, Junqueira LF. Predictors of mortality and heart transplantation in patients with Chagas' cardiomyopathy and ventricular tachycardia treated with implantable cardioverter-defibrillators. *Europace* 2019;**21**:1070–8.
 422. Ezekowitz JA, Rowe BH, Dryden DM, Hooton N, Vandermeer B, Spooner C et al. Systematic review: implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. *Ann Intern Med* 2007;**147**:251–62.
 423. Kolodziejczak M, Andreotti F, Kowalewski M, Buffon A, Ciccone MM, Parati G et al. Implantable cardioverter-defibrillators for primary prevention in patients with ischemic or nonischemic cardiomyopathy: a systematic review and meta-analysis. *Ann Intern Med* 2017;**167**:103–11.
 424. Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. *J Am Coll Cardiol* 2003;**41**:1573–82.
 425. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol* 2008;**51**:1357–65.
 426. Koller MT, Schaer B, Wolbers M, Stichlerling C, Bucher HC, Osswald S. Death without prior appropriate implantable cardioverter-defibrillator therapy: a competing risk study. *Circulation* 2008;**117**:1918–26.
 427. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008;**359**:1009–17.
 428. Blom LJ, Visser M, Christians I, Scholten MF, Bootsma M, van den Berg MP et al. Incidence and predictors of implantable cardioverter-defibrillator therapy and its complications in idiopathic ventricular fibrillation patients. *Europace* 2019;**21**:1519–26.
 429. Milman A, Hochstadt A, Andorin A, Gourraud JB, Sacher F, Mabo P et al. Time-to-first appropriate shock in patients implanted prophylactically with an implantable cardioverter-defibrillator: data from the Survey on Arrhythmic Events in BRUGada Syndrome (SABRUS). *Europace* 2019;**21**:796–802.
 430. Dougherty CM, Hunziker J. Predictors of implantable cardioverter defibrillator shocks during the first year. *J Cardiovasc Nurs* 2009;**24**:21–8. quiz 9–30.
 431. Konstantino Y, Shafat T, Novack V, Novack L, Amit G. Incidence of implantable cardioverter defibrillator therapy and mortality in primary and secondary prevention of sudden cardiac death. *Isr Med Assoc J* 2015;**17**:760–3.
 432. Nagahara D, Fujito T, Mochizuki A, Shimoshige S, Hashimoto A, Miura T. Predictors of appropriate ICD therapy in Japanese patients with structural heart diseases: a major role of prior sustained ventricular tachycardia in secondary prevention. *J Arrhythmia* 2018;**34**:527–35.
 433. van Welsenes GH, van Rees JB, Borleffs CJ, Cannegieter SC, Bax JJ, van Erven L et al. Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients. *Europace* 2011;**13**:389–94.
 434. Zareba W, Moss AJ, Jackson Hall W, Wilber DJ, Ruskin JN, McNitt S et al. MADIT II Investigators. Clinical course and implantable cardioverter defibrillator therapy in postinfarction women with severe left ventricular dysfunction. *J Cardiovasc Electrophysiol* 2005;**16**:1265–70.

435. Santangeli P, Pelargonio G, Dello Russo A, Casella M, Bisceglia C, Bartoletti S et al. Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: a systematic review and meta-analysis. *Heart Rhythm* 2010;**7**:786–82.
436. MacFadden DR, Crystal E, Krahn AD, Mangat I, Healey JS, Dorian P et al. Sex differences in implantable cardioverter-defibrillator outcomes: findings from a prospective defibrillator database. *Ann Intern Med* 2012;**156**:195–203.
437. Seegers J, Conen D, Jung K, Bergau L, Dorenkamp M, Luthje L et al. Sex difference in appropriate shocks but not mortality during long-term follow-up in patients with implantable cardioverter-defibrillators. *Europace* 2016;**18**:1194–202.
438. van der Heijden AC, Thijssen J, Borleffs CJ, van Rees JB, Hoke U, van der Velde ET et al. Gender-specific differences in clinical outcome of primary prevention implantable cardioverter defibrillator recipients. *Heart* 2013;**99**:1244–9.
439. Wijers SC, van der Kolk BY, Tuinenburg AE, Doevendans PA, Vos MA, Meine M. Implementation of guidelines for implantable cardioverter-defibrillator therapy in clinical practice: which patients do benefit? *Neth Heart J* 2013;**21**:274–83.
440. Conen D, Arendacka B, Rover C, Bergau L, Munoz P, Wijers S et al. Gender differences in appropriate shocks and mortality among patients with primary prophylactic implantable cardioverter-defibrillators: systematic review and meta-analysis. *PLoS One* 2016;**11**:e0162756.
441. Ghanbari H, Dalloul G, Hasan R, Daccarett M, Saba S, David S et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2009;**169**:1500–6.
442. Providencia R, Marjon E, Lambiasi PD, Bouzeman A, Defaye P, Klug D et al. Primary prevention implantable cardioverter defibrillator (ICD) therapy in women—data from a Multicenter French Registry. *J Am Heart Assoc* 2016;**5**:1–10.
443. Borleffs CJ, van Rees JB, van Welsenes GH, van der Velde ET, van Erven L, Bax JJ et al. Prognostic importance of atrial fibrillation in implantable cardioverter-defibrillator patients. *J Am Coll Cardiol* 2010;**55**:879–85.
444. Dharma A, Nedios S, Kosiuk J, Richter S, Doering M, Arya A et al. Differences in predictors of implantable cardioverter-defibrillator therapies in patients with ischaemic and non-ischaemic cardiomyopathies. *Europace* 2016;**18**:405–12.
445. Gronefeld GC, Mauss O, Li YG, Klingenhoben T, Hohnloser SH. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: results from a prospective study. *J Cardiovasc Electrophysiol* 2000;**11**:1208–14.
446. Rienstra M, Smit MD, Nieuwland W, Tan ES, Wiesfeld AC, Anthonio RL et al. Persistent atrial fibrillation is associated with appropriate shocks and heart failure in patients with left ventricular dysfunction treated with an implantable cardioverter defibrillator. *Am Heart J* 2007;**153**:120–6.
447. Chang IC, Agamawi YM, Austin E, Adkisson WO, Roukoz H, von Wald LN et al. Usefulness of atrial fibrillation as a marker for adverse cardiovascular outcomes in both primary and secondary prevention in patients with implantable cardioverter-defibrillators. *Am J Cardiol* 2016;**118**:1497–502.
448. van Rees JB, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ et al. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. *J Am Coll Cardiol* 2011;**57**:556–62.
449. Yang JH, Byeon K, Yim HR, Park JW, Park SJ, Huh J et al. Predictors and clinical impact of inappropriate implantable cardioverter-defibrillator shocks in Korean patients. *J Korean Med Sci* 2012;**27**:619–24.
450. Deyell MW, Qi A, Chakraborti S, Yeung-Lai-Wah JA, Tung S, Khoo C et al. Prognostic impact of inappropriate defibrillator shocks in a population cohort. *Heart* 2013;**99**:1250–5.
451. Fernandez-Cisnal A, Arce-Leon A, Arana-Rueda E, Rodriguez-Manero M, Gonzalez-Cambeiro C, Moreno-Arribas J et al. Analyses of inappropriate shocks in a Spanish ICD primary prevention population: predictors and prognoses. *Int J Cardiol* 2015;**195**:188–94.
452. Mustafa U, Dherange P, Reddy R, DeVillier J, Chong J, Ihsan A et al. Atrial fibrillation is associated with higher overall mortality in patients with implantable cardioverter-defibrillator: a systematic review and meta-analysis. *J Am Heart Assoc* 2018;**7**:e010156.
453. Powell BD, Saxon LA, Boehmer JP, Day JD, Gilliam FR, Heidenreich PA et al. Survival after shock therapy in implantable cardioverter-defibrillator and cardiac resynchronization therapy-defibrillator recipients according to rhythm shocked. The ALTITUDE survival by rhythm study. *J Am Coll Cardiol* 2013;**62**:1674–9.
454. Bergau L, Willems R, Sprengeler DJ, Fischer TH, Flevary P, Hasenfuß G et al. Differential multivariable risk prediction of appropriate shock versus competing mortality—a prospective cohort study to estimate benefits from ICD therapy. *Int J Cardiol* 2018;**272**:102–7.
455. Lelakowski J, Piekarczyk J, Rydlewska A, Majewski J, Senderek T, Ząbek A et al. Factors predisposing to ventricular tachyarrhythmia leading to appropriate ICD intervention in patients with coronary artery disease or non-ischaemic dilated cardiomyopathy. *Kardiologia Polska* 2012;**70**:1264–75.
456. Weeke P, Johansen JB, Jorgensen OD, Nielsen JC, Moller M, Videbaek R et al. Mortality and appropriate and inappropriate therapy in patients with ischaemic heart disease and implanted cardioverter-defibrillators for primary prevention: data from the Danish ICD Register. *Europace* 2013;**15**:1150–7.
457. Schaer B, Kuhne M, Reichlin T, Osswald S, Sticherling C. Incidence of and predictors for appropriate implantable cardioverter-defibrillator therapy in patients with a secondary preventive implantable cardioverter-defibrillator indication. *Europace* 2016;**18**:227–31.
458. Lee AKY, Andrade J, Hawkins NM, Alexander G, Bennett MT, Chakraborti S et al. Outcomes of untreated frequent premature ventricular complexes with normal left ventricular function. *Heart* 2019;**105**:1408–13.
459. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C et al. Relationship between burden of premature ventricular complexes and left ventricular function. *Heart Rhythm* 2010;**7**:865–9.
460. Duffee DF, Shen WK, Smith HC. Suppression of frequent premature ventricular contractions and improvement of left ventricular function in patients with presumed idiopathic dilated cardiomyopathy. *Mayo Clin Proc* 1998;**73**:430–3.
461. Hasdemir C, Ulucan C, Yavuzgil O, Yuksel A, Kartal Y, Simsek E et al. Tachycardia-induced cardiomyopathy in patients with idiopathic ventricular arrhythmias: the incidence, clinical and electrophysiologic characteristics, and the predictors. *J Cardiovasc Electrophysiol* 2011;**22**:663–8.
462. Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Induced Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019;**73**:2328–44.
463. Tsuji A, Nagashima M, Hasegawa S, Nagai N, Nishibata K, Goto M et al. Long-term follow-up of idiopathic ventricular arrhythmias in otherwise normal children. *Jpn Circ J* 1995;**59**:654–62.
464. Hasdemir C, Yuksel A, Camli D, Kartal Y, Simsek E, Musayev O et al. Late gadolinium enhancement CMR in patients with tachycardia-induced cardiomyopathy caused by idiopathic ventricular arrhythmias. *Pacing Clin Electrophysiol* 2012;**35**:465–70.
465. Penela D, Martinez M, Fernandez-Armenta J, Aguinaga L, Tercedor L, Ordóñez A et al. Influence of myocardial scar on the response to frequent premature ventricular complex ablation. *Heart* 2018.
466. Bogun F, Crawford T, Chalfoun N, Kuhne M, Sarrazin JF, Wells D et al. Relationship of frequent postinfarction premature ventricular complexes to the reentry circuit of scar-related ventricular tachycardia. *Heart Rhythm* 2008;**5**:367–74.
467. Ellis ER, Josephson ME. Heart failure and tachycardia-induced cardiomyopathy. *Curr Heart Fail Rep* 2013;**10**:296–306.
468. Huizar J. Prospective assessment of premature ventricular contractions suppression in cardiomyopathy (PAPS). 2017. <https://clinicaltrials.gov/ct2/show/NCT03228823>. (18 March 2020, date last accessed).
469. Dabbagh GS, Bogun F. Predictors and therapy of cardiomyopathy caused by frequent ventricular ectopy. *Curr Cardiol Rep* 2017;**19**:80.
470. Macatangay C, Viles-Gonzalez JF, Goldberger JJ. Role of cardiac imaging in evaluating risk for sudden cardiac death. *Cardiac Electrophysiol Clinics* 2017;**9**:639–50.
471. Proclemer A, Bongiorno MG, Dagres N, Sciaraffia E, Todd D, Blomstrom-Lundqvist C. How are European patients at risk of malignant arrhythmias or sudden cardiac death identified and informed about their risk profile: results of the European Heart Rhythm Association survey. *Europace* 2015;**17**:994–8.
472. Deyell MW, Krahn AD, Goldberger JJ. Sudden cardiac death risk stratification. *Circ Res* 2015;**116**:1907–18.
473. Fallavollita JA, Dare JD, Carter RL, Balda S, Canty JM Jr. Denervated myocardium is preferentially associated with sudden cardiac arrest in ischemic cardiomyopathy: a pilot competing risks analysis of cause-specific mortality. *Circ Cardiovasc Imaging* 2017;**10**:1–11.
474. Deng D, Arevalo HJ, Prakosa A, Callans DJ, Trayanova NA. A feasibility study of arrhythmia risk prediction in patients with myocardial infarction and preserved ejection fraction. *Europace* 2016;**18**:iv60–iv66.
475. Brugada P, Talajic M, Smeets J, Mulleneers R, Wellens HJ. The value of the clinical history to assess prognosis of patients with ventricular tachycardia or ventricular fibrillation after myocardial infarction. *Eur Heart J* 1989;**10**:747–52.
476. Sarter BH, Finkle JK, Gerszten RE, Buxton AE. What is the risk of sudden cardiac death in patients presenting with hemodynamically stable sustained ventricular tachycardia after myocardial infarction? *J Am Coll Cardiol* 1996;**28**:122–9.
477. Friedman DJ, Al-Khatib SM, Zeitler EP, Han J, Bardy GH, Poole JE et al. New York Heart Association class and the survival benefit from primary prevention implantable cardioverter defibrillators: a pooled analysis of 4 randomized controlled trials. *Am Heart J* 2017;**191**:21–9.
478. Tung R, Vaseghi M, Frankel DS, Vergara P, Di Biase L, Nagashima K et al. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: an International VT Ablation Center Collaborative Group Study. *Heart Rhythm* 2015;**12**:1997–2007.

479. Bilchick KC, Wang Y, Cheng A, Curtis JP, Dharmarajan K, Stukenborg GJ *et al.* Seattle heart failure and proportional risk models predict benefit from implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2017;**69**:2606–18.
480. Kumar S, Androulakis AF, Sellal JM, Maury P, Gandjbakhch E, Waintraub X *et al.* Multicenter experience with catheter ablation for ventricular tachycardia in Lamin A/C cardiomyopathy. *Circ Arrhythm Electrophysiol* 2016;**9**:1–11.
481. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB *et al.* The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;**113**:1424–33.
482. Santangeli P, Muser D, Zado ES, Magnani S, Khetpal S, Hutchinson MD *et al.* Acute hemodynamic decompensation during catheter ablation of scar-related ventricular tachycardia: incidence, predictors, and impact on mortality. *Circ Arrhythm Electrophysiol* 2015;**8**:68–75.
483. Vakil KP, Roukoz H, Tung R, Levy WC, Anand IS, Shivkumar K *et al.* Mortality prediction using a modified Seattle Heart Failure Model may improve patient selection for ventricular tachycardia ablation. *Am Heart J* 2015;**170**:1099–104.
484. Santangeli P, Frankel DS, Tung R, Vaseghi M, Sauer WH, Tzou WS *et al.* Early mortality after catheter ablation of ventricular tachycardia in patients with structural heart disease. *J Am Coll Cardiol* 2017;**69**:2105–15.
485. Frankel DS, Tung R, Santangeli P, Tzou WS, Vaseghi M, Di Biase L *et al.* Sex and catheter ablation for ventricular tachycardia: an International Ventricular Tachycardia Ablation Center Collaborative Group Study. *JAMA Cardiol* 2016;**1**:938–44.
486. Tzou WS, Tung R, Frankel DS, Vaseghi M, Bunch TJ, Di Biase L *et al.* Ventricular tachycardia ablation in severe heart failure: an International Ventricular Tachycardia Ablation Center Collaboration Analysis. *Circ Arrhythm Electrophysiol* 2017;**10**.
487. Vaseghi M, Hu TY, Tung R, Vergara P, Frankel DS, Di Biase L *et al.* Outcomes of catheter ablation of ventricular tachycardia based on etiology in nonischemic heart disease: an International Ventricular Tachycardia Ablation Center Collaborative study. *JACC Clin Electrophysiol* 2018;**4**:1141–50.
488. Briceno DF, Romero J, Villablanca PA, Londono A, Diaz JC, Maraj I *et al.* Long-term outcomes of different ablation strategies for ventricular tachycardia in patients with structural heart disease: systematic review and meta-analysis. *Europace* 2018;**20**:104–15.
489. Papageorgiou N, Providencia R, Bronis K, Decherer DG, Srinivasan N, Eckardt L *et al.* Catheter ablation for ventricular tachycardia in patients with cardiac sarcoidosis: a systematic review. *Europace* 2018;**20**:682–91.
490. Avila P, Perez-David E, Izquierdo M, Rojas-Gonzalez A, Sanchez-Gomez JM, Ledesma-Carbayo MJ *et al.* Scar extension measured by magnetic resonance-based signal intensity mapping predicts ventricular tachycardia recurrence after substrate ablation in patients with previous myocardial infarction. *JACC Clin Electrophysiol* 2015;**1**:353–65.
491. Berrueto A, Acosta J, Fernandez-Armenta J, Pedrote A, Barrera A, Arana-Rueda E *et al.* Safety, long-term outcomes and predictors of recurrence after first-line combined endoepicardial ventricular tachycardia substrate ablation in arrhythmogenic cardiomyopathy. Impact of arrhythmic substrate distribution pattern. A prospective multicentre study. *Europace* 2017;**19**:607–16.
492. Santangeli P, Zado ES, Supple GE, Haqqani HM, Garcia FC, Tschabrunn CM *et al.* Long-term outcome with catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol* 2015;**8**:1413–21.
493. Dalal D, Jain R, Tandri H, Dong J, Eid SM, Prakasa K *et al.* Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol* 2007;**50**:432–40.
494. Fernandez-Armenta J, Andreu D, Penela D, Trucco E, Cipolletta L, Arbelo E *et al.* Sinus rhythm detection of conducting channels and ventricular tachycardia isthmus in arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2014;**11**:747–54.
495. Oloriz T, Silberbauer J, Maccabelli G, Mizuno H, Baratto F, Kirubakaran S *et al.* Catheter ablation of ventricular arrhythmia in nonischemic cardiomyopathy: anteroseptal versus inferolateral scar sub-types. *Circ Arrhythm Electrophysiol* 2014;**7**:414–23.
496. Ghanbari H, Baser K, Yokokawa M, Stevenson W, Della Bella P, Vergara P *et al.* Noninducibility in postinfarction ventricular tachycardia as an end point for ventricular tachycardia ablation and its effects on outcomes: a meta-analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:677–83.
497. Yokokawa M, Kim HM, Baser K, Stevenson W, Nagashima K, Della Bella P *et al.* Predictive value of programmed ventricular stimulation after catheter ablation of post-infarction ventricular tachycardia. *J Am Coll Cardiol* 2015;**65**:1954–9.
498. Frankel DS, Mountantonakis SE, Zado ES, Anter E, Bala R, Cooper JM *et al.* Noninvasive programmed ventricular stimulation early after ventricular tachycardia ablation to predict risk of late recurrence. *J Am Coll Cardiol* 2012;**59**:1529–35.
499. Oloriz T, Baratto F, Trevisi N, Barbaro M, Bisceglia C, D'Angelo G *et al.* Defining the outcome of ventricular tachycardia ablation: timing and value of programmed ventricular stimulation. *Circ Arrhythm Electrophysiol* 2018;**11**:e005602.
500. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsinn K *et al.* Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med* 2007;**357**:2657–65.
501. Kuck KH, Schaumann A, Eckardt L, Willems S, Ventura R, Delacretaz E *et al.* Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. *Lancet* 2010;**375**:31–40.
502. Tilz RR, Kuck K-H, Käb S, Wegscheider K, Thiem A, Wenzel B *et al.* Rationale and design of BERLIN VT study: a multicenter randomised trial comparing preventive versus deferred ablation of ventricular tachycardia. *BMJ Open* 2019;**9**:e022910.
503. Kuck KH, Tilz RR, Deneke T, Hoffmann BA, Ventura R, Hansen PS *et al.* Impact of substrate modification by catheter ablation on implantable cardioverter-defibrillator interventions in patients with unstable ventricular arrhythmias and coronary artery disease: results from the multicenter randomized controlled SMS (Substrate Modification Study). *Circ Arrhythm Electrophysiol* 2017;**10**.
504. Dukes JW, Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS *et al.* Ventricular ectopy as a predictor of heart failure and death. *J Am Coll Cardiol* 2015;**66**:101–9.
505. Yokokawa M, Good E, Crawford T, Chugh A, Pelosi F Jr, Latchamsetty R *et al.* Recovery from left ventricular dysfunction after ablation of frequent premature ventricular complexes. *Heart Rhythm* 2013;**10**:172–5.
506. Carballeira Pol L, Deyell MW, Frankel DS, Benhayon D, Squara F, Chik W *et al.* Ventricular premature depolarization QRS duration as a new marker of risk for the development of ventricular premature depolarization-induced cardiomyopathy. *Heart Rhythm* 2014;**11**:299–306.
507. Niwano S, Wakisaka Y, Niwano H, Fukaya H, Kurokawa S, Kiryu M *et al.* Prognostic significance of frequent premature ventricular contractions originating from the ventricular outflow tract in patients with normal left ventricular function. *Heart* 2009;**95**:1230–7.
508. Lin CY, Chang SL, Lin YJ, Lo LW, Chung FP, Chen YY *et al.* Long-term outcome of multiform premature ventricular complexes in structurally normal heart. *Int J Cardiol* 2015;**180**:80–5.
509. Del Carpio Munoz F, Syed FF, Noheria A, Cha YM, Friedman PA, Hammill SC *et al.* Characteristics of premature ventricular complexes as correlates of reduced left ventricular systolic function: study of the burden, duration, coupling interval, morphology and site of origin of PVCs. *J Cardiovasc Electrophysiol* 2011;**22**:791–8.
510. Zhong L, Lee YH, Huang XM, Asirvatham SJ, Shen WK, Friedman PA *et al.* Relative efficacy of catheter ablation vs antiarrhythmic drugs in treating premature ventricular contractions: a single-center retrospective study. *Heart Rhythm* 2014;**11**:187–93.
511. Olgun H, Yokokawa M, Baman T, Kim HM, Armstrong W, Good E *et al.* The role of interpolation in PVC-induced cardiomyopathy. *Heart Rhythm* 2011;**8**:1046–9.
512. Leenhardt A, Glaser E, Burguera M, Nurnberg M, Maison-Blanche P, Coumel P. Short-coupled variant of torsade de pointes. A new electrocardiographic entity in the spectrum of idiopathic ventricular tachyarrhythmias. *Circulation* 1994;**89**:206–15.
513. Prystowsky EN, Padanilam BJ, Joshi S, Fogel RI. Ventricular arrhythmias in the absence of structural heart disease. *J Am Coll Cardiol* 2012;**59**:1733–44.
514. Pappone C, Vicedomini G, Manguso F, Saviano M, Baldi M, Pappone A *et al.* Wolff-Parkinson-White syndrome in the era of catheter ablation: insights from a registry study of 2169 patients. *Circulation* 2014;**130**:811–9.
515. Timmermans C, Smeets JL, Rodriguez L-M, Vrochou G, van den Dool A, Wellens HJ. Aborted sudden death in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1995;**76**:492–4.
516. Katritsis DG, Boriani G, Cosio FG, Hindricks G, Jais P, Josephson ME *et al.* European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). *Europace* 2017;**19**:465–511.
517. Katritsis DG, Boriani G, Cosio FG, Hindricks G, Jais P, Josephson ME *et al.* European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular arrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE). *Eur Heart J* 2018;**39**:1442–5.

518. Wackel P, Irving C, Webber S, Beerman L, Arora G. Risk stratification in Wolff-Parkinson-White syndrome: the correlation between noninvasive and invasive testing in pediatric patients. *Pacing Clin Electrophysiol* 2012;**35**:1451–7.
519. Spar DS, Silver ES, Hordof AJ, Liberman L. Relation of the utility of exercise testing for risk assessment in pediatric patients with ventricular preexcitation to pathway location. *Am J Cardiol* 2012;**109**:1011–4.
520. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomstrom-Lundqvist C et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). *Eur Heart J* 2020;**41**:655–720.
521. Medi C, Kalman JM, Haqqani H, Vohra JK, Morton JB, Sparks PB et al. Tachycardia-mediated cardiomyopathy secondary to focal atrial tachycardia: long-term outcome after catheter ablation. *J Am Coll Cardiol* 2009;**53**:1791–7.
522. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax J, Blomstrom-Lundqvist C et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia. *Eur Heart J* 2020;**41**:655–720.
523. Rassi A, Jr., Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, et al. Development and validation of a risk score for predicting death in Chagas? heart disease. *N Engl J Med* 2006;**355**:799–808.
524. Rassi A, Jr., Rassi A. Rassi Score: Another external validation with high performance in patients with chagas cardiomyopathy. *J Am Coll Cardiol* 2019;**73**:1734–5.
525. Martinelli Filho M, Sosa E, Nishioka S, Scanavacca M, Bellotti G, Pileggi F. Clinical and electrophysiologic features of syncope in chronic chagasic heart disease. *J Cardiovasc Electrophysiol* 1994;**5**:563–70.
526. Scanavacca M, Sosa E. Electrophysiologic study in chronic Chagas? heart disease. *Sao Paulo medical journal – Revista paulista de medicina* 1995;**113**:841–50.
527. Rochitte CE, Oliveira PF, Andrade JM, Ianni BM, Parga JR, Avila LF, et al. Myocardial delayed enhancement by magnetic resonance imaging in patients with Chagas? disease: a marker of disease severity. *J Am Coll Cardiol* 2005;**46**:1553–8.
528. Noya-Rabelo MM, Macedo CT, Larocca T, Machado A, Pacheco T, Torreal J, et al. The Presence and Extension of Myocardial Fibrosis in the Undetermined Form of Chagas? Disease: A Study Using Magnetic Resonance. *Arquivos brasileiros de cardiologia* 2018;**110**:124–31.
529. Senra T, Ianni BM, Costa ACP, Mady C, Martinelli-Filho M, Kalil-Filho R, et al. Long-Term Prognostic Value of Myocardial Fibrosis in Patients With Chagas Cardiomyopathy. *J Am Coll Cardiol* 2018;**72**:2577–87.
530. Uellendahl M, Siqueira ME, Calado EB, Kalil-Filho R, Sobral D, Ribeiro C, et al. Cardiac Magnetic Resonance-Verified Myocardial Fibrosis in Chagas Disease: Clinical Correlates and Risk Stratification. *Arquivos brasileiros de cardiologia* 2016;**107**:460–6.
531. Gali WL, Sarabanda AV, Baggio JM, Silva EF, Gomes GG, Junqueira LF. Predictors of mortality and heart transplantation in patients with Chagas? cardiomyopathy and ventricular tachycardia treated with implantable cardioverter-defibrillators. *Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2019;**21**:1070–78.
532. Cardinali-Neto A, Lorga-Filho AM, Silva EF, Lima RP, Palmegiani E, Bestetti RB. Clinical predictors of inducible sustained ventricular tachycardia during electrophysiologic study in patients with chronic Chagas? heart disease. *International Journal of Cardiology Heart & Vascular* 2015;**9**:85–8.
533. Barbosa MP, Carmo AA, Rocha MO, Ribeiro AL. Ventricular arrhythmias in Chagas disease. *Revista da Sociedade Brasileira de Medicina Tropical* 2015;**48**:4–10.
534. Volpe GJ, Moreira HT, Trad HS, Wu KC, Braggion-Santos MF, Santos MK, et al. Left Ventricular Scar and Prognosis in Chronic Chagas Cardiomyopathy. *J Am Coll Cardiol* 2018;**72**:2567–76.
535. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–962.
536. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* 2019;**16**:e301–72.