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EHRA White Paper: knowledge gaps in arrhythmia management—status 2019

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Clinicians accept that there are many unknowns when we make diagnostic and therapeutic decisions. Acceptance of uncertainty is essential for the pursuit of the profession: bedside decisions must often be made on the basis of incomplete evidence. Over the years, physicians sometimes even do not realize anymore which the fundamental gaps in our knowledge are. As clinical scientists, however, we have to halt and consider what we do not know yet, and how we can move forward addressing those unknowns. The European Heart Rhythm Association (EHRA) believes that scanning the field of arrhythmia / cardiac electrophysiology to identify knowledge gaps which are not yet the subject of organized research, should be undertaken on a regular basis. Such a review (White Paper) should concentrate on research

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which is feasible, realistic, and clinically relevant, and should not deal with futuristic aspirations. It fits with the EHRA mission that these White Papers should be shared on a global basis in order to foster collaborative and needed research which will ultimately lead to better care for our patients. The present EHRA White Paper summarizes knowledge gaps in the management of atrial fibrillation, ventricular tachycardia/sudden death and heart failure.

Keywords European Heart Rhythm Association • White Paper • Arrhythmia • Fibrillation • Tachycardia • Heart failure

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Introduction: Knowledge gaps—why are they so important

Clinicians accept that there are many unknowns when we make diagnostic and therapeutic decisions. Acceptance of uncertainty is essential for the pursuit of the profession: bedside decisions must often be made on the basis of incomplete evidence in order to move forward. Over the years, we sometimes even do not realize anymore which the fundamental gaps in our knowledge are. As clinical scientists, however, we have to halt and consider what we do not know yet, and how we can move forward addressing those unknowns.

The knowledge base for clinical and translational aspects of cardiac electrophysiology and arrhythmology is regularly reviewed during the process of producing clinical guidelines and recommendations. Major knowledge gaps are often mentioned in the text, and may even form level of evidence C recommendations. Recently, guidelines task forces have begun to include short sections at the end of their documents in which knowledge gaps, predominantly those that are close to being filled by known ongoing research, are mentioned.

More fundamental reviews of areas for future research which might prove potentially valuable for increasing our knowledge and expanding the evidence base for future therapeutics are rarely undertaken. This is in marked contrast to commercial diagnostic, pharmaceutical and device companies that regularly update their understanding and appreciation of the research data to optimize their potential corporate contribution. Not unreasonably, these deliberations are usually confidential. The European Heart Rhythm Association (EHRA) believes that scanning the field of arrhythmia/cardiac electrophysiology to identify knowledge gaps which are not yet the subject of organized research, should be undertaken on a regular basis. Such a review should concentrate on research, which is feasible, realistic, and clinically relevant, and should not deal with futuristic aspirations. It fits with the EHRA mission that these reviews should be shared on a global basis in order to foster collaborative and needed research which will ultimately lead to better care for our patients. It might also be useful for governmental organizations, health care providers, and medical companies.

The number of unanswered questions that you will find in the text below is impressive. It should not intimidate but motivate the clinician and/or clinical scientist in the quest for better personalized care.

Task Force

This Task Force was convened by EHRA, with the remit to perform a comprehensive review and critical assessment of the current state of the evidence base for arrhythmia management, to identify areas and aspects of arrhythmia therapies that have not been studied or have been insufficiently explored, to evaluate the need for and feasibility of studies to fulfil the missing evidence, and to provide guidance on prioritized research. It is an EHRA policy to sponsor position papers and guidelines without commercial support, and all members volunteered their time. Thus, all members of the Task Force as well as reviewers have disclosed any potential conflict of interest in detail, at the end of this document.

Atrial fibrillation

Pathophysiology and screening

Arrhythmia mechanisms are not generally evaluated on an individual patient basis and are not specifically targeted therapeutically.[1] Mechanistic targeting (*Table 1*) has the potential to sharpen and improve therapeutic choices.[2–4] Current imaging/mapping techniques do not allow the differentiation between ectopic (triggered) activity

Table 1 Knowledge gaps in AF pathophysiology

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Defining actionable patient-specific molecular arrhythmia mechanisms			None	Yes	None
Identifying and targeting key dynamic modulators			None	Yes	None
Achieving atrial targeting of specific molecular arrhythmic mechanisms with drugs			None	Yes	None
Integrated studies of specific molecular/cellular AF pathophysiology, genetics, and external factors			None	Low feasibility at present, but theoretically feasible using 'big data' and AI	Biobank data are being accumulated, but means of analysis are limited

AF, atrial fibrillation; RCT, randomized controlled trial.

and/or re-entry and other cellular/molecular mechanisms.[4–11] Techniques that track cellular metabolic state, such as Raman spectroscopy, could be applied to assess the effectiveness of therapies designed to reverse atrial fibrillation (AF)-related metabolic abnormalities.[1]

Currently, our understanding of the dynamic factors (autonomic fluctuations, atrial stretch, circadian rhythm, ischaemia, inflammation, etc.) that modulate AF risk is based on associations and clinical observations, with limited information about underlying mechanisms.[12–18] The characterization of these dynamic modulators, their interactions, mechanistic basis, and relevance for diverse subgroups of AF-patients is expected to improve AF management. A major challenge to molecular therapeutics is finding a way to modify molecular pathways effectively, safely, and specifically in human atria.[19,20] Recent advances in adeno-associated virus-based vector technology and targeted delivery techniques allow for efficient, safe and long-term gene transfer to the heart.[21–23] Gene knockdown with the use of RNA-interference technology might also be exploited therapeutically.[24] In the future photoacoustic imaging might be applied to evaluate the role of intracellular Ca^{2+} or reactive oxygen species changes in AF occurrence.[1]

The current definition of the type of AF—paroxysmal, persistent, long-standing persistent, and permanent—is based on duration of AF episodes.[25] While this classification does carry some prognostic weight, for example regarding the risk of stroke as well as mortality,[26–29] it falls short in many other regards.[30] Importantly, the success of AF ablation both in patients with paroxysmal as well as in persistent AF is highly variable.[31–33] The same is true with respect to the rate of progression of AF, both from a symptomatic point of view as well as regarding the 'burden of AF'.[34–37] Hence, a more refined classification of AF is highly desirable both from a prognostic point of view as well as to better be able to individually tailor antiarrhythmic therapies including catheter ablation. Incorporation of clinical parameters (including symptom duration, duration of AF, AF burden),[38–40] electrocardiogram (ECG) parameters,[41] biomarkers,[42–48] atrial structure (including invasive assessment of low voltage areas),[49] atrial cardiomyopathy,[50] and imaging parameters[51–54] will be of importance in this regard.[55–57] Atrial fibrillation is generally considered a progressive disease, attributed to electrical and structural remodelling related to both the underlying disease and AF itself, but a significant heterogeneity in the rate and severity of AF progression has been noted in a small proportion of patients who exert yet unexplained 'protection' from AF progression, despite accumulating age-related risk factors and comorbidities. Mechanistic parameters might also be of interest to define new AF classifications such as pulmonary vein (PV)-dependent AF vs. non-PV-dependent AF. Medical treatment has yet to demonstrate clinical efficacy in preventing progression, and the response to antiarrhythmic therapies remains poorly predictable. This may be due to multiple factors ranging from the genetic background and 'high-risk' atrial structure to environmental modifiers and to the late implementation of treatment. These issues have been extremely difficult to address with the existing epidemiological studies, but the advent of the 'big data' and artificial intelligence may make these studies possible.[58]

Furthermore, primary prevention of AF may encompass the characterization of a so called pre-AF-state without an established atrial arrhythmia. The pre-AF state may be expressed and measured on the different scale, including atrial irritability (the electrical component) and atrial myopathy (the structural component). A variety of other measures are likely to be incorporated into the assessment and quantification of the pre-AF state, such as blood biomarkers or echocardiographic strain parameters. The relative weight of these components has not yet been evaluated to develop the risk stratification score, which should the subject of future research.[59,60]

Ten percent of AF-related strokes are a first clinical manifestation of the arrhythmia. Consequently, the development of an effective AF screening strategy should be a public health priority.[61] On the contrary, a recent report concludes that there is still a lack of evidence to assess a proper risk/benefit balance of systematic screening for AF using ECG monitoring in asymptomatic adults.[62] The incidence of screen-detected AF varies between 1.4% and 7.4%[63–66] depending on the duration of ECG screening, the age and the comorbidities of the screened population. There is a lack of data concerning the most appropriate patient profile to enhance AF detection. As of today, we do not know whether ECG based screening detects more AF cases than screening by pulse palpation. There is uncertainty on the optimal duration and the most appropriate tool for screening. The role of

Table 2 Knowledge gaps in AF screening

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
AF screening with stroke as a secondary endpoint				Yes	AFOSS (NCT 03589170) VITAL-AF (NCT 03515057) LOOP (NCT02036450) Ideal MD (NCT 02270151)
AF screening with stroke as a primary outcome				Yes	STROKESTOP II (NCT 02743416)
AF screening after stroke			Yes	Yes	SAFAS (NCT 03570060)
Stroke risk in device identified AHRE/subclinical AF			Yes	Yes	NOAH-AFNET 6 (NCT 02618577) ARTESIA (NCT 01938248)
Biological and clinical significance and difference between subclinical AF and device-detected arrhythmias				Low feasibility	*Post hoc* analyses of NOAH Trial (NCT 02618577) and ARTESiA (NCT 01938248)

AF, atrial fibrillation; AHRE, AF as opposed to device-detected arrhythmia; RCT, randomized controlled trial.

consumer cardiac monitoring using wearables in combination with apps is completely undefined. In cardiac device, patients atrial high rate episodes labelled as subclinical AF (SCAF) occur in around 30–60% of patients.[67,68] However, there is a lack of knowledge on the stroke risk in SCAF, which might occur rarely and last only a short duration. Even more important, we do not know whether earlier detection of SCAF improves clinical outcomes. It is unassessed whether AF screening by any means is cost-effective (*Table 2*).

Subclinical atrial fibrillation, atrial high rate episodes, and device detected arrhythmias

There are controversies due to knowledge gaps that are widely recognized, but not addressed appropriately as yet, partly due to the difficulty conducting the relevant studies (large number of participants are required, relatively low diagnostic yield, need for long, e.g. 5 years, follow-up, which all increase costs). These knowledge gaps include the poorly understood biological and clinical significance of SCAF as opposed to device-detected arrhythmias (AHREs), the unknown 'optimal' threshold for the duration of a SCAF or AHRE episode that determine the need for anticoagulation and the dependence of this threshold on the clinical thromboembolic risk, whether duration, frequency, clustering of SCAF episodes plays a role and whether the concept of a 'temporal relationship' between an AF episode and thromboembolic event is viable. The main frequently asked, but not answered question is whether these episodes are markers of risk or risk factors?[69,70]

Pharmacological therapies in atrial fibrillation, rate and rhythm control

Pharmacological therapy is the cornerstone for the majority of AF patients. Although the impact of antiarrhythmic drugs (AADs) with regard to overall outcome is uncertain for most compounds, such agents are widely used to stabilize sinus rhythm. For some drugs, recent observational trials have provided opposite results with a reduction of stroke and myocardial infarction during long-term use. Head-to-head comparisons of various drugs against each other in well-powered trials are missing, however. An individualized approach for antiarrhythmic therapy in accordance to the underlying atrial pathology is also lacking (*Table 3*).[71,72] Furthermore, combined of rate-control medications such as beta-blockers or calcium-channel blockers with/without digitalis glycosides have also not been systematically studied. There is a new arrange of AADs under development that exploit new targets (e.g. SK channel inhibitors) or new combinations of targets, not necessarily confined to ion channel inhibition (OMT 28; NCT03078738). The relative and added value of these drugs requires considerable research, some of which is ongoing. However, AAD-based research focused on irreversible hard outcomes, such as mortality and stroke, although successfully pioneered with dronedarone, are not yet considered for other agents, including new compounds.[73]

Furthermore, there are many knowledge gaps with regard to cardioversion of AF. The true incidence of stroke in patients with AF <48 h vs. >48 h has not systematically been studied. In addition, it is unclear if all AF patients with a CHA2DS2VASc score of zero need to be anticoagulated during the cardioversion period. The prognostic impact of electrical/pharmacological cardioversion of AF vs. spontaneous conversion is also unclear so far.[74] Furthermore, the pre-treatment period with oral anticoagulants (3 weeks) before cardioversion without the need for a transesophageal echocardiography screening has not been clearly assessed.

Stroke prevention, anticoagulation: strategies and risk stratification

Risk stratification

Stroke prevention is central to the management of AF.[25,75,76] While the risk of stroke is increased five-fold in AF, the risk is not homogeneous and depends on various stroke risk factors. The more common and validated clinical risk factors have been used to formulate stroke risk stratification schemes, which are of varying complexity. Simple schemes such as $CHADS_2$ and CHA_2DS_2VASc have been used in

Table 3 Knowledge gaps in pharmacological therapy of AF

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Optimal rate control therapy: use of digoxin			Very small RCTs with insufficient endpoints	Feasible	RATE-AF (NCT 02391337) BRAKE-AF (NCT03718273)
Optimal therapy in acute symptomatic AF			Lack of studies on rhythm vs. rate control in patients with acute symptomatic AF	Feasible	ACWAS (NCT 02248753)
Early rhythm control in AF			No RCTs	Feasible	EAST (NCT 01288352)
Rate vs. rhythm control for post-operative AF			No RCTs	Feasible	No acronym NCT 02132767
Rate vs. rhythm control in atrial flutter/atrial tachycardia			No RCTs	Feasible	None
IV sotalol for cardioversion of AF			No RCTs	Feasible	None
Structural (pathological) effects of antiarrhythmic drugs in atrial tissue			No RCT		None
Systematic combination of antiarrhythmic drugs to improve efficacy			Yes	Feasible	None
Impact of antiplatelet and antithrombotic therapy on atrial tissue structure (remodelling)			Yes	Feasible	None
Stroke rate in patients undergoing cardioversion of AF <48 h without anticoagulation			Yes	Feasible	None

AF, atrial fibrillation; RCT, randomized controlled trial.

clinical guidelines. They have also been used to artificially categorize patients into low-, moderate-, and high-risk strata. All clinical scores only have modest predictive value for identifying the high-risk patients that sustain events (e.g. c-index 0.63).[2] Attempts to improve prediction with more complex clinical scores only result in modest improvements in prediction (e.g. c-index ~0.65). The addition of biomarkers ('biological markers' whether blood, urine, or imaging)[77,78] improve on prediction, but again, predictive value remains modest (c-index <0.7). Many of the recent biomarker studies have been tested in selected anticoagulated clinical trial cohorts, however, to precisely assess the value of biomarkers for stroke prediction, studies in non-anticoagulated populations are needed.[79] Given that the majority of high-risk AF patients are anticoagulated, the feasibility of such a study remains uncertain. It is unknown if biomarker-based scores may practically help in refining stroke risk assessment especially in patients with low CHA_2DS_2VASc scores.

Thus, existing risk stratification scores for thromboembolic risk include traditional risk factors and do not account for so-called emerging risk factors such as obesity, sleep apnoea, borderline hypertension, and, apart from less widely accepted scores (e.g. ATRIA), renal impairment. It is also noteworthy that relatively easily obtainable echocardiography-derived parameters have not been incorporated in the stratification systems, apart from left ventricular ejection fraction (LVEF), and studies on the additive value of different echo-derived parameters have been small and suboptimally designed and reports have not been consistent. The impact of valvular abnormalities excluding rheumatic mitral valve disease/stenosis and metallic prosthetic valves, has not been well-established, although they are indicators of poorer outcome with regard to stroke and bleeding. The role of echocardiography in risk stratification remains under-appreciated.[80] The knowledge gaps in risk stratification systems include the no 'zero' thromboembolic risk in low-risk patients (CHA_2DS_2VASc 0), wide heterogeneity in stroke rates among patients CHA_2DS_2VASc 1 due to the differential impact of individual components (e.g. age vs. other risk factors), lack of accounting for 'additional' risk factors, and inability to quantify the 'residual' risk.[81]

Anticoagulation strategies

The approach to stroke prevention has changed with the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), which offer better efficacy, safety, and convenience compared with warfarin.[82,83] Observational studies suggest that there may be only marginal benefits of the NOACs on stroke prevention when compared with very well managed warfarin with good anticoagulation control (high individual TTR, >75%), but serious bleeding may be lower with NOACs.[84] It is uncertain if NOACs can be used in patients with significant valvular heart disease, or severe renal impairment (including those with renal replacement therapy). While small pharmacokinetic studies are ongoing, large outcome randomized controlled trials (RCTs) are lacking. The pivotal Phase 3 randomized trials excluded patients with creatinine clearance (CrCl) <30 mL/min (25 mL/min for

Table 4 Knowledge gaps in anticoagulation and stroke prevention in AF

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
LAA occluder vs. NOAC			Yes	Feasible	CLOSURE-AF NCT03463317
LAA occluder in high-risk patients vs. best medical care			Registries, single arm and propensity-matched cohorts	Feasible	(1) Closure AF (NCT03463317) (2) ASAP TOO (NCT02928497) (3) A3ICH (NCT03243175) (4) SAFE-LAAC (NCT03445949) (5) Occlusion-AF (NCT03642509) (6) PRAGUE-17 (NCT02426944)
Combined procedure: AF ablation + LAA occluder vs. AF ablation only			Yes	Feasible: larger RCT trial needed	None
LAAO post-procedural antithrombotic treatment: ASS vs. no treatment vs. low-dose NOAC?			Yes	RCT comparing NOAC vs. APT vs. no treatment	None focusing on post-implant treatment
Head-to-head comparison of different LAAO devices/technologies			None	Feasible	None
Optimal therapeutic approach for stroke prevention in AF dependent on LAA morphology, LAA blood flow velocity, and endocardial remodelling parameters			None	Feasible	None
Assessment of stroke and bleeding risk in patients with valvular abnormalities		Yes	Yes	Feasible	VIALE (NCT02069132) DECISIVE (NCT02982850) Rivaroxaban compared with vitamin K antagonist upon development of cardiovascular calcification (NCT02066662) CAPTURE (NCT03488420)
Assessment of stroke and bleeding risk in patients undergoing biological prosthesis		Yes	Yes	Feasible	Dabigatran in patients with atrial fibrillation and mitral biological prostheses (NCT03183843) RIVER (NCT02303795) Rivaroxaban or aspirin for biological aortic prosthesis (NCT02974920) CAREAVR (NCT02626871)
Risk stratification for stroke and the use of OAC in patients with post-operative AF		Yes	Yes	Feasible	Apixaban vs. warfarin for the management of post-operative atrial fibrillation (NCT02889562)
Can the 'residual' stroke risk be better quantified or reduced and by what means?			Yes	Theoretically feasible	None

AF, atrial fibrillation; LAA, left atrial appendage; LAAO, left atrial appendage occlusion; NOAC, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulants; RCT, randomized controlled trial.

apixaban).[82] Also, whether NOACs can be prospectively started in the early phase after an ischaemic stroke, or in those patients who had sustained an intracranial haemorrhage (ICH) is not proven. In the RCTs, NOACs were associated with lower ICH rates compared with warfarin, but patients with prior ICH were excluded from entering the trials (*Table 4*). Furthermore, anticoagulation regimes for different types of atrial flutter or atrial tachycardia are not established by prospective clinical trials. In addition, new therapeutic options for stroke prevention such as factor XI inhibitors (NCT00890812) or tecafarin (NCT00691470) have to be studied in prospective RCTs.

Left atrial appendage occlusion

At this point, data are lacking on whether left atrial appendage occlusion (LAAO) can be compared against NOACs. Current practice is

Table 5 Knowledge gaps in ablation of AF

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Effect on mortality, bleeding, and stroke			Registries, small studies, and meta-analysis	Yes	CABANA NCT00911508 EAST NCT01288352
Early intervention; timing of ablation			Small prospective and observational clinical trials	Yes	EAST NCT01288352
Anticoagulation after ablation			Retrospective registry data; small observational studies	Yes	OCEAN NCT02168829
Substrate-based ablation intervention		Yes	DECAAF I; small prospective studies	Yes	DECAAF II NCT02529319
Complications; atrio-oesophageal fistula	Yes	Yes	Small observational trials	Yes	OPERA NCT03246594
AV node ablation and ventricular pacing as alternative to PVI in AF subgroups		Yes	Retrospective trials, small prospective trials, meta-analyses, registries, and observational data	Yes	CAAN-AF NCT01522898 JAVA-CRT NCT02946853

AF, atrial fibrillation; AV, atrioventricular; PVI, pulmonary vein isolation; RCT, randomized controlled trial.

to continue antiplatelet therapy post-LAAO implantation, however, this therapy has not been fully established with regard to post-procedural stroke prevention. Randomized controlled trials and observational studies suggest that NOACs are superior for stroke prevention to aspirin in non-valvular AF patients with additional CHA_2DS_2VASc risk parameters, with no difference in major bleeding or ICH risk. Ongoing trials (*Table 4*) will address some of these issues. In addition to the listed larger registries, there are other ongoing studies dealing with the effect of LAAO in various conditions or subgroups: (i) Left Atrial Appendage Occlusion vs. New Oral Anticoagulants for Stroke Prevention in Patients With Non-valvular Atrial Fibrillation, (ii) Evaluation of WATCHMAN Left Atrial Appendage Occlusion Device in Patients With Atrial Fibrillation vs. Rivaroxaban, (iii) A Pilot Study of Edoxaban in Patients With Non-Valvular Atrial Fibrillation and Left Atrial Appendage Closure, (iv) Optimal Antiplatelet Therapy Following Left Atrial Appendage Closure (SAFE-LAAC), (v) Safety and Efficacy of Left Atrial Appendage Closure vs. Antithrombotic Therapy in Patients With Atrial Fibrillation Undergoing Drug-Eluting Stent Implantation Due to Complex Coronary Artery Disease, (vi) Avoiding Anticoagulation After IntraCerebral Haemorrhage (A3ICH), and (vii) AMPLATZER™ Amulet™ LAA Occluder Trial (Amulet IDE).

Nevertheless, some simple issues assessing the interaction of left atrial appendage (LAA) and stroke are still not evaluated. The impact of LAA antatomy on LAA thrombogenesis, of endocardial remodelling on the outcome after LAAO and of thrombogenic markers on LAAO are unclear.[85]

Catheter/surgical ablation of atrial fibrillation

Atrial fibrillation catheter ablation has been shown to be an effective rhythm control strategy in patients with paroxysmal and persistent AF. Cornerstone of treatment is durable isolation of the pulmonary veins (PVI). However, recurrence rate of AF after ablation is high and more than 50% of patients treated may not experience freedom from AF after a single ablation intervention, particularly in persistent AF.[86] Despite the introduction of multiple scores prediction of recurrence risk is complex and currently not sufficiently possible. In a substantial number of patients AF is promoted by structural changes of the atrial myocardium as suggested by magnetic resonance imaging (MRI) and/or left atrial voltage mapping.[50,87] These areas have been identified as targets for catheter ablation. The pathophysiology underlying atrial fibrosis, fatty infiltrates,[57] amyloidosis, dynamics of disease progression, and the potential influence of catheter ablation on these pathologies are unknown.[50]

Multiple studies/trials (CABANA, CASTLE AF etc.) have shown that catheter ablation when compared with AAD therapy significantly improves quality of life in patients with symptomatic AF.[86] Observational studies and registries suggest a reduced incidence of stroke and also a lower mortality after catheter ablation.[88] However, no randomized study could show an effect on outcomes including morbidity, cardiovascular mortality, stroke, or total mortality. In a recent large scale randomized clinical trial (CABANA) comparing catheter ablation and drug therapy quality of life was significantly better in patients undergoing ablation, while the study primary endpoint (mortality, major bleeding, and stroke) was neutral.[89] In AF patients and heart failure with reduced ejection fraction catheter ablation significantly improved ejection fraction.[90] There are no adequately powered trials for the endpoint of mortality. No conclusive data are available on the role of catheter ablation for patients with asymptomatic AF or AF and heart failure with preserved ejection fraction.

In addition, the concept of atrioventricular(AV) node ablation with consecutive right and/or left ventricular pacing deserves further evaluation. Proper indication of AV node ablation, particularly in elderly patients with AF or in patients who failed multiple PVI procedures, is clinically important. The APAF-CRT trial (Atrioventricular Junction Ablation and Biventricular Pacing for Atrial Fibrillation and Heart

Failure; NCT 02137187) demonstrated differences in outcomes in heart failure patients with AF: Ablation + CRT was superior to pharmacological therapy in reducing heart failure and hospitalization and improving quality of life in elderly patients with permanent AF and narrow QRS (Brignole *et al.*[91]). Overall, comparative trials evaluating potential effects on outcome benefits (heart failure, stroke, cardiovascular mortality, and total mortality) need to be evaluated in double blind studies including sham controls or in studies enrolling asymptomatic patients (*Table 5*).

Current guidelines for indications for AF catheter ablation use ECG-phenotyped groups (paroxysmal AF, persistent AF) for recommendations as well as lack of efficacy of AADs.[25] Such phenotype-based grouping does not reflect the complex spectrum of pathophysiology and pathology underlying AF and trials evaluating personalized and pathology-based indications are needed. Experimental and clinical data support the perspective that patients with higher burden and longer history of AF may develop atrial structural remodelling and often evolve to forms of AF with worse response to drugs and ablation.[86] It is unclear whether early intervention using catheter ablation is beneficial and stops and prevents the progression to therapy-resistant substrates. Clinical trials investigating the role of AF ablation timing are currently under way (e.g. EAST). However, further longitudinal follow-up studies with advanced imaging technologies such as MRI are needed. Moreover, structured trials evaluating indications for re-ablation after AF-recurrence also comparing different treatment strategies are warranted.

Pulmonary vein isolation is the present cornerstone of AF ablation.[86] Different technologies [point-by-point radiofrequency (RF) ablation, cryo-ablation, and other balloon-based ablation technologies] have been reported to achieve this goal. In patients with paroxysmal AF no differences in arrhythmia recurrence after ablation have been found between point-by-point RF ablation and cryo-balloon ablation.[92] However, generally accepted data are not available for non-paroxysmal AF.

Multiple studies have evaluated the role of extra-PV ablation strategies especially in patients with non-paroxysmal AF (linear lines, ablation of complex fractionated electrograms, low-voltage area ablation, LAAO isolation, debulking of the posterior wall). Most strategies failed to prove benefits in the frame of prospective randomized trials.[93] This may be at least partially due to lack of definition for and systematic application of solid ablation endpoints.

Various novel software and hardware tools have been introduced to improve ablation safety and outcome. While observational data indicate benefits of such innovations randomized trials failed to show such benefits.[94]

The use of anticoagulation before and during the ablation procedure is supported by various clinical trials and presently well standardized and established.[95] Less is known about the need for and duration of oral anticoagulation following the procedure. Observational studies indicate reduced risk of stroke after ablation, however, such data need validation in randomized trials.[88]

The mechanism and prevention of some severe complications, such as atrio-oesophageal fistula, need to be established. In addition, the long-term consequences of radiation and subclinical cerebral lesions following AF ablation are poorly understood. Long-term consequences of subclinical stroke need to be established and compared with cognitive decline at long term in non-ablated AF patients.

The role of surgical ablation needs to be defined as a stand-alone procedure or in combination with other cardiac surgeries. Trials studying this may set the basis to compare PVI by catheter ablation and surgical PVI as a stand-alone procedure in subsequent trials. Finally, as for catheter ablation the impact of surgical ablation on hard endpoints needs to be clarified. Furthermore, optimal therapy of patients with failed AF ablation needs to be defined.

Device therapies in atrial fibrillation

Whether PM implantation and atrioventricular node (AVN) ablation should be done as a single or in staged procedures is not well determined. Retrospective series have been published.[96–99] The prospective Ablate and Pace Trial reported prospective data on patients using both strategies, but the respective numbers and outcomes are not detailed.[100] Only few data on simultaneous leadless PM implantation and AVN ablation exists.[101,102] Whether AF ablation might be non-inferior (or even superior) to a 'pace and ablate' strategy has only been assessed in very small retrospective settings.[103–106] Furthermore, little evidence exists as to which device (model, vendor etc.) and which functionality (sensor,[107–110] programming features algorithms,[111,112] diagnostic possibilities,[113,114] etc.) works best in AF patients, especially using modern devices. This may be of importance as a 'class effect' of devices is unclear and in fact unlikely to be the case, both regarding quality of life and, possible, hard clinical endpoints.[115]

His-bundle pacing (HBP) is being increasingly adopted as an alternative to right or biventricular pacing. Little is known if HBP is superior in terms of clinical outcome. A randomized trial with His/paraHis pacing in 16 patients has been published.[116] Furthermore, AVN ablation in this setting may be challenging due to the proximity of the ablation target site and the pacing lead. The largest series includes 42[117] and 37 patients.[118] An early case series,[119] and a case report,[120] have been published.

Sudden death due to ventricular arrhythmias shortly following AVN ablation has prompted pacing at a higher baseline rate (90 b.p.m.) for the first weeks, to mitigate repolarization abnormalities associated with a sudden drop in heart rate. There are only two non-randomized studies (with 255 and 69 patients) supporting this strategy.[121,122]

The mode of delivery of anti-tachycardia pacing (ATP) at the atrial level showed an evolution in recent years (resulting in so called 'reactive ATP'),[123–131] so that delivery of atrial ATP during more regular atrial tachyarrhythmias may result in arrhythmia termination and prevention of its evolution to a persistent/permanent form.[128–133] While reactive atrial ATP has been validated in patients with bradyarrhythmias with a randomized clinical trial (MINERVA trial),[128–133] there is lack of controlled evaluation in patients with a dual-chamber implantable cardioverter-defibrillator (ICD) or with cardiac resynchronization therapy (CRT) devices (*Table 6*).[134,135] Data derived from a large dataset of remote monitoring, analysed through propensity score, appear to confirm a clinical benefit, but no RCT is currently planned in these settings.[136]

'Out of the box' programming of pacemakers, ICDs and CRT devices can be proposed for an average patient but may not be optimal in specific cases.[115] The perspective of a 'tailored' use of devices can include a specific 'individual programming', 'disease specific' programming, or a programming according to predefined specific characteristics. Although some recommendations on device

Table 6 Knowledge gaps in AF device therapy

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Timing of AVN ablation and PM implantation			Yes	Yes	None
His bundle pacing and AVN			Yes	Yes	None
Pacing rate after AVN ablation			Yes	Yes	None
AF ablation vs. 'Ablate and Pace'			Only PABA-CHF trial with small sample size and no hard endpoints	Yes	None
Comparison of single-chamber pacemakers in patients with AF (incl. features, sensor etc.)			Yes	Yes	Partly
Hard outcome data on atrial ATP out of the setting of sinus node disease			Yes	Yes	AT-PATCH: NCT03209583
Optimal device programming			Yes	Yes	No acronyms: NCT03422705 NCT03627585 NCT02964650 NCT03556189 NCT03338374

AF, atrial fibrillation; AVN, atrioventricular node; PM, pacemaker; RCT, randomized controlled trial.

programming have been published,[137–140] they are not fully validated by solid data, collected and validated in randomized trials. Disease-specific and patient-tailored approaches to device programming need to be more precisely defined and validated in prospective studies,[141] as done for detection intervals or detection time in ICDs.[142–147]

Atrial fibrillation in orphan diseases

Frequent comorbidities such as arterial hypertension or diabetes mellitus induce atrial remodelling that favours ectopia and intraatrial conduction delays, conditioning the development, and perpetuation of AF.[25] Infrequent diseases such as hereditary arrhythmogenic disorders[148] or infiltrative cardiovascular diseases also can be associated with disorders of atrial rhythm.[149] In the case of infiltrative heart disease, the accumulation of deposits in the myocyte or in the interstitial space produces an increase in myocardial thickness, with development of ventricular diastolic dysfunction and, subsequently, the appearance of atrial remodelling.[50,149] This is especially true in cardiac amyloidosis where diverse proteins can give rise to amyloid deposits in the heart, with different evolution, diagnosis and treatment according to the subtype: cardiac amyloidosis due to senile transthyretin (ATTRwt) presents with AF in 43–67% of the cases, whereas hereditary transthyretin (ATTRm) is found in 10%. In these patients, frequently a stroke is the first manifestation of the disease.[50,150] On the other hand, recent studies show that AF does not have a negative impact on the survival of patients with ATTRwt.[151] Other infiltrative cardiomyopathies related to the appearance of AF are Danon's disease and Emery-Dreifuss cardiomyopathy,[87] associated with a high premature thromboembolic risk,[152] and sarcoidosis with cardiac involvement, in which up to 32% of supraventricular arrhythmias have been observed, with AF being the most frequent type.[153] Finally, isolated cases of AF have been reported in patients with Wegener's disease and Fabry disease, with resolution of the arrhythmia after treatment of the underlying disease.[154,155]

Regarding hereditary arrhythmogenic disorders, the prevalence of atrial arrhythmias has been shown to be variable.[25] In patients younger than 50 years with genetically demonstrated long QT syndrome (LQTS) the prevalence of AF is approximately 2%, being significantly higher in men than in women and more frequent in Type 1 than in 2 and 3.[156] Kirchhof *et al.*[157] reported that both prolonged atrial action potential and refractory periods in LQTS induce polymorphic atrial tachycardias that can degenerate into AF. These patients have a relative risk of 18 to present with AF before 50 years of age.[156] In short QT syndrome (SQTS), AF incidence ranges between 26% and 70%, being more frequent in Type 2 SQTS. In these patients, shortening of the QT leads to a transmural dispersion of the refractory period, which causes atrial re-entry leading to AF.[148] In the Brugada syndrome (BrS), spontaneous atrial arrhythmias have been described in 6–38% of patients. The prevalence of latent BrS in patients who undergo pharmacological cardioversion with flecainide is 5.8% in patients with AF.[158] The increased duration of intraatrial conduction observed in these patients could contribute to the development of AF.[159] Finally, catecholaminergic ventricular tachycardia (VT) has been associated with AF in approximately 40% of cases.[25] Atrial arrhythmias in this group of patients can trigger late post-potentials and induce ventricular arrhythmias due to triggered activity,[160] and also cause inappropriate discharges in patients with ICD.[148]

In conclusion, AF can be the initial manifestation of rare diseases in the general population, and, in addition to the usual therapeutic arsenal,

Table 7 Knowledge gaps in risk prediction of ventricular arrhythmias and SCD

Knowledge gaps	Available evidence	Feasibility of study	Ongoing trials
Personalized risk prediction	The selection of best candidates to ICD therapy is usually based on the inclusion criteria of main primary prevention trials	Intermediate	None
Temporal changes of the individual risk for SCD	Not definite role for evolution of heart disease, type of therapy, electrical and anatomical remodelling	High	Long-term follow-up in previous published trials (MADIT-II, SCD-HeFT, etc.)
Use of cardiac MRI in risk stratification	Role of LGE for SCD risk	High	Several observational studies
Information on large population	Data on several ICD registries	High	Several observational studies
Electrical storm management	Information obtained from single-centre registry	High	None

ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; SCD, sudden cardiac death.

treatment of the underlying disease could contribute to the resolution of arrhythmia. In hereditary channelopathies, pharmacological treatment of AF is difficult due to proarrhythmic ventricular effects of most AADs, and therefore, AF ablation is recommended in many patients.[161]

Thus, important knowledge gaps remain in this field: (i) Biomarker panels/imaging modalities to identify or predict the presence of atrial cardiomyopathy in orphan diseases? (ii) Time course of AF development in certain orphan diseases? (iii) Impact of orphan diseases on atrial thrombogenesis in the absence of AF? (iv) Different subcohorts of orphan disease patients with paroxysmal or persistent AF? (v) Factors leading to progression from paroxysmal AF to persistent AF? (vi) Effects of certain diseases specific therapies (immunosuppressive drugs, antibody therapy, etc.) on AF? Due to the low prevalence/incidence of the orphan diseases, however, several knowledge gaps will never be solved.

Ventricular arrhythmia and sudden death

Risk prediction

Without any doubt ventricular arrhythmias and sudden death have been one of the fields of major development in cardiology over the last decades.[162–169]

From the knowledge of ventricular arrhythmias and sudden death pathophysiology, cardiological community has advanced in the recognition of patients at risk and also in the management of these patients. Basically, we have some tools to recognize large populations at risk, and we have some means to treat and prevent sudden death, but we are still having a large number of gaps in our knowledge including the impact of the autonomic nervous system. Major gaps in this field include (see also *Table 7*):

(1) A *personalized risk prediction* for sudden cardiac death (SCD) appears fundamental for selection of patients that might receive or might not receive ICD for primary prevention of SCD. Personalized risk prediction for patients with ischaemic or non-ischaemic cardiomyopathy and severe reduction of LVEF (<35%) is lacking, because in clinical practice the selection of best candidates to ICD therapy is usually based on the inclusion criteria of main primary prevention trials. The main interest would probably be the identification of patients with low individual risk for SCD that would not need the ICD.

(2) A personalized risk prediction for patients with ischaemic or non-ischaemic cardiomyopathy and only moderately reduced or preserved ejection fraction is also not available. In this field, we do not know exactly which patients may have a substantial risk for SCD, and therefore, require protection with an ICD.

(3) Another conceptual gap is to understand if a certain risk prediction would remain stable over time. Are there temporal changes of the individual risk for SCD depending on age, favourable ventricular reverse remodelling, alternative therapies for underlying heart disease? Is it necessary to reassess periodically the individual risk?

(4) A systematic use of cardiac MRI in risk stratification of patients with ischaemic or non-ischaemic cardiomyopathy needs a large prospective assessment. In particular, can we properly identify and characterize the value of the vulnerable scars? Can we use the degree of inhomogeneity and physical characteristics of the scar as a marker for future arrhythmia development? It is known that late gadolinium enhancement (LGE) is a powerful predictor of ventricular arrhythmic risk in patients with ventricular dysfunction, irrespective of ischaemic and non-ischaemic cardiomyopathy aetiology, but the prognostic power of LGE in patients with mild reduction of ejection fraction needs to be confirmed to improve patient selection for ICD implantation.[166]

(5) We also lack information on large populations, trying to understand the true risk for SCD in subpopulations not identified by present ICD eligibility criteria and not well represented in the main published trials. Moreover, the best approach to patients who need ICD replacement, but who may not be at persistent risk of SCD due to improvement in LVEF, should be prospectively evaluated.[167,169]

(6) Finally, we lack complete information on patients who experienced electrical storms trying to understand the main causes, the underlying electrical and anatomical substrates, the short- and long-term effects, and the optimal type of management, etc. The best strategy to reduce ICD shock should be individualized to ensure that patients receiving ICD therapy experience the maximal benefit, while minimizing the adverse consequences.[162–166]

A survey at the various European countries could be useful to identify a future and universal strategy of properly selection and treatment of patients without clear and well defined indication to

Table 8 Knowledge gaps in pharmacological therapies for VT/SCD

Knowledge gaps	Available evidence	Feasibility of study	Ongoing trials
Role of combination of potassium and sodium channel blockers (amiodarone + propafenone/flecainid) in patients with ICD and frequent adequate interventions/ arrhythmic storm	Observational	Moderate	None
Safety of Class IC in combination with beta-blockers in patients with ICD and frequent adequate interventions/ arrhythmic storm	Observational	Feasible	None
Azimilide in patients with ICD and frequent adequate interventions/arrhythmic storm	RCT SHIELD, SHIELD-2 Underpowered	Likely	None
Use of AAD during resuscitation for refractory VF/VT	Underpowered trials	Moderate	None
Role of ranolazine (inhibitor of late I_{Na}) in preveng non-sustained VT and SCD in patients post-ACS	MERLIN-TIMI 36, *post hoc* analysis	Moderate	RAID trial (NCT NCT01215253)
Targeted therapy with AAD for treatment of frequent ventricular ectopy	Observational	Likely	None
Targeted AAD therapy for cardiac channelopathies	Observational	Moderate	None
Role of late sodium current blockers (mexiletine, lidocaine) in preventing TdP by reducing drug-induced QTc prolongation	Healthy volunteers	Likely	None

AAD, antiarrhythmic drug; ACS, acute coronary syndrome; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

appropriate therapy, such as ICD implantation, in order to reduce the still high burden of SCD.[167]

Pharmacological therapies

Antiarrhythmic drugs were until the end of the eighties the cornerstone of therapy for ventricular tachyarrhythmias. Their use was based on their efficacy in experimental settings which, however, did not demonstrate any clear impact on mortality in clinical trials. The armamentarium of arrhythmia therapy was revolutionized with the introduction of interventional approaches: catheter ablation and ICD. In fact, rapid progress of interventional therapy of arrhythmias has been driven also by the demonstration of increased mortality in the CAST trial with Class IC AAD highlighting the hitherto underestimated proarrhythmic potential of AAD. The development of Class I and Class III drugs for the treatment of ventricular arrhythmias and prevention of SCD almost completely ceased thereafter.[167]

Until present no convincing evidence is available for reducing arrhythmic mortality by specific AADs (*Table 8*). The only drug used in patients with high risk of SCD due to malignant ventricular arrhythmia is amiodarone. This is mainly due to neutral mortality impact of amiodarone in patients with heart failure with reduced LVEF in the SCD-HEFT trial.[170] Thus, trials with AAD were not able to reduce arrhythmic mortality in neither secondary nor primary preventative indication.

Most of the currently available AAD affect multiple electrophysiological targets in various tissues of the heart and are used empirically for a wide spectrum of arrhythmias. This is the main reason of their adverse proarrhythmic potential. There is an unmet need for highly selective AAD targeting precisely the arrhythmia mechanism crucial for the individual patient. It has been demonstrated experimentally that several such mechanisms exhibit targetable selective chamber occurrence and/or up-regulation in various syndromes and posses potentially modifiable properties, e.g. atrial-specific K+-currents (IKur, TASK-1 I NaL), RyR2, SK channel.[171]

With the widespread use of ICDs a new clinical scenario emerged: ICD is a palliative therapy and patients continue to have ventricular arrhythmias frequently cumulated into arrhythmic storms which trigger ICD discharges. Suppressing their occurrence is a very important unmet clinical need. Currently, two drugs have some promising potential in this indication—ranolazine and azimilide. Ranolazine, a late sodium current inhibitor, has shown promising antiarrhythmic potential in *post hoc* analyses of the MERLIN TIMI-36 trial and is currently tested in a RCT (RAID—Ranolazine And the Implantable DefibrillaTor). Azimilide (an iKr and IKs repolarizing current inhibitor) showed in the prematurely terminated SHIELD-2 trial promise as a safe and effective drug in reducing all-cause shocks, unplanned hospitalizations, and emergency interventions in ICD patients.[172]

In spite of the enormous progress of interventional therapy for ventricular arrhythmias it is clear that localized destruction of myocardial tissue achieved by catheter ablation in diseased myocardium is largely a palliative therapy. Complete elimination of arrhythmogenic substrate in diseased hearts is rarely possible. Antiarrhythmic drugs will be needed in the future to precisely target the arrhythmogenic mechanism on the cellular membrane level in individual patients. Genetic testing allows for identifying such targets and allows for choosing the appropriate drug: therapeutic use of mexiletine in Type 3 LQTS is an example. In this condition genetically mediated gain of

Table 9 Knowledge gaps in device therapies for VT/SCD

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Impact of modern medical treatment on the utility of ICD therapy			One RCT (DANISH trial)	Conduction of large RCT feasible but with significant difficulties	EU-CERT-ICD (NCT02064192, prospective observational)
Device therapies for protection of patients with LVEF >35% but high individual risk for SCD			None	Personalized risk prediction needed, but in principle feasible	PRESERVE-EF (NCT02124018) SMART-MI (NCT02594488)
Role of subcutaneous ICD compared with the transvenous systems			Registries (EFFORTLESS and others)	RCT already being conducted	PRAETORIAN (NCT01296022)

ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; SCD, sudden cardiac death; VT, ventricular tachycardia.

function of the slow Na current prolongs of action potential and QT interval. This can be counteracted by inhibiting the delayed Na current by several AAD, however, the ideal one with 'pure' properties targeting uniquely this current is still missing. Nevertheless, this approach shows considerable promise for the future of AAD for treating ventricular arrhythmias.[173]

Device therapies to prevent ventricular tachycardia/sudden cardiac death and lead management

Device therapies have been a major breakthrough in treatment of ventricular arrhythmias and prevention of SCD.[174] The ICD can effectively terminate life-threatening arrhythmias and prevent SCD.[170,175] Impaired LVEF with a cut-off mostly set at 35% is a major risk factor for SCD in patients with structural heart disease[176] and current European Society of Cardiology (ESC) guidelines recommend ICD implantation for primary prevention of SCD in patients with ischaemic or non-ischaemic cardiomyopathy and LVEF ≤35%.[167] Despite the success and the wide implementation of this therapy,[177] several knowledge gaps remain or have emerged. As described in the preceding chapters, one major gap is the correct identification of patients that are truly at increased risk. Although a reduced LVEF is a major risk factor, several other factors may influence the individual risk and have an impact on the need for ICD therapy such as clinical characteristics,[178] fibrosis of the left ventricle as assessed by modern imaging techniques,[179] autonomic dysregulation[180] etc. Personalized risk stratification guiding ICD implantation is definitely needed, but currently no established method for such a personalized approach exists (*Table 9*). In addition, the role of a wearable defibrillator is not clearly established.

The need for personalized application of ICD therapy is underlined by the fact that the majority of SCD cases occur in patients with only moderately reduced or preserved LVEF.[181] Although these patients have a lower SCD risk in relative terms than patients with severely reduced LVEF, they are much more numerous as a result of modern successful therapy for heart failure. Therefore, in absolute terms the majority of SCD cases finally occur in exactly this low-risk population that is left unprotected with current treatment strategies.[182] Our knowledge regarding personalized risk stratification in these patients with the aim to identify the high-risk subgroup within this low-risk group and protect it by ICD implantation is very limited.

A further knowledge gap (*Table 9*) is the impact of modern medical treatment on the utility of the ICD. Modern optimal heart failure treatment reduces not only total mortality but also SCD.[183,184] The impact of the advances of the last decades on the need for device therapies is completely unknown. Recently, the DANISH trial indicated a reduced utility of ICD therapy under modern treatment,[185] and these results have already had an effect on clinical practice.[186] Technical developments such as the subcutaneous defibrillator[187–189] may change benefit and risk of device therapies for prevention of SCD compared with transvenous systems. More data are expected in this field in the near future. Finally, the need for ICD implantation after catheter ablation of VT, particularly in patients with preserved or only moderately reduced ejection fraction, is currently unknown.

There are numerous gaps in evidence in the topic of lead management, which have recently been outlined in a recent EHRA consensus document.[190] Some of the gaps (see also *Table 10*) are listed below. (i) *Data on extraction tools:* It is well accepted that a variety of extraction tools is necessary to maximize patient safety as well as procedural success. Comparison of safety and efficacy of the different tools is problematic, as some devices (e.g. snares) may be used as backup solutions for difficult cases. Nevertheless, multicentre studies are necessary for acquiring data, especially with the introduction of new tools for which sparse data exist (e.g. occlusion balloons[191]). (ii) *Risk stratification:* There are a number of risk factors associated with lead extraction procedures. Further research may provide scores for risk-stratification which may help with management strategies. (iii) *Management of infected leads:* Although in case of infected devices a complete removal is recommended, the following points need to be

Table 10 Knowledge gaps in lead management

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Data on extraction tools			Yes	Yes	RELEASE (NCT03688412)
Risk stratification for lead extraction			Yes	Yes	None
Management of infected leads			Yes	Yes	None
Management of abandoned leads			Yes	Yes	None
Special patient populations			No	Yes	None

RCT, randomized controlled trial.

further evaluated: (a) Defining the role of additional diagnostic tools (e.g. positron emission tomography-computed tomography) in patients with occult infections. (b) Clinical effectiveness of different antibiotic therapies and their cost-effectiveness. (c) Determine the safety of 1-stage contralateral device replacement compared with delayed device replacement as a management scheme in local and systemic infection. (iv) *Management of abandoned and recalled leads*: Abandoned or recalled pacemaker and ICD leads create a challenging decision-making process. The main issues are around clearly defining: (a) the risk associated with lead abandonment and (b) whether the potential benefit of lead extraction outweighs the risk of the procedure. There are few data on the lead burden that results in venous access issues and superior vena cava syndrome, and consensus documents[192,193] are based on expert opinion as to the numbers of abandoned leads that justify extraction. For leads under advisory or recall, surveillance and data collection are essential to aid with clinical decision making.[194] (v) *Special patient populations:* There exists a strong need to generate a scientific basis for future, evidence-based lead extraction recommendations in special patient populations. Such special patient populations consist of but are not restricted to paediatric patients, grown-up congenital heart disease (GUCH) patients. Common to all these special patient populations is the fact that the numbers of such patients in single institutional series, even in high-volume centres, are too small to create statistically solid data. Therefore, it is of utmost importance to perform future studies based on a data pooling of multiple centres, either in the form of multicentre studies or registries.

Catheter ablation

Catheter ablation is increasingly used for the treatment of recurrent VT in a wide spectrum of patients with structural heart disease of different aetiologies. In general, VT ablation is considered to be a symptomatic therapy with no clear impact on mortality. However, information on the indication and timing of the procedure, ablation techniques and outcomes are mainly derived from post-infarct patients and often extrapolated to the highly heterogeneous non-ischaemic patient population. Of importance, the currently available RCTs comparing the efficacy of VT ablation with ICD implantation vs. ICD implantation only and vs. anti-arrhythmic drugs have been conducted in post-myocardial infarction patients (Smash VT, VTACH, Vanish).[195–197] There are no data comparing AADs and catheter ablation in patients with non-ischaemic cardiomyopathy, which is of particular interest as these patients are often younger with more preserved cardiac function and less comorbidity. In addition, although two small randomized trials (Smash VT, VTACH) suggested a potential benefit of 'prophylactic' ablation after a first episode of VT in selected patients with post-myocardial infarction VT, the optimal timing of VT ablation remains unknown for the majority of the patients. In patients with ischaemic cardiomyopathy, substrate-based ablation has been demonstrated to be superior to limited ablation of the clinically documented stable VT only.[198] However, the most appropriate substrate-based ablation strategy remains unknown since the efficacy of different substrate-based ablation techniques has never been directly compared. Finally, although some observational studies have suggested that systematic use of multipolar mapping catheters and image integration might improve post-myocardial infarction VT ablation outcome,[199,200] data arising from multicentre randomized study confirming these findings is lacking. Another gap in evidence in the field of VT ablation is the need for ICD implantation in patients with preserved left ventricular systolic function and tolerated monomorphic VT that undergo apparently successful VT ablation. Currently, the overwhelming majority of these patients undergo ICD implantation even if successfully ablated. However, there are no data that demonstrate either the necessity or the lack of necessity for ICD implantation (see *Tables 11–13*).

Heart failure

Pharmacological therapies

Pharmacological therapy of arrhythmia in the present of heart failure is difficult, since the only currently approved AADs in this clinical indication is amiodarone. Furthermore, the effect of modern heart failure medication an arrhythmia occurrence is limited. The enclosed table summarizes the current knowledge gaps in the field (*Table 14*).

New monitoring devices/technologies

Pacemakers and defibrillators have various diagnostic capabilities that offer a promising tool to guide heart failure treatment and to prevent adverse clinical events by providing early warning of clinical deterioration.[201] In addition, remote monitoring has become standard of care in the follow-up of such patients, thus improving the ability to continuously monitor parameters relevant to the course of heart failure.

Table 11 Knowledge gaps in catheter ablation in post-MI ventricular tachycardia

Knowledge gaps	Available evidence	Feasibility of study	Ongoing trials
Effect on survival	Pooled data from observational studies (7, 8)	Moderate	BERLIN VT (NCT02501005) VANISH 2 trial (NCT02830360)
Timing of ablation in patients with ICDs	Observational (9)	Yes	PARTITA trial (NCT01547208) BERLIN VT (NCT02501005) VANISH 2 trial (NCT02830360)
Indication for primary endo-epicardial ablation approach	Observational, one RCT (10)	Moderate	EPILOGUE trial (NCT02358746)
Comparison between different substrate ablation techniques on outcome		Moderate	None
Impact of image integration (CT/MRI) on outcome	Observational (5)	Yes	None
Comparison between multipolar/single tip catheters on outcome, safety, procedural duration, and costs	Small RCT, observational (5, 6)	Yes	None

CT, computed tomography; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; MRI, magnetic resonance imaging; RCT, randomized controlled trial.

Table 12 Knowledge gaps in catheter ablation of ventricular tachycardia in DCM

Knowledge gaps	Available evidence	Feasibility of study	Ongoing trials
Comparison between effect of anti-arrhythmic drugs/catheter ablation on outcome	None	Yes	None
Timing of ablation	None	Yes	None
Relevance of underlying aetiology on ablation indication and timing	None	Moderate	None

DCM, dilated cardiomyopathy.

Table 13 Knowledge gaps in catheter ablation of ventricular tachycardia in ARVC

Knowledge gap	Available evidence	Feasibility of study	Ongoing trials
Comparison between primary endo-epicardial ablation approach vs. patient-tailored approach (epicardial after endocardial failure)	Observational study	Yes	None

ARVC, arrhythmogenic right ventricular cardiomyopathy.

However, despite considerable research into device based heart failure monitoring, only one study using ICD-based multiparameter monitoring[202] has been able to demonstrate an improvement in clinical outcomes, whereas others have provided different results showing no benefit from remote monitoring. Thus, currently the potential of remote monitoring to improve clinical outcome is still debated. In addition, monitoring of pulmonary artery pressures using a wireless sensor[203] has been shown to improve clinical outcomes and these two approaches are cited with a Class IIb recommendation in current heart failure guidelines.[204]

Therefore, there is a clear clinical need to better understand how implantable heart failure monitoring can be improved to translate into better outcomes (*Table 14*). A crucial element to achieve this aim is further progress in the different technological aspects of monitoring.[209–212] It needs to be clarified which sensors or which multiparameter combinations of sensors are particularly useful to direct heart failure management. The possibility of a combined use of information from implantable and external sensors needs to be further explored. The technical set-up of remote device monitoring may have an important impact and it has been suggested that a higher level of connectivity with more frequent data transmission is linked to better outcomes.[213] Solutions including automatic intelligence systems may help to facilitate data processing and automatic analysis of large amounts of diagnostic information. Furthermore, more effective

Table 14 Knowledge gaps in pharmacological therapies in heart failure

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Effect of digitalis in patients in HF patients suffering from AF			No RCT on effects of digoxin on morbidity and mortality in AF, added to standard therapy. Destructive meta-analyses have incriminated digoxin, whilst prescription bias and confounding by indication hamper proper evaluation; also clinical impression and randomized data in SR show reduced HF hospitalization	Feasible: to show that digoxin reduces repeated HF hospitalization and death	DECISION trial https://www.zonmw.nl/nl/onderzoek-resultaten/doelmatigheidsonderzoek/programmas/project-detail/goed-gebruik-geneesmiddelen/digoxin-evaluation-in-chronic-heart-failure-investigational-study-in-outpatients-in-the-netherlands/
Beta-blocker therapy not effective in reducing mortality in AF and HF			*Post hoc* analyses suggest that beta-blockers are not effective in reducing mortality in AF and HF (individual patient data analysis from randomized studies.[205] BB may increase BNP in permanent AF.[206]	Feasible: 1st do a mechanistic study to dissect beneficial from deleterious effects of BB in AF; 2nd perform RCT	None
Effects of ARNI on sudden death and incidence of AF and whether prevention of AF is beneficial		MRA reduce incidence of AF in HFrEF, however, no effect on mortality (EMPHASIS)	Predefined analysis of PARADIGM trial: Sacubitril's effect on incidence of AF unknown as is potentially related effect on survival	Feasible; *post hoc* results suggest no effect on incidence of AF	None
HFpEF and AF: morbidity and mortality			Management of AF in HFpEF uncertain since multiple mechanisms play a role Separate effects of drugs (MRA, drugs acting on actin-myosin binding), AF ablation, and rehabilitation are unknown	To show that a comprehensive mechanism driven treatment improves survival and morbidity	None
HFpEF and persistent AF, role of diagnostic cardioversion in work-up towards chronic rhythm control is uncertain	Yes		Difficult to separate HF from AF symptoms in HFpEF complicated by AF or vice versa		None
SCD is suggested as the most common mode of death in HFPEF. An ILR may reveal incidence of sustained VT and facilitate ICD implantation	Yes		Limited data from HFPEF studies IPRESERVE, CHARM-Preserved, and TIME-CHF: most deaths in HFPEF are cardiovascular death (60–70% of all deaths), sudden cardiac death is most common mode of death (26–28%), followed by HF death (14–21%)	To show mechanisms of sudden demise (arrhythmic, non-arrhythmic) and identify treatment schemes including drugs and ICD	VIP-HF (NCT01989299)

Continued

Table 14 *Continued*

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Reduction of ventricular arrhythmias in HF/ICD patients using late sodium channel blockade (ranolazine)			Preliminary data suggest efficacy of ranolazine. It may have antiarrhythmic and antiischemic effects	Ranolazine to reduce VAs in people with ICD on top of standard therapy	RAID study (NCT01215253)
Is digoxin beneficial in acute management of acute decompensated heart failure (ADHF)		Observational data on nitroprusside, dobutamine, and diuretics	Management of AHF syndromes is challenging and most previous drugs failed to decrease post-discharge mortality and readmission rates	Feasible: short-term digoxin may appear beneficial	DIG-START-AHF (NCT02544815)
Is there a role for sacubitril/valsartan in acute decompensated HF in patients with HFrEF?			Effects unknown in patients hospitalized with ADHF. After PIONEER-HF we have one large RCT showing reduction HF hospitalization and reduced BNP		PIONEER-HF ClinicalTrials.gov Identifier: NCT02554890 Velazquez *et al.*[207]
Safety and efficacy of istaroxime in treatment of ADHF?		It will provide mechanistic data, no HF/arrhythmia endpoints	Effects of Istaroxime in ADHF unknown. New drug with lusitropic and inotropic effects		NCT02617446
Prospective assessment of premature ventricular contractions suppression in cardiomyopathy		Observational data in 10's of patients	Frequent PVCs have shown to induce a reversible cardiomyopathy	Feasible: to show that AAD (amiodarone) or VPB ablation improve CMP	PAPS (NCT03228823) CAT-PVC (NCT02924285)
Treatment of inflammatory HF/acute myocarditis using IL-1 blocker		ARAMIS is a 120 patients study	IL-1β blocker anakinra in acute myocarditis	Feasible	ARAMIS (NCT03018834)
Treatment of inflammatory HF/CMP using IL-1 blocker Canakinumab					CANTOS Subanalysis (NCT01327846) Canakinumab reduces HF hospitalizations among responders (patients who reach CRP <2); small effect of hospitalization with highest dose: Everett *et al.*[208]

Continued

Table 14 *Continued*

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (Clinical Trial.gov)
Can drugs be withdrawn in recovered DCM?			TRED-HF—this trial was designed to test the safety and feasibility of heart failure therapy withdrawal in patients with recovered DCM	Shows that withdrawal is associated with recurrence of HF	TRED-HF: do not withdraw HF drugs in recovered DCM. Future studies needed to distinguish patients at risk of recurrence from those who are not; needs detailed analysis of cause of HF in DCM patients
Low dose NOAC to reduce stroke in severe HFrEF?			Low-dose rivaroxaban use in HF significantly reduced the risk for thromboembolic events in the COMMANDER HF trial population		COMMANDER-HF (NCT01877915)
Studies on interventions other than pharmacological, or drugs not directly affecting SCD or arrhythmias					
Stem cell therapy for heart failure		55 patients in a Phase I/II, Placebo-Controlled RCT		Feasible	TAC-HFT-II (NCT02503280)
Stem cell therapy for heart failure (DCM)		66 patients; Completen 2017		Feasible	REMEDIUM Repetitive intramyocardial CD34+ cell therapy in dilated cardiomyopathy (REMEDIUM)
Stem cell therapy for heart failure		9 patients included; completion of study 2011		Feasible	PROMETHEUS (NCT00587990)
Anti-diabetic drugs to reduce HF hospitalization in high-risk patients		EMPA-HEART, ClinicalTrials.gov Identifier: NCT02998970—effects of SGLT2 inhibitor Empagliflozin on LV reversed remodelling (less LVH etc.) in 97 patients with T2DM and CVD	SGLT2 inhibitors to reduce CV endpoints including HF hospitalization in T2DM; preliminary data from	Feasible	DECLARE-TIMI-58 (NCT01730534)
Renal sympathetic modification in patients with heart failure			Renal denervation decreases sympathetic nerves activity. RD may improve cardiac	To show renal sympathetic modification reduces MACCE in HF patients	NCT01402726

Continued

Table 14 *Continued*

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited knowledge (small trials or registries, but no RCT)	Resolution of gap (in principle) feasible	Upcoming trials in the field (ClinicalTrial.gov)
			function and reduce CV events including arrhythmias		
Effect of AF ablation in patients with HFrEF on optimal medical therapy including MRA			Data from CASTLE-AF suggest that catheter ablation may reduce mortality and HF hospitalization. Further data needed. CAVE: catheter ablation vs. medical therapy in congested hearts with AF (CATCH-AF, NCT02686749) stopped in 2018 for lack of enrolment	To show that effective catheter ablation using robust cryoballoon technology decreases mortality and morbidity in AF patients suffering from HF	RACE-8 Soon to be announced in ClinicalTrials.gov
Oncological heart failure and SCD	Yes			Yes	None

AF, atrial fibrillation; ADHF, acute decompensated heart failure (ADHF); BB, beta-blockers; BNP, brain natriuretic peptide; CVD, cardiovascular diseases; DCM, dilated cardiomyopathy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVH, left ventricular hypertrophy; MACCE, major adverse cardiac and cerebrovascular events; RCT, randomized controlled trial; SCD, sudden cardiac death; T2DM, type 2 diabetes mellitus; VA, ventricular arrhythmia; VT, ventricular tachycardia.

clinical response mechanisms to device mediated alerts are needed in order to incorporate the information from monitoring into meaningful action. As the importance of person entered medicine is increasingly recognized, the feasibility of integrating patients into the information loop of remote monitoring thereby enabling self-directed treatment adjustments needs to be further explored.[214] Subcutaneously implanted loop recorders are today used to monitor rhythm abnormalities, but this information and other sensors incorporated into these devices may also be helpful for the purpose of heart failure monitoring. Other implantable technology, in particular the use of central pressure sensors needs to be further explored. Finally, the selection criteria of patient groups most suitable for specific monitoring approaches need to be established. Given that implantable heart failure monitoring can be further improved by research addressing the above issues, the impact on mortality and morbidity needs to be re-established (see *Table 15*).

Pacing technologies and cardiac resynchronization therapy

Cardiac resynchronization therapy has been clinically introduced more than two decades ago, and its use in the selected population of heart failure patients has been well consolidated by the recommendations of different international societies of cardiology.[185,215–220] As shown in *Table 16*, there are still a significant number of questions about the use of CRT in some patient cohorts that have not been systematically addressed by RCTs. Although the benefit of CRT is dependent upon QRS duration and morphology, there is recent evidence that PR interval may play a key role in response to CRT; however, prospective evidence is missing.[221–223] One of the most clinically relevant issues is, whether the risk for SCD progressively declines over time after CRT or whether death due to competing risks may significantly reduce the protective benefit of an ICD particularly in non-ischaemic cardiomyopathy.[185] Of similar clinical relevance is the benefit of CRT in patients with AF, and whether ablation of AV node shall be systematically performed, has been studied only in (large) registries.[90,91,144] Multiple prospectively designed registries have shown that a large proportion of patients is referred to CRT for upgrade from implantable pulse generator or ICD; outcome of small studies and registries is inconsistent.[216,219,220] In an attempt to improve response rate to CRT, endocardial pacing has been proposed as a more physiological way of resynchronizing the heart.[224–227] The initial evidence from a single RCT and small observational studies indicates the feasibility and symptomatic benefit, which however is counterbalanced by an increased risk of lead failure and thromboembolic events. The incremental benefit on prognosis and reduction in symptoms of endocardial pacing over conventional pacing is also unknown.[224–227] Additional gaps in knowledge have been identified in the device type selection in patients with conventional indication to pacing (regardless of ejection fraction); indeed, it is unknown whether HBP, or CRT have an equal benefit in terms of reverse remodelling, survival, device longevity, and complications (*Table 16*).[228–234]

Apart from the missing evidence in the patient populations listed in *Table 16*, there is a number of emerging indications to CRT or HBP that may need future consideration including patients who develop a left bundle branch block or complete atrioventricular block after transcutaneous aortic valve implantation, or patients who have a

Table 15 Knowledge gaps in monitoring technologies in heart failure

Knowledge gaps	Available evidence	Feasibility of study	Ongoing trials
Need for defibrillator therapy in patients receiving a CRT device for heart failure	Conflicting observational data, no data from RCT	Moderate	RESET-CRT (NCT03494933)
Predictors of heart failure reversibility by eliminating/reducing (tachy-) arrhythmia burden	Observational, CASTLE-AF?	Moderate	None
Factors associated with PVC induced LV systolic dysfunction (cardiomyopathy)	Observational	Moderate	None
Aetiological role of left bundle branch block induced dyssynchrony in dilated cardiomyopathy	Observational	Low	None
Prediction of RV pacing-induced LV/RV dysfunction and/or AV-valvular regurgitation	Observational	Moderate	None
Discrimination between arrhythmia induced HF and HF induced arrhythmias	Observational	Moderate	None
Arrhythmia attributable factors in initiation and progression of heart failure	Observational	Low	None

CRT, cardiac resynchronization therapy; HF, heart failure; LV, left ventricle; PVC, premature ventricular complex; RV, right ventricle; RCT, randomized controlled trial.

Table 16 Knowledge gaps in pacing and CRT therapy in heart failure

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited; no RCT	Resolution gap feasible	Upcoming trials in the field (clinical trial.gov)
Device type selection (CRT-D or CRT-P) in *de novo* patients			Subanalyses of COMPANION, DANISH trials show no significant difference in outcome between CRT-D and CRT-P; meta-analysis using Bayesian approach shows 1.5% absolute risk reduction by CRT-D vs. ICD or CRT-P	A properly powered prospectively designed RCT is missing. Data from DANISH trial provides excellent data for power analysis of a new trial	RESET-ICD (primary prevention; CRT-D vs. CRT-P; DCM and ICM); planned, n = 2030 and 361 events; tested is non-inferiority of CRT-P vs. CRT-D (all-cause mortality). Anticipated endstudy completion date: May 2021 (www.clinicaltrials.gov: NCT03494933)
Downgrading in CRT patients without past ICD interventions (from CRT-D to CRT-P)			Single arm cohort study (DECODE): 7% of patients without ICD indication had event. A meta-analysis showed reduced anti-arrhythmic therapy in CRT responders and very low absolute arrhythmic risk in patients who increase their EF >45%	Needed is a randomized study investigating non-inferiority of downgrading from CRT-D to CRT-P in patients who showed good response to CRT and need 'box change'. Outcome may be combination of all-cause mortality and quality of life	None
Device upgrade from ICD or IPG to CRT-P/D			Upgrade to CRT device in patients with pacing-induced cardiomyopathy seems logical and has been tested in small randomized trials or registries. Large prospective RCTs are not available. Furthermore, there are controversial recommendations between the ESC 2013 guidelines for cardiac pacing (Class IB) and the 2016 ESC guidelines for the management of heart failure (Class IIb B)	A prospective RCTs comparing upgrade vs. no upgrade in patients with pacing-induced cardiomyopathy needs to be designed. Change in LVEF may be used as surrogate endpoint of morbidity and mortality to avoid a large trial assessing morbidity and mortality	Budapest trial and Cardia-MRI upgrade trial (USA)

Continued

Table 16 *Continued*

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited; no RCT	Resolution gap feasible	Upcoming trials in the field (clinical trial.gov)
HBP vs. BiV pacing in patients with CRT indication			There are multiple cases reports, and several single centre prospectively designed studies assessing the benefit of HBP in patients with CRT indications. One recently published study showed impressive left ventricular reverse remodelling results at 3 year follow-up	A controlled randomized trial comparing CRT vs. His pacing is needed to assess the efficacy but also the safety and long-term feasibility of His pacing when compared with CRT	There are several planned or ongoing studies comparing direct His-pacing as an alternative to biventricular pacing in symptomatic HFrEF Patients with true LBBB. Chronic pacing threshold, narrowing of the QRS, decrease in LV end-systolic volume >15%, and reduction in hospitalization are some of the endpoints
Device type selection (IPG, CRT-P, or HB pacing) in HFrEF patients with standard indication to pacemaker			Only one large randomized trial (Block-HF trial) showed a benefit (composite endpoint including mortality, heart failure decompensation, or increase in left ventricular end-systolic volume >15%) of CRT over RVA pacing in patients with LVEF < 50%. In contrast to this study, a subanlysis of the BIOPACE trial did not show a benefit of CRT over RVA pacing in patients with LVEF <50%	There are limited data available in this group of patients	HOPE-HF trial enrolling for brady and CRT
Device type selection (IPG, CRT-P, or HB pacing) in patients with standard indication to pacemaker			The randomized BIOPACE and BLOCK-HF trials addressed the potential benefit of BiV vs. RV pacing in patients with high degree/complete AV block. BIOPACE has never been published; results presented at a major international congress contradicted the finding of BLOCK-HF study. Recently, multiple single-centre studies reported the feasibility and excellent outcome of HBP in patients with standard indication to pacing	RCT in patients with Class I indication for pacemaker implantation for advanced or complete AV block. Three arms design: standard RV, HBP, or BiV pacing. Outcome shall be on soft and hard endpoints including atrial fibrillation recurrence	
CRT in patients with atrial fibrillation			CASTLE-AF included a small proportion of patients with CRT and paroxysmal and persistent AF. Beside small observational studies, there is no evidence for the value of pulmonary vein isolation performed before CRT implantation. The same holds for systematic use of His-bundle ablation	RCT on treatment strategy—pulmonary vein isolation first and then CRT-P/CRT-D vs. PVI alone. Also RCT comparing early AV ablation in CRT patients with permanent atrial fibrillation vs. device based algorithm for increasing the percentage of pacing or pharmacological therapy. Study outcome shall consider both hard and soft endpoints	

Continued

Table 16 *Continued*

Knowledge gaps	Less than 10 case reports	More than 11 case reports	Limited; no RCT	Resolution gap feasible	Upcoming trials in the field (clinical trial.gov)
Endocardial vs. conventional CRT			Small studies showed the haemodynamic benefit of endocardial vs. conventional epicardial CRT. The long-term ALSYNC, WISE-CRT, and SELECT-LV studies showed good CRT benefits of endocardial CRT systems, but also complications. Finally, a novel pacing approach with pacing the interventricular septum has been proposed	A prospective study testing comparing conventional biventricular pacing to endocardial CRT is highly desirable. However, technical issues of each of the alternative approaches represent a major challenge to conduct a randomized controlled study	
CRT in non-LBBB patients with first degree AV block and QRS duration 120–150 ms			Substudies in randomized RethinQ (narrow QRS) and MADIT-CRT (non-LBBB patients) show CRT benefit in patients with PR >230 ms	Required would be a randomized study in patients with long PR: no-pace/ICD vs. CRT-P/CRT-D; endpoints: echo and combined clinical endpoint	

CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; HBP, His-bundle pacing; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PVI, pulmonary vein isolation; RCT, randomized controlled trial.

Table 17 Knowledge gaps in assist devices in heart failure

Scientific question	Available evidence	Feasibility of study	Ongoing trials
Benefit from ICD in VAD	Meta-analysis	Yes	None
Benefit of VAD in VT/VF ablation	Multicentre observational	Yes	None
Rhythm vs. rate AF management in VAD	Observational	Moderate	None
VAD to assist cardiac arrest management	Observational	Likely	None
Use of VAD to suppress incessant VA	Small observational	Likely	None
Catheter ablation of VA in VAD patients	Observational	Likely	None

AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; VAD, ventricular assist device; VF, ventricular fibrillation; VT, ventricular tachycardia.

hypertrophic cardiomyopathy, or presents with functional severe mitral regurgitation. Of future interest is the role of personalized computational models in prediction of SCD, reverse remodelling (CRT/HBP responder), and heart failure hospitalization. Although all these latter groups of patients or approaches are of interest, we still need more evidence from large prospective single-centre studies before embarking on large RCTs. For these reasons, they are not included in *Table 16*.

Assist devices

While they are increasing in their use around the world, ventricular assist devices (VAD) remain a relatively rarely deployed therapy in a complex and sick population. Randomized studies are both ethically challenging and study patients are difficult to recruit in this setting. As such there is a paucity of good quality data describing the optimal management strategy associated with the use of these devices. *Table 17* summarizes knowledge gaps, based on the importance in terms of potential cost benefit and feasibility of studies being able to provide clinically useful evidence. There are no data describing when, if and what the role of VAD are in managing refractory sustained ventricular arrhythmia (VA). This is important because it is well recognized that off-loading the failing heart may reduce arrhythmia burden[235] and that VA are more common after left ventricular assist device (LVAD) implantation (see *Table 17*). Therefore, it is unclear whether LVAD reduces VA in the longer term or whether patients with refractory VA who are going to undergo LVAD should have

catheter ablation first. At present there is however no evidence that LVAD is an appropriate therapy for patients with intractable VA. Whether this means that VAD is not a useful therapy for cardiac arrest victims and in whom it should be deployed is unclear. There are a few reports of use of circulatory support for ablation of sustained VT in vulnerable patients, e.g. GUCH, but there is no evidence describing its value compared with conventional approaches or how often it is required.[236] Some observational studies suggest that VAD are associated with lower procedural success and higher mortality and complications,[237] while others suggest better than expected outcome.[238] This may reflect the higher complexity of patients selected for this therapy. Circulatory support devices such as the Impella have been used for support during VT ablation and can improve cerebral circulation during haemodynamically compromising tachycardia[239] but whether this results in better outcomes for VT ablation is not clear.

Management of arrhythmia in ventricular assist device

Atrial fibrillation is common after VAD implantation. The literature suggests that it is not associated with mortality and stroke risk[240] but is associated with significant cost and morbidity.[241] Data are needed as to how to manage or prevent AF post-LVAD placement as this has potential to significantly improve outcomes and cost of these procedures (see *Table 17*). There is no evidence that any form of rhythm control confers mortality or stroke benefit and AF may resolve after VAD implantation in over 40% of patients.[242] Ventricular arrhythmia storm is common early after LVAD implant.[243] Observational data reports that catheter ablation is feasible in patients with VAD. Successful ablation is associated with better outcome (possibly reflecting degree of patient pathology).[244] There are no data defining at what point catheter ablation should be used in preference to medical therapy or what medical therapy may be optimal in this patient group. Data suggests that ICD's may be protective in older generation LVAD, but there are non-randomized data suggesting that there may be no benefit to ICDs in non-pulsatile LVAD.[245,246] There are no randomized data examining whether either primary or secondary prevention ICD confer mortality benefit in LVAD.[247] Programming of ICD to limit inappropriate therapies has been shown in one, small, randomized trial to have no impact on shock frequency.[248]

Supplementary material

Supplementary material is available at *Europace* online.

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