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EHRA/HFA POSITION PAPER

European Heart Rhythm Association/Heart Failure Association joint consensus document on arrhythmias in heart failure, endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society

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Introduction

Arrhythmias confer a substantial risk of mortality and morbidity in patients with heart failure (HF), and this represents a major healthcare burden worldwide. There are at least 15 million patients with HF in Europe alone.[1] The overall prevalence of HF ranges between 2 and 3%, but increases sharply after 75 years of age, reaching 10–20% among those in the eighth decade of life.[1]

Heart failure hospitalizations are increasing, and many of these may be related to cardiac arrhythmias. Indeed, episodes of decompensation may be related to arrhythmias, such as atrial fibrillation (AF). Atrial fibrillation *per se* contributes to an increased risk of mortality and morbidity from stroke and thromboembolism, and silent AF is common among patients with HF, not infrequently leading to a first presentation of AF with an ischaemic stroke.[2] New developments in stroke prevention offer additional challenges in the HF patient.

Sudden cardiac death (SCD) is also a major cause of mortality among HF patients and is commonly related to cardiac arrhythmias, particularly ventricular arrhythmias (VAs).[3] In addition, associated co-morbidities, such as renal impairment, may influence cardiac arrhythmias, their complications, associated treatments, and prognostic implications.[4]

New developments in cardiac monitoring, cardiac resynchronization therapy (CRT), and other implantable devices have been introduced. These allow better detection and treatment of cardiac arrhythmias in HF, opening more opportunities for improvements in management.

To address the management of arrhythmias in HF, a Task Force was convened by the European Heart Rhythm Association (EHRA) and the Heart Failure Association (HFA), endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS), with the remit to comprehensively review the published evidence available, to publish a joint consensus document on arrhythmias in HF patients, and to provide up-to-date recommendations for use in clinical practice.

Epidemiology of arrhythmias in heart failure

Atrial fibrillation

Prevalence

The two constantly growing global health problems (that is, HF and AF) often co-exist, or may precipitate one another. Recent registry-based reports show that ~40% of patients hospitalized for

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HF already have a history of AF, up to 50% of patients have AF at baseline, and nearly 20% of patients may experience new-onset AF during the hospitalization.[5] In the EuroObservational Research Programme HF Long-Term Registry, AF was documented in 44% of patients hospitalized for acute HF and in 37.6% of patients with chronic HF (CHF).[6] The prevalence of AF among outpatients with HF is generally lower, ranging from 25 to 37%.[7] Patients with co-existing HF and AF are older, more frequently females, and have lower prevalence of coronary artery disease and higher prevalence of valvular heart disease or chronic non-cardiac diseases compared with HF patients without AF.[7]

The prevalence of AF increases with increasing severity of HF,[7] from <5% in patients with the New York Heart Association (NYHA) functional Class I symptoms[8] to nearly 50% in the NYHA Class IV patients.[9] The prevalence of AF is high in HF patients with preserved left ventricular (LV) ejection fraction (HF-pEF) as well. The co-existence of HF and AF may be, at least partly, explained by the presence of common risk factors, such as age, arterial hypertension, diabetes mellitus (DM), obesity, valvular dysfunction, and coronary artery disease.[7] However, data from preclinical and clinical HF studies suggest that there is a distinct myocardial substrate for AF, beyond the myocardial alterations attributable to common risk factors.[10,11]

Heart failure has been identified to be an independent risk factor for the occurence of AF [hazard ratio (HR) 3.20; 95% CI 1.99–5.16].[12] However, some studies have not identified AF as an independent risk factor for HF (see Supplementary material online, *Table S1*),[13–38] and the controversy may be partly explained by the complex epidemiology of HF and co-existence of AF that involves bilateral self-perpetuating mechanisms.

Of note, ivabradine [an inhibitor of the pacemaker I_f current, which may be used for the treatment of symptomatic CHF with left ventricular ejection fraction (LVEF) ≤35% and heart rate >75 b.p.m. in patients with sinus rhythm who are already taking beta-blockers, or when beta-blockers are contraindicated or not tolerated[39]] has been associated with a 15% increased risk of the occurrence of AF (risk ratio 1.15; 95% CI 1.07–1.24, $P = 0.0027$) in a meta-analysis of all randomized trials of ivabradine (a total of >20 000 patients), whereby the estimated number needed to harm would be 208 (95% CI 122–667) per year of treatment with ivabradine.[40]

Impact

The onset of AF may aggravate the signs and symptoms of HF, as also reflected by a peak oxygen consumption that is higher at anerobic threshold but lower at overall peak in permanent AF patients.[41] In the Framingham study, for example, the incidence of HF among AF subjects was 33 per 1000 person-years, and the incidence of AF among HF subjects was 54 per 1000 person-years.[22] In AF subjects, subsequent development of HF was associated with increased mortality (men: HR 2.7; 95% CI 1.9–3.7; women: HR 3.1; 95% CI 2.2–4.2). Likewise, the development of AF in HF subjects was also associated with increased mortality (men: HR 1.6; 95% CI 1.2–2.1; women: HR 2.7; 95% CI 2.0–3.6).[22] The relative contribution of AF and HF to the clinical status of many patients remains difficult to determine, as HF often begets AF and AF begets HF.

The two most common underlying cardiac disorders in patients presenting with stroke are AF and HF accounting for 15 and 9% of all strokes, respectively.[42] At least a half of HF patients with stroke also have AF, and in such patients 82% of all strokes are cardioembolic.[43]

Non-valvular AF bears a five-fold greater risk of ischaemic stroke and systemic embolism compared with sinus rhythm, and the risk further increases by ∼40% with the occurrence of HF. In turn, HF confers a 17-fold greater risk of stroke in the first month of diagnosis, and the occurrence of AF increases the risk by two- to three-fold[13–38] (see Supplementary material online, *Table S1* for an overview of clinical studies). Many patients apparently in sinus rhythm may also have 'silent' AF episodes associated with similar (or even greater) stroke risk as symptomatic AF, especially in the presence of AF.[44–46]

Heart failure has been inconsistently identified as an independent stroke risk factor in AF patients, but HF definitions in the trials were variable.[47] Accumulating data suggest that the stroke risk with HF-pEF is similar to HF with reduced ejection fraction (HF-rEF; or even greater).[48–50]

In summary, one-third of HF patients have AF, which may occcur without specific symptoms (silent AF), but remains a common cause of stroke and worsening of HF symptoms.

Ventricular arrhythmias

Prevalence

Ventricular arrhythmias straddle the spectrum from isolated and asymptomatic ventricular ectopy on an electrocardiogram (ECG) through to fatal ventricular fibrillation (VF). Coupled with their enourmously high spontaneous variability, this makes assessment of their prevalence and incidence within the CHF population extremely difficult. They are especially common in those with ischaemic aetiology and with a lower LVEF.[51] The risk of VA is also increased by concurrent co-morbidities, such as electrolyte disturbances, obstructive sleep apnoea (SA), hypoxaemia, catecholamine excess, and renal and hepatic dysfunction along with pro-arrhythmic drug effects.[4] Although both ventricular premature beats (VPBs) or non-sustained ventricular tachycardia (NSVT) as well as sustained ventricular tachycardia (VT)/VF are part of a broader definition of VAs in CHF, we know there is a large clinical gap between VPBs/NSVT and sustained VT/VF causing SCD. Although VAs (VPBs or NSVT) are common in HF, we cannot conclude that such VAs are necessarily associated with an increased risk of SCD. A sub-analysis of the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) trial has, however, demonstrated that rapid-rate NSVT in HF patients is associated with appropriate implantable cardioverter defibrillator (ICD) shock and all-cause mortality.[52]

Ambulatory ECG recordings detect VPBs or ectopy in virtually all CHF patients, especially common during sleep.[53] In general, the occurrence of SCD increases sharply within a few hours of rising in the morning.[54] On the other hand, in specific hereditary disorders such as Brugada's syndrome and J-wave syndrome, fatal VAs often occur during sleep. There has been little primary epidemiological evidence on the prevalence of VA in the general CHF population

Table 1 Studies of the natural history of ventricular arrhythmias in chronic heart failure: some examples

Author	Description	*N*	Prevalence/incidence
Studies of ventricular tachyarrhythmias in HF-rEF			
Podrid *et al.*[55]	Review of 13 case series baseline prevalences	1322	VPBs = 87%, NSVT = 45%
Cleland *et al.*[56]	Review of six CHF RCTs baseline	516–1080	Couplets or VPBs > 30/h = 60–80% NSVT = 30–60%
Liao *et al.*[57]	Sampling of national insurance data	7894	Incidence of VT/VF/SCD = 1.95% per year
Baldassero *et al.*[58]	Registry baseline	5517	Prevalence NSVT = 28.7%
Packer *et al.*[59]	SCD-HeFT trial FU	2521	Incidence of VT-related death 1.2% in the ICD group, 2.4% on amiodarone, and 3.0% on placebo
Studies of ventricular bradyarrhythmias in HF-rEF			
Cleland *et al.*[60]	Registry	11 016	Prevalence bradyarrhythmia = 6.0%
Studies of ventricular tachyarrhythmias in HF-pEF			
McMurray *et al.*[61]	I-Preserve trial baseline	4133	Prevalence of ICD use = 0.3%

CHF, chronic heart failure; HF-rEF, heart failure with reduced ejection fraction; HF-pEF, heart failure with preserved ejection fraction; ICD, implanted cardioverter defibrillator; NSVT, non-sustained ventricular tachycardia; RCT, randomized controlled trial; VPB, ventricular premature beats; VF, ventricular fibrillation; VT, ventricular tachycardia.

(*Table 1*). In the vast majority of cases, VAs are a complication of CHF secondary to cardiac damage, but they also can directly cause HF.[51]

In reviewing 13 early studies of VA in CHF, Podrid *et al.*[55] reported that 87% of CHF patients manifest VPBs or couplets and 45% had NSVT. Cleland *et al.* reviewed the field in 2002 and summarized the early drug trials in CHF [SOLVD (Studies of Left Ventricular Dysfunction), V-HeFT (Vasodilator Heart Failure Trial) I and II, PROMISE (Prospective Randomized Milrinone Survival Evaluation), and GESICA (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina) trials], which showed a prevalence of NSVT of 30–60% with little difference between NYHA Class II and III CHF. Taking into account that the detection of arrhythmias depends on the methods applied (e.g. resting ECG, Holter etc.), and that all these techniques have their limitations, the prevalence of VPBs and NSVTs is high and it is reasonable to assume that almost all patients with HF may have some degree of VA.

The most recent survey utilizing Taiwan's national health insurance database that covers the entire population analysed 7894 patients aged 40 years or over hospitalized for HF (but with no prior VT/VF/SCD or ICD) taken from a random sample of 1 million subject.[57] During a mean of 3.7 years of follow-up (FU), new-onset VT/VF/SCD as a combined endpoint occurred in 567 patients (7.2%, or 1.95% per annum). Multivariate analysis revealed an increased risk of VT/VF/SCD with age (2% increase per year), male gender (HR = 1.27; CI 1.07–1.51), co-existing coronary artery disease (HR = 1.42; CI 1.19–1.68), DM (HR = 1.45; CI 1.21–1.74), chronic kidney disease (CKD; HR = 1.55; CI 1.26–1.90), and interestingly, a reduced risk in patients taking a statin drug (adjusted HR = 0.57; CI 0.47–0.70).[57]

Impact

Ventricular arrhythmias are frequently seen as the cause of sudden death or resuscitated sudden death in CHF.[3] Indeed, 50% of all deaths in advanced CHF are sudden and the assumption has been that a significant proportion of these are due to VT/VF.[62] As the severity of CHF increases, the percentage of deaths described as sudden decreases, although the absolute risk of VA and sudden death probably continues to increase. Chronic heart failur doubled the risk of subsequent serious VA in the TOVA (Triggers Of Ventricular Arrhythmias) study of 1140 ICD implantees (44% with baseline CHF).[63] The risk of ICD discharge for VT or VF at 1 year was 12.1% among patients with CHF and 6.5% among those without.

In a large (5517 patient) outpatient registry of CHF, 28.7% of which with history of VT and left bundle branch block (LBBB, which were present in 25.2% patients), were associated with an increased risk of mortality (HR 1.70; 95% CI 1.41–2.05) and sudden death (HR 1.58; CI 1.21–2.06) over a 1-year FU period.[58] In the same study, VT (i.e. episode >3 beats in 24 h Holter) was an independent predictor of both total mortality (HR 1.76; 95% CI 1.28–2.42) and sudden death (HR 1.96; 95% CI 1.25–3.08) at 1 year. Ventricular tachycardia was not associated significantly with LBBB in this report.

In 2521 subjects in the SCD-HeFT trial (randomized to ICD, amiodarone, or placebo, all with Class II or III HF and followed up for a median of 45.5 months), adjudication for mode of death was performed, classifying death into sudden death presumed to be VT-related, bradyarrhythmic, HF-related, or a result of other causes.[59] During FU, deaths occurred in 182 of 829 subjects (22.0%) randomized to receive an ICD, in 240 of 845 subjects (28.4%) randomized to amiodarone, and in 244 of 847 subjects (28.8%) randomized to placebo. Of these, cardiac mortality resulting from sudden death presumed to be ventricular tachyarrhythmic occurred in only 37 subjects (4.5%) in the ICD group, in 75 subjects (8.9%) in the amiodarone group, and in 95 subjects (11.2%) on placebo. This mode-of-death analysis of SCD-HeFT suggests that the ICD-related reduction in mortality was almost all due to protection from sudden death presumed to be ventricular tachyarrhythmic.

Ventricular arrhythmias in heart failure with preserved ejection fraction

Typically, discussions on the risk of VA in CHF mainly refer to HF-rEF. Although patients with HF-pEF have a high rate of supraventricular arrhythmias, the occurrence of VA appears to be lower in the few studies focusing on this population.[61,64] In the major treatment trials that have recruited HF-pEF patients in any numbers [I-Preserve (Irbesartan in Heart Failure with Preserved Ejection Fraction), DIG-PEF (Digitalis Investigation Group-Preserved Ejection Fraction), CHARM-Preserved (Candesartan in Heart failure Assessment of Reduction of Mortality and morbidity), and PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure)], the rates of ICD use have been low (0.3–0.8%) as has antiarrhythmic drug (AAD) use (8.7–10%).[61,65–67]

Hypertrophic cardiomyopathy (HC) may result in HF-pEF and HF-rEF, and is associated with an increased rate of SCD of ~1%/year.[68,69]

In summary, AF and VAs are very common in CHF, particularly in patients with reduced LVEF. Ventricular arrhythmias are associated with an increased risk of sudden death. Implantable cardioverter defibrillators have reduced this risk, but it remains a common mode of death for many end-stage HF patients.

Other arrhythmias in heart failure including bradycardia

Atrial tachycardia and atrial flutter

Various pathophysiological mechanisms operating in HF create potent arrhythmogenic substrates, triggers, and modulators, which facilitate the development of cardiac arrhythmias in HF patients. Thus, such patients may also experience focal atrial tachycardias (ATs) or atrial macroreentrant arrhythmias [atrial flutter (AFl) and AF].[70] The exact prevalence of AT/AFl in HF is less well known, but it has been suggested that at least 30% of HF patients have non-sustained AT.[9]

The presence of atrial tachyarrhythmias may influence CRT or sometimes may induce inappropriate therapy from the implantable defibrillator.[71,72] Indeed, paroxysmal ATs may be particularly challenging to differentiate from HF-related sinus tachycardia. Sudden changes in heart rate should draw attention to the diagnosis, and an electrophysiology (EP) study may even be needed for a definite diagnosis.[73] In general, atrioventricular (AV) node slowing agents are less effective, many antiarrhythmic drugs are contraindicated due to HF, and electrical cardioversion is of little help in focal ATs. Since catheter ablation (CA) can be technically demanding due to the presence of HF and/or device electrodes in cardiac chambers, AT recurrence rates may be higher than in patients without HF and a hybrid epicardial–endocardial ablation may be considered in selected patients (i.e. symptomatic patients with ATs refractory to antiarrhythmic drugs).[74] Ablation of the AV node with pacemaker implantation may be a therapeutic option in these patients. In case of permanent AF, AV node ablation is most effective for making possible >95–98% biventricular pacing, a value linked to CRT efficacy and long-term survival.[75] Although AFl is much more likely to be cured by ablation than AF, AFl must be treated the same as AF with respect to the risk of thromboembolic events.[76]

Bradyarrhythmias

The EuroHeart Failure survey ($n = 11\,016$) showed that 6% of patients with a HF-related admission also had bradycardia; in the whole cohort, over 8% had a pacemaker implanted and their clinical course was complicated by a bradyarrhythmia in about one in six patients.[60] However, this may underestimate pacing requirements in patients who had an ICD implanted. Reversible bradycardia and AV block may result from drug toxicity during HF treatment (e.g. digoxin, beta-blockers, etc.), electrolyte disorders, etc. Irreversible conduction disturbances require pacemaker therapy, whereby the need for cardiac resynchronization and/or defibrillator must be considered. Chronotropic incompetence during exercise is another common finding in HF patients. Prevalence depends on cut-off, which is not uniformly defined, but ranges between 70% and more commonly 80–85% of the predicted maximal heart rate during exercise.[77] Chronotropic incompetence has been reported in ~30% of patients,[78] and more advanced stages have been suggested as a marker of worse prognosis.[79]

In summary, regular supraventricular tachycardias are also common in HF. The selection of AADs is limited and CA may be considered even though associated with a lower success rate in HF.

Cardiac arrhythmias in heart failure post-myocardial infarction

Prevalence

Cardiac arrhythmias are common in the post-myocardial infarction (MI) period, especially if HF develops. The likelihood of arrhythmia-related death is highest during the acute phase of an infarction, and remains higher than for the general population.

In the CARISMA (Cardiac Arrhythmias and Risk Stratification After MyoCardial Infarction) study using continuous rhythm monitoring (implanted event recorder) in HF patients following acute MI, new-onset AF was the most common arrhythmia (28% of patients within 2 years).[80] Atrial fibrillation in the post-MI setting is associated with an increased risk of mortality, stroke/thromboembolism, HF exacerbation, longer hospital stays, and higher healthcare costs. The detailed management of AF patients presenting with an acute coronary syndrome (ACS), requiring percutaneous coronary intervention (PCI), or stenting has recently been reviewed in a joint European consensus document, endorsed by the HRS and APHRS.[81]

Impact

Ventricular arrhythmias also carry a grave prognosis in the post-MI setting, when HF is present. Of all patients having an MI, 25–35% will die before receiving medical attention, most often from VF. Nonetheless, in-hospital mortality has fallen from ~11% in 1990 to ~9% in 1999, to 4.4% in 2006.[82] Most of the decline was due to decreasing mortality among patients with ST-elevation myocardial

infarction (STEMI) as a consequence of early reperfusion therapy (thrombolysis/primary PCI). Both reperfusion modalities lead to a decrease in arrhythmias and death, but VAs following primary PCI were one-fourth to 50% less common than with standard medical therapy in a recent study.[83] According to an analysis by the National Registry of MI, in-hospital mortality rate was 5.7% among those receiving reperfusion therapy, when compared with 14.8% among those who were eligible for but did not receive such treatment.[84]

In a meta-analysis of 23 studies of primary PCI (3872 patients) and thrombolysis (3867 patients), mortality rate at 4–6 weeks after treatment was significantly lower among those who underwent primary PCI (7 vs. 9%; $P = 0.0002$).[85] In another analysis, the arrhythmia rate was lower in patients with primary PCI in acute MI (46.2%) than in those receiving thrombolytic therapy (64%; $P < 0.01$) and depended on the achieved thrombolysis in myocardial infarction (TIMI) flow, which was higher with primary PCI (mean 2.46 ± 0.21), than the flow achieved after thrombolysis (mean 2.12 ± 0.16).[86] Overall, the lowest arrhythmia rate was found in patients with TIMI 3 flow (17.2%) achieved with any procedure after acute myocardial infarction.

In HF patients continuously monitored following acute MI in the CARISMA study, 21.9% showed episodes of significant bradycardia. Interestingly, sinus bradycardia and higher degree AV block (the latter observed in 9.8% of patients), but not VT, were significantly associated with an increased all-cause mortality.[80]

Natural history of the infarct

Late HF and death may result from progressive LV dilatation and deterioration of LV function, a process known as remodelling, which is initiated by expansion of the infarcted myocardium and may lead to formation of an LV aneurysm. The infarcted myocardium or an LV aneurysm may also predispose for VAs. The extent of LV damage is the major determinant of arrhythmia risk in post-MI patients. Indeed, patients admitted to the hospital with acute MI complicated by HF have a much higher risk for in-hospital morbidity and mortality, and are less likely to be treated with reperfusion therapy and medications with proven mortality benefit.[87]

A challenge to management of arrhythmia and mortality risk after acute MI is the changing substrate within the first 3 months after MI. The Healing and Early Afterload Reducing Therapy (HEART) Study[88] studied 352 patients with Q-wave anterior MI treated with reperfusion therapy and ramipril. Only 3.4% had normal LV function on Day 1, but by Day 90, 66% had improved their LVEF with a mean improvement of 4.5, and 22% had complete recovery by Day 90; however, despite early revascularization, early mortality and sudden death risk remained high. In 16 793 patients presenting with catheterization for MI, significant early mortality was observed in patients with LVEF 35% or evidence of conduction system disease (LBBB or right bundle branch block).[89] Among 2997 patients with MI, 30-day SCD incidence was 1.2%, whereas it was 1.2%/year thereafter.[90]

Thus, LV function and the risk of SCD appear to improve in a significant proportion of patients following reperfusion, but in the first 30 days after MI the risk of SCD remains high.

Other clinical scenarios

Arrhythmia-induced heart failure

In addition to worsening the pre-existent HF, persistent cardiac arrhythmia with uncontrolled ventricular rate and/or irregular ventricular contraction may result in LV dilatation and systolic dysfunction with signs and symptoms of HF (so-called tachycardia-induced cardiomyopathy).[51] True prevalence of tachycardia-induced cardiomyopathy is unknown (and likely underestimated).[91] With effective treatment of the culprit arrhythmia, the condition is partially or completely reversible, depending on the presence or absence of other structural heart disease.[92] The diagnosis can be made when recovery of the LV dysfunction without other identifiable causes occurs after solving the arrhythmia.

Most commonly, chronic HF-rEF may be induced by high ventricular rate AF or frequent VPBs.[93] When systolic HF occurs in the setting of frequent premature beats, the arrhythmia burden usually exceeds 10 000 beats in a 24 h period or 15–20% of all cardiac cycles in a 24 h period.[94] Also, a premature ventricular QRS complex duration of ≥140 ms has been associated with greater likelihood for the LV function impairment and less reversible LV dysfunction.[95,96] After successful CA of the substrate of the spontaneous arrhythmias, a significant improvement in ventricular function, in many cases complete normalization of LV systolic function, has been reported.[97] Most of the patients with complete reversal of LV dysfunction have premature beats originating in the outflow region of the ventricles and no associated structural heart disease.

In the setting of AF, treatment of the arrhythmia (i.e. rhythm control with cardioversion, antiarrhythmic drugs or AF ablation, or rate control with drugs or ablate and pace strategy) usually improves LV function, but in some patients with chronic AF and controlled ventricular rate the recovery of depressed LV function may be achieved only by AV junction ablation with permanent pacing.[98] In addition, it has been reported that on routine monitoring prior to AF ablation, most patients with impaired LV function had a controlled ventricular rate,[99] thus suggesting that regularity of ventricular contraction, and not only the rate, may play a role in the development of tachycardia-induced cardiomyopathy. Atrial flutter may also lead to LV dysfunction, which is usually reversed with AFl ablation.[100]

Less commonly, 'non-paroxysmal' supraventricular tachycardias such as incessant AT due to increased automaticity of an ectopic atrial pacemaker, incessant AV reciprocating tachycardia (that is, persistent junctional reciprocating tachycardia), or incessant non-reentrant AV nodal tachycardia may cause LV dysfunction, and complete recovery of LV function after CA is evident in most patients.[73,101]

Conditions associated with altered LV synchrony, such as LBBB, may lead to worsening of the LV global function and clinically overt HF.[102] Left bundle branch block is commonly present in patients with structural heart disease, but a LBBB-induced cardiomyopathy has been recently described in six patients with previously normal LVEF and no identifiable cause of cardiomyopathy other than LBBB; CRT resulted in the near resolution of the specific cardiomyopathy in all six patients.[103] Ventricular pre-excitation and

chronic right ventricular (RV) pacing have been also associated with tachycardia-induced cardiomyopathy.[104]

Given the potential for reversal of LV dysfunction with appropriate treatment, arrhythmia-induced HF should be suspected in patients with newly diagnosed LV dysfunction and a persistent or frequently occurring tachycardia or premature ventricular complexes. However, the culprit arrhythmia may not be evident at the time of patient presentation, a true tachycardia is not necessary to induce LV dysfunction (e.g. in AF), and the co-existent underlying structural disease does not exclude tachycardia-induced cardiomyopathy. Evidence of previously normal LV function or LV dysfunction disproportional to the severity of underlying heart disease should raise a suspicion of tachycardia-induced cardiomyopathy, and patients diagnosed with 'idiopathic' dilated cardiomyopathy should be intensively monitored for subclinical arrhythmias. Once the treatment of arrhythmia has been initiated, close monitoring of HF symptoms and LV function is needed for definite diagnosis of tachycardia-induced cardiomyopathy, which can be made only after documentation of improvement in HF and LV dysfunction.[91]

Although improvement in LV function may be seen only a week following the arrhythmia treatment, recovery of LV function usually takes 3–4 months or more.[105] In case of arrhythmia recurrence, or with HF medication withdrawal, a rapid decline in LV function with delayed recovery after arrhythmia cessation has been reported, suggesting the presence of persistent structural myocardial abnormalities in patients with tachycardia-induced cardiomyopathy.[91] Hence, maintenance of proper medical regimen for HF and regular monitoring for arrhythmia recurrence is advised even after complete LVEF recovery, and ICD therapy for primary prevention of SCD should be considered in patients with persistent residual LV dysfunction.[106]

Cardiac arrhythmias in patients with sleep apnoea and heart failure

Sleep apnoea (a repetitive collapse of the upper airway during sleep, with chronic intermittent hypoxia and recurrent arousals) has the two principal phenotypes, obstructive SA (OSA) and central SA (CSA).[53,107] Large oscillations in intrathoracic pressure with intermittent hypoxaemia, hypercapnia, and catecholamine surges ultimately result in endothelial dysfunction, autonomic dysregulation, altered haemostasis, increased oxidative stress, inflammation and metabolic dysfunction, and cardiac structural changes such as increased LV mass index and left atrial volume occur even in patients with previously normal hearts.[108,109] Sleep apnoea commonly co-exists with many conditions, including hypertension, coronary disease, HF, CKD, and stroke, but is an independent risk factor for cardiovascular morbidity and mortality.[107]

True prevalence of SA is likely underestimated, and available data suggest that SA is present in ~50% of HF patients, with CSA being slightly more prevalent in HF-rEF and OSA in HF-pEF, both causing similar pathophysiological alterations in HF.[110] Sleep apnoea is associated with a spectrum of conduction disorders and cardiac arrhythmias. Bradycardia is common (some degree of conduction block has been reported in ~10% of SA patients, with prolonged [>3 s] pauses during apnoea), and increased prevalence of VAs ranging from VPBs to malignant VTs has also been reported. Obstructive sleep apnoea and AF share some common risk factors (e.g. HF, ageing, hypertension, coronary disease, obesity, etc.), which may contribute to frequent co-existence of the two conditions. However, OSA has been reported to independently increase the risk of incident AF and AF recurrence post cardioversion or AF ablation.[111,112]

Oxygen administration and treatment with continuous positive airway pressure alone, or in combination with atrial overdrive pacing, reduce the burden of cardiac arrhythmias and conduction disorders in SA patients.[112] Importantly, effective SA treatment also reduces mortality in HF patients with SA.[107,113,114]

Cardiac arrhythmias in patients with chronic kidney disease and heart failure

Chronic kidney disease is defined as evidence of renal impairment or a glomerular filtration rate (GFR) of $\leq$60 ml/min/1.73 m^2.[115] Hypertension and DM are the most common causes of CKD, and CKD is an independent risk factor for cardiovascular diseases (CVDs), associated with increased prevalence of HF, ischaemic heart disease, valvular calcification, and cardiac arrhythmias (most commonly AF).[116,117] A complex cardiac and renal interreaction, often referred to as the 'cardiorenal syndrome', is characterized by left ventricular hypertrophy and LV dysfunction.[117] Increasing evidence suggest that pathophysiology and complications of CVD may differ in patients with and without CKD, and management strategies evaluated in the general population may have different risk–benefit rations in CKD patients.

Less than one in five HF patients has a normal GFR, and HF prevalence in CKD patients increases with severity of renal dysfunction. Premature CVD (most commonly HF or coronary disease) is the leading cause of death in CKD patients (mortality is slightly higher with HF-pEF compared with HF-rEF).[117] The risk of SCD incrementaly increases with a decreasing GFR, accounting for 25% of all-cause mortality in patents with end-stage renal disease (ESRD), likely due to combined influence of underlying CVD and dialysis-specific factors (e.g. rapid acute electrolyte and fluid shifts, chronic electrolyte imbalance, etc.). About half of SCDs in the general population are due to VT or VF, but in CKD events underlying SCDs are less well known, with a wide range of VAs being observed. More data are needed to inform optimal strategies for SCD prevention in CKD patients. Data on the prevention of SCD using antiarrhythmic drug therapy are lacking, and device implantation in ESRD patients is associated with a five-fold greater risk of complications and four-fold higher short-term mortality.[117] Beta-blockers (cardioselective and non-cardioselective) can be safely administered in CKD patients without dose reduction, and their use has been associated with reduction in cardiovascular mortality.

Overall, patients with HF and CKD have a high burden of cardiac arrhythmias. Almost a third of patients with CKD have AF, and a half of AF patients may have some degree of renal dysfunction. The risk of AF increases with increasing severity of renal impairment, and incident AF further contributes to the risk of ESRD. Heart failure patients with both AF and CKD have higher mortality and

higher risk of stroke compared with HF patients with only AF or CKD.[116] In HF patients with AF and mild-to-moderate CKD, oral anticoagulation is warranted, with careful monitoring due to an increased risk of bleeding. Data on patients with ESRD are insufficient to support *routine* use of oral anticoagulant therapy for the primary stroke prevention, but in ESRD patients with prior stroke the risk of recurrent event is so high that the use of well-managed warfarin seems justified (individual patient values and preferences should be also considered).[118–120]

Other cardiac arrhythmias (e.g. AFl and atrioventricular nodal reentrant tachycardia) are less common in patients with HF in CKD. Most antiarrhythmic drugs can be used in ESRD without dose adjustments, and CA may be associated with an increased risk of vascular access complications, but is not contraindicated in patients on dialysis. Owing to autonomic dysfunction, bradycardia is not rare in CKD patients and may require pacemaker therapy.[117]

Drug-induced long QT syndrome in patients with heart failure

It is well known that LV hypertrophy and congestive HF are associated with abnormalities of ventricular repolarization.[121] Both diseases can be considered as risk factors for drug-induced long QT syndrome, which may be caused by numerous cardiac as well as non-cardiac drugs. Drug-induced excessive corrected QT interval (QTc) prolongation is often associated with torsade de pointes polymorphic VT. QT interval depends on heart rate, and despite its limitations, Bazett's formula is most often used in clinical practice for heart rate correction.[99] This arrhythmia may cease spontaneously or degenerate into VF. Females have longer QT intervals and are more prone to torsade de pointes after puberty. The list of drugs affecting the QTc interval continues to grow, and an updated list of specific drugs that may prolong the QTc interval can be found at www.qtdrugs.org. Among those, amiodarone is often used in HF patients, e.g. for rate/rhythm control in AF and also to treat VT, but at the same time often induces QT prolongation associated with arrhythmogeneity. Patients who have a history of amiodarone-induced (torsades de pointes) tachycardia have an increased risk of SCD[122] and should be closely monitored for QT time. In addition, sotalol bears a considerable risk of drug-induced long QT syndrome and VA.[123,124]

In HF patients taking such drugs, regular ECG measurements should be considered, and electrolyte disturbances (particularly hypokalaemia) should be corrected before starting treatment. A serum potassium level above 4 mmol/L may be desirable in HF patients.[125] A normal QRS duration should be provided, since in particular polymorphic ventricular tachyarrhythmias are often associated with QTc values exceeding 500 ms or more.[126,127] When such abnormal QTc values are observed, complete withdrawal of the causative drug or at least a substantial dose reduction should be considered.

Heart failure due to familial cardiomyopathy—SCN5A mutations

In rare cases, familial dilated cardiomyopathy may result from a mutation in the SCN5A gene. The patients often present with cardiac conduction abnormalities and/or a Brugada syndrome like phenotype.[128] Several drugs have been reported to induce or aggravate the Brugada ECG phenotype (i.e. the typical ECG manifestation), and to increase the risk of ventricular tachyarrhythmias (e.g. antiarrhythmic drugs, local anaesthetics, see www.brugadadrugs.org). It is necessary to advise affected patients not to use these drugs, or to do so only in controlled conditions.

Arrhythmias in patients with left ventricular assist devices

Ventricular assist device therapy has been successfully used in patients with incessant ventricular tachyarrhythmia. However, assist device therapy itself is associated with an increased risk for ventricular tachyarrhythmia.[129] The underlying mechanism is unclear and may include, besides others, scarring at the LV insertion site, operative trauma, mechanical unloading of the LV, suction of the LV wall, and myocardial ischaemia.[130] It has to be considered that patients who receive a LV assist device have a high intrinsic arrhythmic risk. Most of these patients have an ICD. The available data suggest that concurrent ICD and assist device therapy is feasible and safe.[131,132] Some centres routinely implant an ICD after assist device implantation. However, the prognostic benefit of ICDs in left ventricular assist device (LVAD) patients remains to be determined. Furthermore, optimal ICD programming has not been defined and should be performed on an individual patient basis.[133]

Other cardiomyopathies

Several other forms of cardiomyopathy such as arrhythythmogenic right ventricular cardiomyopathy, sarcoidosis, and hypertrophic cardiomyopathies are associated with an increased risk of VA and SCD, may, or may not be associated with HF symptoms as reviewed previously.[69,134,135]

Pathophysiology—a brief overview

Arrhythmogenesis in cardiac remodelling and chronic heart failure

Ventricular arrhythmias are an important mechanism to explain SCD in the HF population. These patients frequently go through transitions/adaptations that are collectively called ventricular remodelling. This encompasses (molecular) changes in electrical, structural, metabolic, and contractile variables, all aimed at the preservation of adequate cardiac output. Numerous signalling pathways have been documented to be responsible for these (maladaptive) remodelling processes and arrhythmogenic events, including the beta-adrenergic pathway, renin angiotensin aldosterone system (RAAS), and Ca-Calmodulin-dependent kinase II (CaMKII)- and calcineurin-mediated signalling.[136]

The 'external' triggers of arrhythmias such as mechanical stretch (volume), neurohumoral activation, or other stressors

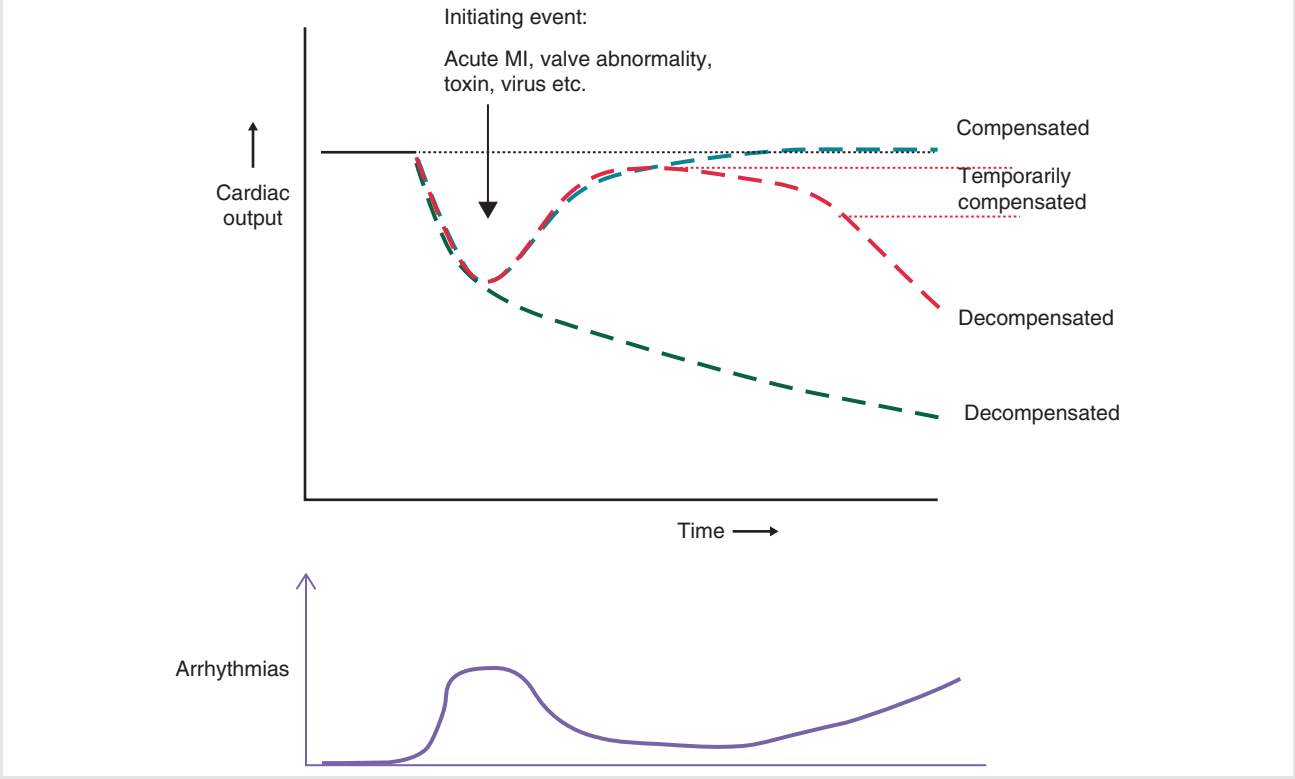

Figure 1 Arrhythmogenesis during the transition to chronic heart failure.

(e.g. systemic inflammation) deserve mention. Progression of the disease will recapitulate these events (over and over) but at a more severe level, with progressive pump dysfunction[137] (*Figure 1*).

Normal contractile performance is a delicate balance between numerous cellular processes. It is a balanced interplay between individual transsarcolemmal sodium (Na)-, potassium (K)-, and calcium (Ca)-channel currents and the intracellular Ca transient, which together shape the action potential (AP).

Ventricular remodelling and arrhythmogenesis

Mechanical stretch (increased myocardial wall tension) and neurohumoral activation trigger an inotropic response that initially results in a supernatural (compensatory) contractile performance, but at the same time are strong triggers of myocardial hypertrophy and fibrosis. At an early stage cardiomyocytes are chracterized by prolonged APs, larger calcium transients, and increased intercellular heterogeneity in repolarization (electrical remodelling). Several ion currents/pumps are downregulated, including potassium (K) channels, whereas the sarcolemmal Na/Ca exchanger may perform at a higher level. Ca-stored intracellularly in the sarcoplasmic reticulum (SR) and Ca turnover are increased. Arrhythmias in the form of ectopic beats may occur in this setting due to (i) spontaneous Ca release of the overloaded SR that will create inward currents after [delayed after-depolarization, ADs, and/or before (early ADs)] repolarization, and/or (ii) window currents that reinitiate depolarizations.

Numerous factors can perpetuate these ectopic beats to tachycardias: altered excitability, changes in cell-to-cell connectivity (downregulation of connexins), spatial dispersion of repolarization, and increased fibrosis during remodelling leading to impaired conduction (and conduction block), important ingredients for re-entrant arrhythmias.[137]

In the dilated heart with systolic (and diastolic) dysfunction, the cells are exhausted and cannot maintain a proper $[Ca]_i$ equilibrium: defective Ca homeostasis, in which regulatory mechanisms are no longer functioning properly. More ion currents are dysregulated, such as an increased late Na current and a reduced transient outward current (Ito). The microdomain of the calcium-release channel of the SR (ryanodine receptor) is altered. This further prolongs and destabilizes the AP, leading to heterogeneities in APs between ventricular regions, which will favour re-entrant arrhythmias. The Ca transient is severely reduced in amplitude and increased in duration. Moreover, there is an increased diastolic Ca concentration, which limits performance further.

In the whole heart, the normal cavity wall thickness ratio is no longer present (dilatation). Conduction is further slowed, interstitial fibrosis more dominantly present, energetics reduced with mitochondrial dysfunction, increased oxygen stress, and apoptosis: all factors reinforcing the negative turns. Additionally, these changes in chamber geometry and altered activation patterns facilitate the pathogenesis of complex arrhythmias.

In summary, arrhythmias in HF are a consequence of altered cardiomyocyte properties and myocardial tissue composition in HF facilitates sustained arrhythmias.

Detection of arrhythmias

Rhythm evaluation in HF aims to: (i) establish diagnosis and monitor patients with suspected arrhythmia-related symptoms, (ii) assess the risk of SCD or arterial embolism, and (iii) identify asymptomatic ('silent') arrhythmias that may contribute to the progression of LV dysfunction.[138,139]

Palpitations or syncope raise the suspicion for paroxysmal arrhythmias, but patients may present with less specific symptoms.[140] Arrhythmias are common in HF and should be considered as a trigger of clinical deterioration. However, recorded rhythm abnormalities need to be correlated with concurrent symptoms. Broad complex tachycardia in HF patients should be managed as VT in the absence of convincing evidence for aberrant conduction of a supraventricular rhythm.[141] Sustained VTs (30 s) are rarely asymptomatic in HF patients, and the diagnostic approach is guided by the presence of symptoms and degree of structural heart disease. As in general, arrhythmias are very common in HF patients, the aim for rhythm monitoring and its value for the management depends on the clinical condition (*Table 2*).

In patients with advanced HF (EF < 35%), NSVTs are very common on 24 h ambulatory ECGs (60–80% of patients), but not independently associated with worse outcomes.[142,143] In HF patients with less severely reduced EF (35–50%), NSVTs may indicate an increased risk,[144] but at present there is no evidence that suppression of NSVTs improves prognosis.

Table 2 Rhythm monitoring in heart failure patients

Clinical condition	Aim for rhythm monitoring
No arrhythmia-related symptoms	
Stable HF patients with EF <35%	• Screening for AF • No additional value for SCD risk
Stable HF patients with EF 35–50%	• Screening for AF • Value for SCD prophylaxis not established
Stable HF patients with preserved EF	• Screening for AF • Value for SCD prophylaxis not established
Post-myocardial infarction, EF <40%	• Detect asymptomatic arrhythmias that may require therapy
Symptoms suspicious for arrhythmias	
Symptoms at rest	• Correlate arrhythmia with symptoms
Symptoms during exercise	• Correlate arrhythmia with symptoms
Syncope in patients with reduced EF or structural heart disease	• Evaluate risk for SCD and sustained VT

AF, atrial fibrillation; EF, ejection fraction; HF, heart failure; SCD, sudden cardiac death; VT, ventricular tachycardia.

The role of rhythm monitoring in HF-pEF patients has not been established. Therefore, routine ambulatory screening for VAs in HF patients without related symptoms is not recommended. Following acute MI, the incidence of both AF and VAs is increased. In the CARISMA study, continuous arrhythmia monitoring by an implantable loop recorder in patients with reduced EF (<40%) for 2 years following acute MI detected potentially relevant arrhythmias in 46% of all patients, which were mostly (86%) asymptomatic,[80] suggesting a potential benefit of closer rhythm monitoring in patients following acute MI.

The majority of symptomatic HF patients with severely reduced EF are eligible for ICD implantation. Current ICDs allow several zones for VT/VF detection and therapy defined as an interval, which should contain the relevant VT rate (cycle length). However, in the absence of documented VTs, patient-specific adaptation of detection criteria does not provide benefit over standardized empirical ICD programming.[145] In patients with primary prevention ICDs, slow VTs are rare and usually tolerated.[146]

The recent MADIT-RIT (Multicenter Automated Defibrillator Implantation Trial to Reduce Inappropriate Therapy) (all had primary prevention indication for ICD) and ADVANCE (Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients) III (75% had primary prevention indication) trials indicated that allowing for a longer VT duration before therapy or limiting detection/therapy to fast VTs and VF may be safe and even provide morbidity and mortality benefit.[147,148] Therefore, in asymptomatic patients with ICDs for primary prevention, programming according to the detection criteria specified in these studies may be considered. However, evidence is yet insufficient for 'permissive' VT programming in secondary prevention of VAs.

In patients with recurrent VA, VT rate can be slower than the programmed lower rate limit for detection (e.g. related to antiarrhythmic drug therapy) and thus escape ICD therapy. Therefore, in patients with arrhythmia symptoms but no corresponding episodes recorded by the ICD, programming of an additional detection zone may be indicated to guide clinical management. While most recent devices are by default programmed to detect atrial arrhythmias, rate and sensitivity adjustments may be needed in individual patients to achieve appropriate atrial monitoring. The current ESC guidelines also recommend remote monitoring for implanted devices, not only to detect VAs and device-related problems but also to allow early detection of AF, which otherwise may remain unnoticed and untreated before the next visit.[197]

Symptoms are poor markers for AF. AF episodes are silent in 20–40% of patients,[149] and AF is more commonly seen in patients with HF. In the ASSERT (ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial), silent atrial tachyarrhythmias of >6 min duration (these were adjudicated events rather than all being atrial high rate episodes of >6 min) were associated with an increased stroke risk.[150] Heart failure (with preserved or with reduced EF) is a strong risk factor for incidental AF and indicates

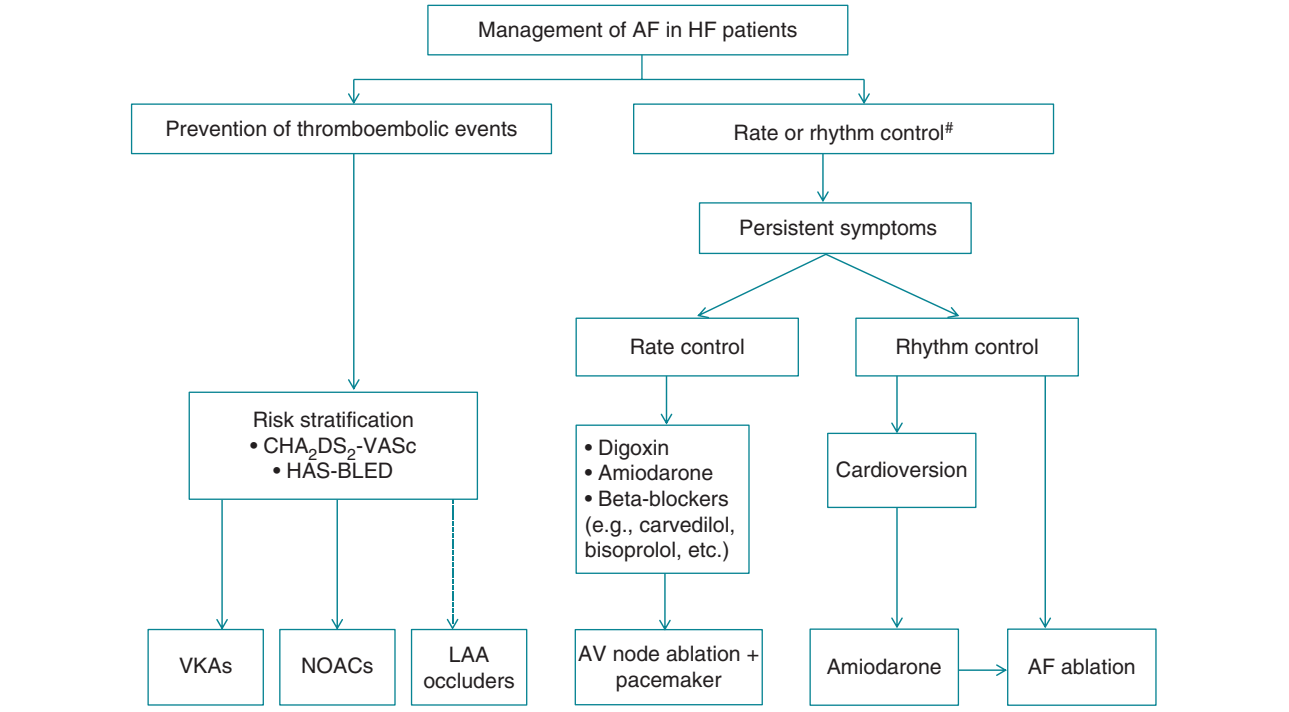

Figure 2 Management of atrial fibrillation in heart failure patients. #As recommended by current guidelines. AV, atrioventricular; AF, atrial fibrillation; HF, heart failure; LAA, left atrial appendage; NOACs, non-vitamin K-dependent oral anticoagulants; VKAs, vitamin K antagonists.

the need for closer rhythm monitoring in patients without prior history of AF—thus, pulse taking and ECG recording should be part of a routine in all HF patients, and AF screening in such patients may be useful.[44] However, sensitivity of sporadic ECGs in detecting paroxysmal AF is low. Even though sensitivity improves by regular ambulatory Holter recordings, the majority of patients with paroxysmal AF may not be detected. Ongoing studies evaluate the role of implanted loop recorders for the first diagnosis of AF in high-risk patients.[151] New technologies may help with AF detection, including smartphone devices,[45] especially for those who do not have devices (many of who have HF and the device would help in AF detection).

In summary, frequent routine rhythm monitoring is indicated in HF patients to detect AF, whereas rhythm screening or therapy for asymptomatic VAs is generally not recommended.

Management aspects

Atrial fibrillation

A recommended management strategy for AF in HF patients is shown in *Figure 2*.

Risk stratification and anticoagulation

The ESC AF guidelines recommend the use of the CHA_2DS_2-VASc score, to initially identify patients at truly low risk of stroke[76] who do not need any antithrombotic treatment; thereafter, all others with ≥1 stroke risk factors can be offered effective stroke prevention, which is oral anticoagulant therapy either with vitamin K antagonists (VKAs) or with a non-VKA oral anticoagulants (NOACs).[152] The 'C' in the CHA_2DS_2-VASc score refers to congestive HF, moderate-to-severe LV systolic dysfunction on cardiac imaging, or recent decompensated HF irrespective of EF (thus, including HF-rEF and HF-pEF). Thus, any AF patient with HF (who would score at least one point on the CHA_2DS_2-VASc score) or those with (asymptomatic or symptomatic) moderate-severe LV systolic dysfunction should be offered OAC. Bleeding risk is assessed using the HAS-BLED score, to 'flag up' the patients potentially at risk of bleeding, and to address the correctable risk factors.[153]

If VKAs are used, good quality international normalized ratio (INR) control is necessary, aiming for a high time in therapeutic range (TTR, >70%) given the relationship of TTR to thromboembolism and bleeding.[154,155] Liver congestion may interfere with VKAs, resulting in INRs outside the therapeutic range. Indeed, HF is one of the co-morbidities associated with achieving a poor TTR, and is one of the comorbidities to be considered within the SAMe-TT_2R_2 score that can help decision-making between those likely to do well on a VKA (SAMe-TT_2R_2 score 0–2) and those unlikely to do well (SAMe-TT_2R_2 score >2), where a NOAC would be a better option.[156,157] Importantly, increased INR might not reliably reflect the extent of reduced coagulation, due to concomitant deficiency in the anticoagulant liver-dependent proteins,

which re-balance haemostasis and may protect from spontaneous bleeding.

Pertinent subgroup analyses of the four landmark trials with NOAC for stroke prevention in AF revealed no heterogeneity in the NOAC effects with respect to HF status.[158–160] Caution with NOACs is needed in patients with renal dysfunction, especially since dabigatran is highly renally excreted (80%) and others (rivaroxaban, apixaban, and edoxaban) may need a dose adjustment in moderate renal impairment.[161]

Since the left atrial appendage (LAA) is the principal site of AF-related thrombus formation, percutaneous LAA closure may be considered in AF patients with a high stroke risk and contraindications (or difficulties) for long-term oral anticoagulant therapy, while surgical LAA excision may be performed in patients undergoing open heart surgery.[162] However, pathophysiology of AF-related thrombogenesis is complex and more randomized data are needed to better define the exact role of non-pharmacological thromboprophylaxis in AF patients.

Rate control and rhythm control

There is no direct evidence in favour of rhythm control strategy over rate control in patients with AF and HF. Indeed, available data from randomized trials suggest that there is no difference in cardiovascular mortality, all-cause death, or worsening of HF between the two strategies in AF patients with HF, which is mostly attributed to unfavourable effects of antiarrhythmic drugs on survival.[163,164] Hence, the guidelines recommend that, in HF patients, AF management should commonly start with rate control, while rhythm control should be attempted in case of persistent AF symptoms (however, in haemodynamically compromised HF patients with AF and a high ventricular rate urgent direct current, cardioversion may be indicated).[165] However, cardioversion may only transiently restore sinus rhythm. The expected recurrence rate is very high. In most cases, it is usually better to start with a rate-control strategy. Beta-blockers are standard therapy in CHF and titration should also consider lenient heart rate control during AF (<110 b.p.m.). Digitalis represents second line, preferably in combination with beta-blockers. Amiodarone may be used for rate control if beta-blockers and digitalis are not effective.

Recent data from large observational studies suggest that patients undergoing rhythm control may perform better than those in rate control in terms of longer survival[164] and decreased stroke incidence.[166] Indeed, a relationship of AF duration with the presence of cerebral lesions detected by magnetic resonance imaging and decline in cognitive function has been documented.[167] Since the ANROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe heart failure Evaluating morbidity DecreAse) trial showed that dronedarone may be harmful in patients with advanced HF,[168] amiodarone should be the drug of choice for rhythm control in HF patients. However, amiodarone achieves only modest success in rhythm control and exposes patients to side effects.[169,170]

Catheter ablation—whether as pulmonary vein isolation or His ablation plus pacemaker—of AF in HF patients may be considered when amiodarone fails to control symptoms. *Table 3* lists relevant studies, all including limited sample populations, investigating CA outcomes in AF patients with impaired LVEF, highlighting its beneficial effects on LVEF, symptoms, quality of life (QoL), and exercise capacity.[171–175,177–183]

In addition, two meta-analyses[184,185] showed no difference compared with those without HF in freedom from AF after CA with respect to HF status and significant LVEF improvement by 11.1% (95% CI 7.1–15.2, $P < 0.001$). In the largest meta-analyses on this topic, CA efficacy in patients with AF improves especially when performed early in the natural history of AF ($P = 0.030$) and HF ($P = 0.045$), and provides long-term benefits on LVEF, thus reducing the proportion of patients who would subsequently experience an LVEF decrease to <35% ($P < 0.001$).[186] In support of these data, one long-term multicentre study reported that 62% of HF patients were arrhythmia free about 4 years after an extensive CA.[181] Indeed, we are awaiting clear evidence supporting (or not) the need for a more extensive CA approach in HF patients, but for now, the effects seem similar as in patients without HF.[187]

To date, only three small randomized controlled trials (RCTs) have directly compared rate and rhythm control by atrial fibrillation catheter ablation (AFCA) specifically in HF patients, and the results consistently showed better outcomes with AFCA rhythm control (*Table 3*).[177,180,183] These trial data have confirmed the observational series in terms of freedom from AF, improvement in LVEF, and QoL. It has to be emphasized that, even in experienced clinicians, the success rate of AFCA in HF is considerably lower than in patients without structural heart disease, often necessitating multiple procedures along with an increased risk of complications. Until more data become available, e.g. CASTLE-AF (Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (using a mortality and hospitalization endpoint)),[188] rhythm control by AF ablation should be recommended to patients with the greatest likelihood of success. However, so far it is not clear whether AFCA can cure AF in HF patients. To date, the strongest predictors of rhythm control failure are an enlarged left atrium and arrhythmia duration.[189,190]

Concerning the rate-control strategy, beta-blockers have usually been recommended as the first-line therapy in HF patients. However, a recent large meta-analysis has questioned this approach, finding that beta-blocker therapy led to a significant reduction in all-cause mortality in HF patients with sinus rhythm (HR 0.73, CI 0.67–0.80; $P < 0.001$), but not in patients with AF (HR 0.97, CI 0.83–1.14; $P = 0.73$).[191] Thus, beta-blockers should not be prescribed with the only aim of improving prognosis in patients with concomitant HF and AF. If such monotherapy is insufficient for adequate rate control, digoxin should be added.[192] No significant difference was found between strict vs. lenient rate control with respect to cardiovascular morbidity and mortality, symptoms, and QoL in a *post hoc* analysis, but more data are needed.[193] Patients with uncontrolled heart rate and/or pronounced AF symptoms in whom pharmacotherapy has been exhausted (or was associated with intolerable side effects), and AF ablation was unsuccessful or was rejected (or not indicated), should be considered for AV node ablation, preceded by biventricular pacing to control heart rate.[194–196]

Table 3 Observational and randomized studies investigating the outcomes of catheter ablation of atrial fibrillation in patients with impaired LFEF

Author (year)	Study design	*N*	Summary of findings					
			FU months	Success (single)	Redo	Success (final)	EF (%)	Other parameters
Hsu *et al.* (2004)[171]	Obs	58	12	28%	50%	78%	35 → 56	↑LVD, QoL, exercise capacity, and NYHA
Chen *et al.* (2004)[172]	Obs	94	14	52%	22%	73%	36 → 41	↑QoL
Tondo *et al.* (2006)[173]	Obs	40	14	55%	33%	87%	33 → 47	↑Exercise capacity and QoL
Gentlesk *et al.* (2007)[174]	Obs	67	6	55%	31%	86%	42 → 56	–
Nademanee *et al.* (2008)[175]	Obs	129	27	–	21%	79%	30 → 37	–
Lutomsky *et al.* (2008)[176]	Obs	18	6	50%	–	–	41 → 52	–
Khan *et al.* (2008)[177]	RCT	41	6	78%	10%	88%	27 → 35	↑QoL and 6MWT
De Potter *et al.* (2010)[178]	Obs	36	16	50%	31%	69%	41 → 58	–
Cha *et al.* (2011)[179]	Obs	111	12	–	–	76%	35 → 56	↑QoL
MacDonald *et al.* (2011)[180]	RCT	22	10	50%	–	50%	36 → 41	↑QoL
Anselmino *et al.* (2013)[181]	Obs	196	46	45%	30%	62%	40 → 50	↑NYHA and mitral regurgitation
Calvo *et al.* (2013)[182]	Obs	36	6	70%	31%	83%	41 → 48	–
Jones *et al.* (2013)[183]	RCT	26	12	68%	19%	88%	21 → 32	↑Peak oxygen consumption, BNP, and QoL

Obs, observational; RCT, randomized clinical trial; FU, follow-up; EF, ejection fraction; LVD, left ventricular dysfunction; QoL, quality of life; NYHA, New York Heart Association; 6MWT, 6 min walking test; BNP, brain natriuretic peptide.

In summary, in HF, rate control using beta-blockers and (as second line) digitalis is often the appropriate choice in recurrent or persistent AF. Catheter ablation of AF or ablation of the AV node (with subsequent pacemaker implantation) may be indicated in symptomatic or refractory tachyarrhythmic AF.

Ventricular arrhythmias

The management of VAs has recently been addressed by a joint consensus document from EHRA, HRS, and APHRS.[197] Risk stratification and management of patients with HC has been recently extensively reviewed.[69] *Figure 3* and *4* show the management of ventricular tachcyarrhythmias in HF patients. The majority of large RCT studies have used all-cause mortality as a primary endpoint. Although this hard endpoint is indisputable, it does not necessarily reflect an effect on arrhythmia. Sudden death has been used as a proxy for arrhythmic death, which most commonly is caused by ventricular tachyarrhythmia.

Therapy with standard heart failure agents

In all HF patients presenting with VT, the ongoing standard HF therapy with an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), beta-blocker, and mineralocorticoid receptor antagonist (MRA) should be optimized (Class I, level A indication). Therapy with an ACE-I often causes a modest improvement in EF, whereas a substantial improvement is often seen with beta-blockers. All conditions which might facilitate the development of VAs should be corrected (electrolyte disturbances, pro-arrhythmic effects of concomitant therapy, and inappropriate medication such as NSAID etc.). The need for revascularization should be considered in patients with known or suspected ischaemic heart disease and ventricular tachycardia.

Therapy with antiarrhythmic agents

Beta-blockers remain the cornerstone in CHF therapy with well-documented ability to reduce total mortality by ~35%, and with a ~40–45% reduction in SCD.[198,199]

Amiodarone therapy resulted in lower mortality in the moderately sized GESICA trial,[200] but no beneficial effect on mortality was seen in the CHF-STAT (Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy) study[169] or the large-scale SCD-HeFT trial.[201] Two meta-analyses have both shown that mortality is reduced by amiodarone therapy, but it should be realized that the patient characteristics in these analysis are heterogeneous.[202,203] Thus, avoidance of this drug in severe HF or discontinuation of amiodarone in patients with clinical deterioration should be considered. However, in a large proportion of VT patients, amiodarone is the only reasonable antiarrhythmic therapy option. Amiodarone should not be routinely given to HF patients with non-sustained VT, due to the lack of documentation of effects and risk of toxicity (Class III, level A indication).[152,204] Amiodarone may be a reasonable choice of therapy in optimally treated HF patients with previous sustained VT who are not candidates for an ICD (Class IIb, level C indication). In HF patients treated with an ICD and symptomatic VAs or recurrent shocks, despite optimal HF treatment and device re-programming, amiodarone is recommended (Class I, level C indication).

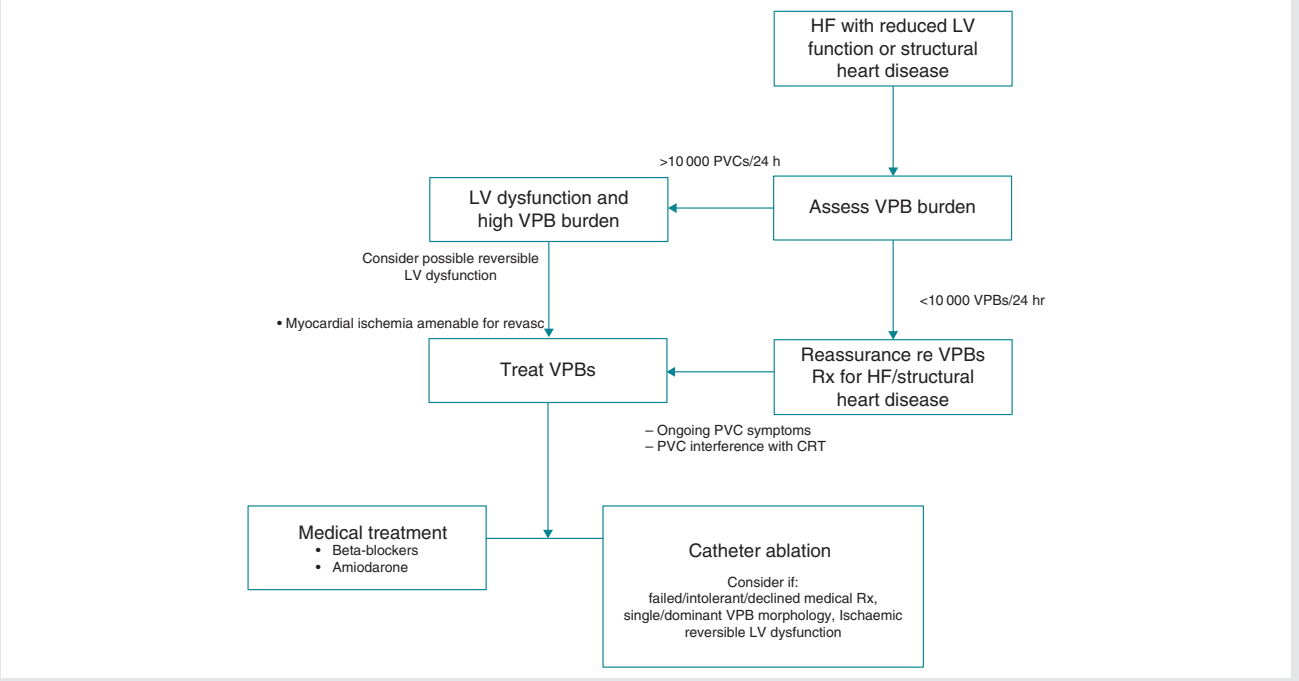

Figure 3 Management of ventricular premature beats in heart failure. Figure modified from Torp Pedersen *et al.*[196] HF, heart failure; LV, left ventricular; VPBs, ventricular premature beats.

Sotalol, which exerts both beta-adrenergic blocker and Class III effects, has significant potential for proarrhythmia and worsening of HF, and should be avoided in HF patients with severe ventricular dysfunction and HF decompensation.[205] Proarrhythmia risk may be less of a consideration if the patient has an ICD. In line with this, Class IA and IC drugs, as well as dronedarone, are all contraindicated in HF patients.[152]

Of the newer Class III AADs, studies on azimilide and celivarone[206] have unfortunately been disappointing. Ranolazine, which is an inhibitor of the late sodium current and additionally has effects on the sodium-dependent calcium channels during ischaemia, has in smaller studies shown promising beneficial effects,[207,208] but larger scale studies are needed especially in HF patients.

Risk stratification

Patients with HF have a significantly increased risk of VA and death, and the most important risk factors of death are HF symptoms and low LVEF. Apart from symptomatic HF and low LVEF as risk markers, limited amount of evidence is available regarding the impact of NSVT.[209]

Microvolt T-wave alternans, which measures beat-to-beat oscillations in T-wave amplitude, may contain some prognostic information despite varying data and the absence of data to support a strategy of risk stratification with this test to decide on patients who might benefit from an ICD.[210] Invasive electrophysiological studies with programmed ventricular stimulation have a more limited clinical predictive value in non-ischaemic cardiomyopathy compared with its use in ischaemic heart disease, where demonstration of inducible monomorphic ventricular tachycardia is associated with a high risk for SCD. Evaluation of heart rate variability and baroreflex sensitivity, which are indices of the autonomic nervous system function, also have a limited value.[211] The presence of myocardial scarring on MRI using gadolinium as well as semi-quantitative measurement of adrenergic innervation by MIBG scans may identify high-risk patients, but data are sparse and the clinical relevance remains to be documented.[212,213]

In summary, beta-blockers and as a second-line amiodarone remain the most effective AADs to reduce the incidence of symptomatic ventricular tachyarrhythmias in HF. Device therapy has to be considered for sustained VA or in patients with severely reduced LVEF (see the section 'Device therapy').

Management of arrhythmias in heart failure post-myocardial infarction

The management of cardiac arrhythmias in the setting of ACSs has recently been addressed in a joint consensus document from EHRA, the Acute Coronary Care Association (ACCA), and the European Association of Percutaneous Cardiovascular Interventions (EAPCI).[214] The antithrombotic management strategies for AF patients presenting with an ACS and/or undergoing coronary intervention has been detailed in a joint European consensus document, endorsed by the HRS and APHRS.[81]

Post-MI patients are at risk for a variety of events, including unstable angina, re-infarction, HF, arrhythmias, systemic thromboembolism, and sudden death. Many drugs have been recommended for the treatment of post-MI patients, but most

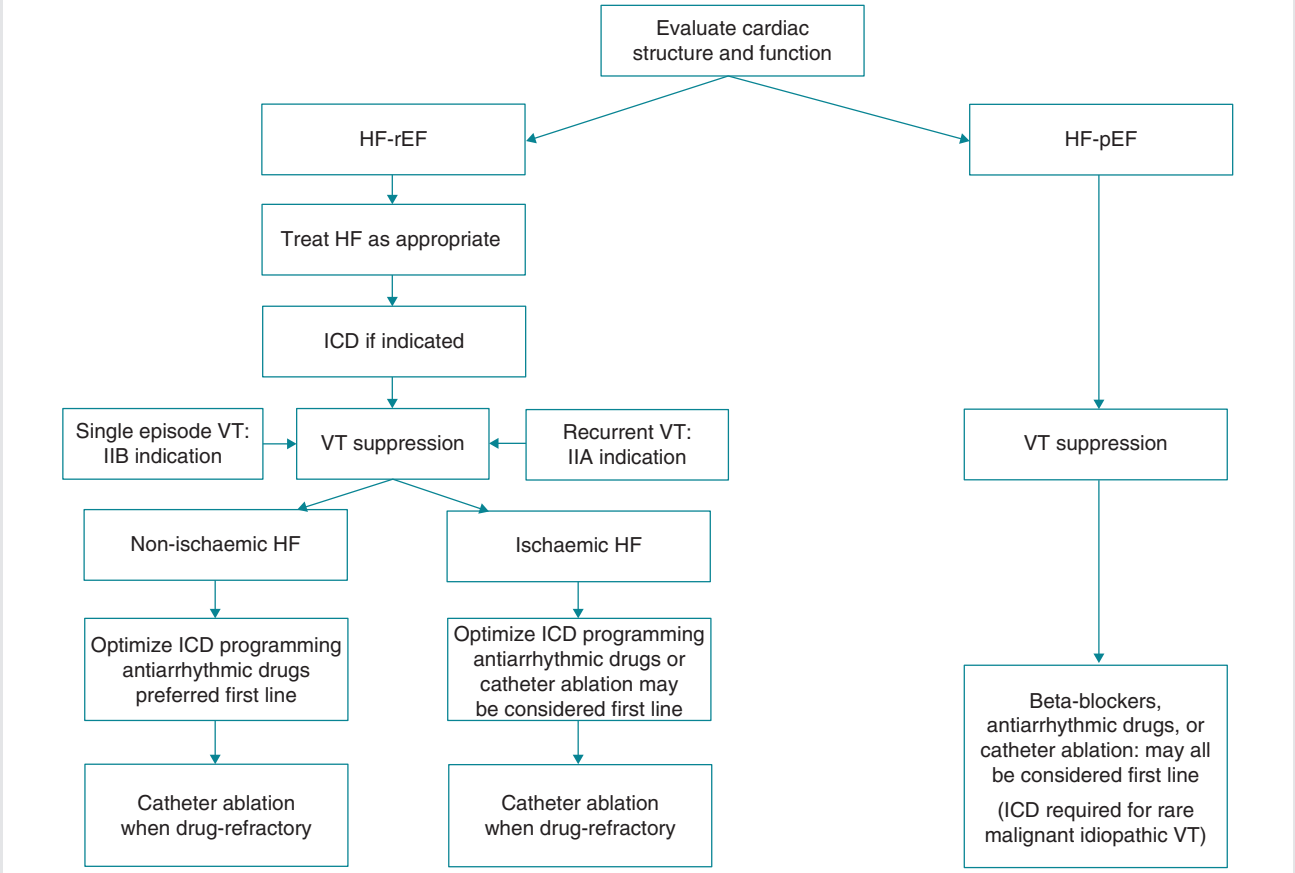

Figure 4 Evaluation and management of sustained monomorphic ventricular tachycardia. Figure modified from Torp Pedersen *et al.*[196] HF-rEF, heart failure with reduced ejection fraction; HF-pEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; HF, heart failure; VT, ventricular tachycardia.

of the information about their efficacy was obtained in the pre-reperfusion era and not all have been tested in randomized trials. Finally, device therapy is not of benefit at early post-MI stages. In a meta-analysis from 2006, 25–60% of patients with acute MI developed LV systolic dysfunction in the early phase and the majority of these patients displayed HF symptoms.[215] Thus, post-MI, management of arrhythmias has to be commonly viewed in the context of HF.

Management of ventricular arrhythmias early after myocardial infarction

Patients who have VAs will either need to receive an ICD if the arrhythmia is sustained >48 h after an MI or undergo electrophysiological testing if the arrhythmia is non-sustained VT to evaluate for inducible sustained monomorphic VT.[216] There is no place for empirical treatment with antiarrhythmic agents because of the risk of pro-arrhythmic effects. The best antiarrhythmic therapy is complete revascularization, if possible, and optimized medical therapies including ACE-Is and beta-blockers. In the FINGER trial results among 2130 patients, those who underwent revascularization after acute MI had a significantly lower rate of SCD than did those who did not undergo revascularization (HR for non-revascularized patients 2.1; CI 1.2–3.7).[217]

Patients developing VF in the acute stage (first 24–48 h) of an MI may be at higher risk of in-hospital mortality, but do not have a higher long-term all-cause or SCD mortality.[218] However, patients who experience VAs beyond the first 48 h after STEMI should receive an ICD device if the arrhythmias are sustained VT/VF, provided the arrhythmia is not due to transient or reversible ischaemia, re-infarction, or correctable metabolic or electrolyte abnormalities; or undergo electrophysiological testing for worrisome complex ventricular ectopy (e.g. runs of non-sustained VT) to help in the selection of appropriate therapy.

Although current guidelines recommend prophylactic ICD implantation after STEMI and a depressed LVEF which remains low (35%) after 40 days have elapsed, the prognoses of these patients may be better than those observed in the early randomized trials of ICDs, particularly because reperfusion treatment has improved, and the use of life-saving drugs is higher.

There is a strong argument for the routine use of beta-blockers post-infarction. There is no role for the empirical use of other antiarrhythmic drugs in post-infarct patients. All antiarrhythmics

have the potential to provoke arrhythmias as well as decrease them and, in clinical trials, several Class I antiarrhythmic drugs have been associated with an increase in mortality rather than a decrease.

In post-MI patients, including those with an ICD, presenting with electrical storm (≥3 separate episodes of VT within a 24 h period) not due to a transient reversible cause, or incessant VT, or in patients with symptomatic sustained monomorphic VT that recurs despite antiarrhythmic drug therapy or when antiarrhythmic drugs are not tolerated or not desired, CA may serve as an important and viable treatment option.[219–221]

Risk stratification

Although there was a period when several risk stratifiers were being evaluated in the first 7–14 days post-MI and considered to assess the risk of SCD post-MI and to guide prophylactic or therapeutic interventions, these tests were not finally adopted due to their low positive predictive value (≤15–25%).[222] The list of the proposed tests includes late potentials assessed by signal-averaged ECG, non-sustained VT detected on ambulatory ECG (Holter), heart rate variability, baroreflex sensitivity, programmed ventricular stimulation via an EP study, T-wave alternans, etc. Only LVEF of ≤35% after the first month post-MI is an independent predictor of SCD. The current guidelines recommend that evaluation of the need for a primary preventive ICD may, in some cases, be postponed until 3 months after revascularization procedures, to allow adequate time for recovery of LV function.[223]

The role of electrophysiological testing in post-MI patients who do not have overt VAs is controversial.[224] There is a consensus that testing is not necessary in patients who have normal LV function. Testing may be considered in patients who have impaired LV function (LVEF ≤40% at ≥4 days post-MI or revascularization), particularly if non-sustained VT is seen on the ECG or a Holter monitor.

Bridging the first 30–40 days post-myocardial infarction

In high-risk post-MI patients, prophylactic ICDs may significantly improve survival. However, the evidence is for the period beyond the first 40 days post-MI. Earlier prophylactic ICD implantation in the first 30–40 days post-MI was tested in two trials, the DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) and the IRIS studies, and found to have no benefit even with a tendency towards harm due to an increase in non-sudden deaths.[225,226] Although early ICD implantation was associated with a lower risk of sudden cardiac or arrhythmic death, the risk of non-arrhythmic death was higher, counterbalancing potential overall benefits of ICDs in this early period. However, both trials had low rates of primary PCI as a reperfusion strategy. In another trial [BEST-ICD (Beta-blocker Strategy plus Implantable Cradioverter-Defibrillator)],[227] among 142 post-MI patients on optimal medical treatment randomized to EP-guided therapy, no survival benefit was confirmed in the ICD-receiving patients. However, only 15–25% of patients received primary PCI in this study; the mean LVEF was 31%. Hence, ICD implantation is not recommended in the first month post-MI, related to the documented increased risk of non-sudden or non-arrhythmic death during this period.

Instead, one could bridge these patients with medical therapy that should include beta-blocker, ACE-I, or ARB and an MRA agent (e.g. eplerenone). For eplerenone, the evidence is favourable for the protection it confers during the first month post-MI and beyond.[228] Thus, an aldosterone antagonist is recommended for patients with STEMI and no contraindications who are already receiving an ACE-I and beta-blocker, and who have an LVEF of ≤40% and either symptomatic HF or DM. The recent REMINDER (Role of Eplerenone in acute Myocardial INfarction – Double-blind, Early treatment initiation, Randomised, placebo-controlled, multi-centre study) trial indicates that among 1012 MI patients with EF >40%, early (within 24 h) administration of eplerenone led to lower cardiovascular mortality, HF, and VT/VF at a mean FU of 10.5 months compared with placebo.[229]

A wearable cardioverter defibrillator during the post-MI mandatory ICD implantation waiting period has been proposed, which is 40 days in the non-revascularized patient, or 3 months if revascularization has been performed.[230] Others have recommended access to a home automatic external defibrillator, but this strategy did not significantly improve overall survival, when compared with relying on conventional resuscitation methods.[231]

With successful reperfusion and revascularization, infarct size is largely limited, and this further translates into better preserved LV function, a decreased possibility for an arrhythmogenic substrate to be established, and thus lower need for an ICD; the number of ischaemic episodes, which might serve as arrhythmia triggers, is also decreased, while there is a much better chance to prevent HF and neurohormonal activation, all leading to lower morbidity and mortality, including a lower rate of SCD. Thus, in the era of primary PCI, there is a decreased incidence of VAs and a lower SCD rate, while the role of early prophylactic ICD implantation appears weaker.[157,173,217,232–234]

There may be a role for targeted primary prevention ICD implantation after STEMI treated with primary PCI with early ICD implantation limited to patients with inducible VT at an EP study performed at 7–14 days post-MI.[224,235]

Mid- and long-term post-myocardial infarction arrhythmia management

For patients with either HF-PEF or HF-REF who have survived life-threatening VAs in the form of aborted out-of-hospital cardiac arrest, sustained monomorphic VT, or recurrent episodes of syncope and inducible VT at an EP study, implantation of an ICD offers the best protection from SCD (*secondary prevention*), in accordance with the current guidelines, provided that the issue of revascularization has been optimally addressed. Among these patients, those who also have an indication for CRT should receive a combined cardiac resynchronization therapy-defibrillator (CRT-D) device.

For patients needing prophylactic ICD implantation for *primary prevention* of SCD, adherence to current guidelines is recommended, keeping in mind that even in the most liberal recommendation of an ICD implant provided by the MADIT II study (all patients with prior MI and LVEF <30%), most of the ICD benefit was observed for those patients who had an ICD implanted after the first 6 months post-MI.[236,237] Similarly, in the

PreSCD II registry, all-cause mortality was significantly reduced only if the ICD was implanted late (>11 months) after MI.[238] This is in keeping with the progressive recovery of the LV function and a decrease in infarct size over the period of the first 6 months following reperfusion and revascularization.

For patients with an electrical storm or patients already having an ICD who develop frequent recurrences and shocks or develop an electrical storm or incessant VT, radiofrequency ablation therapy needs to be considered.

In summary, patients with HF post-MI are at particular risk for arrhythmias and the early phase (3 months) post-MI requires individual risk assessment to guide management.

Device therapy

Implantable cardioverter defibrillator

It is well established that compared with best antiarrhythmic therapy (essentially amiodarone), ICDs are superior in reducing mortality by 20–24% over a 2- to 5-year FU period in patients with HF-pEF or HF-rEF with previous cardiac arrest or documented VF or sustained VT, or with syncope and clinical or inducible sustained VT (secondary prevention).

Three major secondary prevention trials (AVID,[239] CASH,[240] and CIDS[241]) are summarized in Supplementary material online, *Table S2*. A meta-analysis showed a significant reduction in death from any cause with ICD therapy with a net HR (ICD : amiodarone) of 0.72 (95% CI 0.60–0.87; $P = 0.0006$).[242] For the outcome of arrhythmic death, the HR was 0.50 (95% CI 0.37–0.67; $P < 0.0001$). Survival was extended by a mean of 4.4 months by ICD treatment during a FU period of 6 years. Patients with an LVEF of ≤35% obtained a significantly higher benefit from ICD therapy than those with preserved LV function.

Thus, patients with HF who develop sustained ventricular tachyarrhythmia (either sustained monomorphic or polymorphic VT, VF or recurrent syncope with inducible sustained VT at the electrophysiological study) are candidates for ICD implantation, as long as they have a reasonable life-expectancy (>1 year), irrespective of their LVEF status.

Implantable cardioverter defibrillators have also been proved effective in primary prevention of SCD in high-risk patients with HF-rEF who have not yet developed a malignant VA[201,236,243–245] (see Supplementary material online, *Table S3*). All-cause mortality was reduced by 54% over 27 months in the MADIT trial in patients with a low LVEF of <35% and prior MI, 29% over 2 years in the MADIT II study of patients with an LVEF of <30% and previous MI (NYHA class was I–III in both studies), and 24% over 5 years ($P = 0.007$) in the SCD-HeFT study of patients with a low LVEF, NYHA Class II or III, and either ischaemic or non-ischaemic cardiomyopathy. The mortality in the optimal medical treatment arms of both of these trials was around 7–10% per year. Similar results have been suggested by primary prevention trials including patients with non-ischaemic dilated cardiomyopathy.

In SCD-HeFT, ICD therapy was associated with a reduction in all-cause mortality in patients with NYHA Class II or III HF and LVEF ≤35%, due solely to a reduction in sudden deaths presumed to be caused by ventricular tachyarrhythmias, and was not offset by an adverse effect on HF or non-cardiac deaths.[59] Furthermore, the greatest benefit was observed in patients with NYHA Class II HF. In SCD-HeFT, NYHA Class III patients had a high mortality rate due to pump failure, which may have offset benefit of the ICD in reducing arrhythmic death.

Thus, primary prevention of SCD with implantation of an ICD is recommended in a patient with symptomatic HF (NYHA Class II–III) and an LVEF of ≤35% despite ≥3 months of treatment with optimal pharmacological HF therapy, who is expected to survive for >1 year with good functional status. If the underlying aetiology is ischaemic heart disease and >40 days have elapsed after an acute MI, the indication is Class I/level A; if the underlying disease is non-ischaemic cardiomyopathy, the indication is Class I/level B. Also, ICD therapy is recommended for primary prevention of SCD in selected patients with HF-rEF at least 40 days post-MI with an LVEF of ≤30% and NYHA Class I symptoms while receiving optimal medical therapy, who are expected to live >1 year (Class I; level B).

In primary as well as secondary prevention, ICD may avert SCD, but not prevent arrhythmias. Therefore, ICD therapy often needs to be accompanied by optimized medical antiarrhythmic treatment (e.g. optimally titrated beta-blockers and amiodarone) to reduce symptomatic episodes.

Cardiac resynchronization therapy

Among patients having an indication for an ICD, a CRT-D device is recommended in those also having symptoms of HF of NYHA Class II, III, or ambulatory IV, an LVEF of ≤35%, and a QRS duration of ≥120 ms, as evident from various CRT studies summarized in Supplementary material online, *Table S4*.[246–254] To ensure effective CRT with >95% of ventricular pacing and long-term survival similar to patients in sinus rhythm, AV junction ablation is needed in patients with permanent AF.[75]

Implantable cardioverter defibrillator devices in patients with left ventricular assist devices

Ventricular arrhythmias are common in patients having LVADs ranging from 22 to 52% of patients developing sustained VT/VF episodes in the post-operative period, with most of them occurring during the first few weeks after surgery, but with a high likelihood of future recurrence.[129,255,256] Ventricular arrhythmias are better tolerated by LVAD patients compared with other HF patients, but symptoms may develop, including hemodynamic instability, and these arrhythmias seem to reduce patient's general survival and survival to heart transplantation.[257]

Thus, apart from the need for ICD implantation for secondary prevention in patients with LVADs who develop sustained ventricular tachyarrhythmias, some have suggested prophylactic ICD placement in this particular patient population, although reports provide conflicting results.[258,259]

In summary, evidence supports primary prophylactic ICD in patients with HF with persistently reduced LVEF (≤35% NYHA Class II–III, in ischaemic cardiomyopathy with an LVEF of ≤30%, and also NYHA Class I).

Arrhythmias in acute heart failure

Epidemiology and impact

Arrhythmias are common in patients with acute heart failure (AHF). In the ADHERE (Acute Decompensated Heart Failure National Registry), a large-scale, prospective multicentre database of >100 000 patients hospitalized for AHF, 31% of patients had a history of AF.[260] The incidence of AF on admission increases with age and the severity of CHF as well as AHF.[261] New-onset AF is a frequent cause for HF exacerbation, and patients with AHF and new-onset AF have a more complicated hospital course and higher mortality rates than those with no AF.

Ventricular arrhythmias (particularly NSVT) are also common. However, limited data exist concerning their exact incidence. In the EuroHeart Failure survey,[262] 2% of AHF patients presented with VA on admission. In the ADHERE registry, almost 10% of patients had a history of ventricular tachycardia or VF.[260]

In AHF, clinically relevant bradyarrhythmias (severe sinus bradycardia, sinus pauses, and high-degree AV block) seem to be less frequent than AF and NSVT. They are often the consequence of terminal events in AHF (severe hypoxaemia, acidosis, and severe electrolyte abnormalities like hypokalaemia). Frequently, drugs slowing heart rate and/or AV conduction (beta-blockers and antiarrhythmic drugs) are involved. Patients with inferior ST-segment myocardial infarction (MI) are at an increased risk to develop bradycardia due to second- or third-degree AV block.

Patients with AHF admitted to emergency or intensive care units routineously undergo continuous ECG monitoring. In daily practice, a detailed assessment of the quality and quantity of the monitored arrhythmias is not routinely performed. Therefore, sporadic and short lasting arrhythmias (e.g. NSVT) often remain undetected. Studies suggest that documented new arrhythmias during an exacerbation of HF, in general, identify a high-risk patient group with higher intra-hospital and 60-day morbidity and mortality.[263]

Mechanisms

Acute HF predisposes to atrial and VAs. Haemodynamic deterioration, increased filling pressures resulting in atrial and ventricular stretch, elevated sympathetic tone with increased levels of endogenous catecholamines, and ischaemia and inflammation are involved in the pathogenesis of arrhythmias in AHF. New AF develops in up to 10% of patients receiving exogenous catecholamines (dobutamine, adrenalin, and noradrenalin) as well as phosphodiesterase inhibitors (milrinone) and even calcium sensitizers (levosimendan).[264]

Atrial fibrillation may result from AHF, but may also cause AHF. New-onset AF is a well-known cause for acute cardiac decompensation in patients with both acute HF-REF and HF-PEF. Twenty-five to 30% of patients presenting with acute HF-pEF have recent onset of AF with a rapid ventricular response. In patients with acute MI, HF is an important risk factor for the development of AF and VAs.[265]

Data regarding arrhythmia mechanisms on a cellular level are limited. Mechanisms include abnormal impulse formation by enhanced and abnormal automaticity and triggered activity (resulting from delayed ADs) which may be a consequence of acute stretch. In patients with a history of MI, sustained ventricular tachycardia resulting from re-entry around and within areas of scar may been favoured in the setting of AHF.

Treatment

New-onset AF in the setting of AHF may require urgent electrical cardioversion. However, cardioversion may only transiently restore sinus rhythm. The expected recurrence rate is very high. In many cases, it is usually better to start with a rate-control strategy. In patients with acute HF, beta-blockers may cause haemodynamic detoriation. When these drugs are given intravenously, blood pressure should be monitored carefully. Owing to the increased sympathetic tone, digitalis is only slightly effective. Class I antiarrhythmic agents (e.g. flecainide and propafenone) are associated with potential proarrhythmia and should not be used in patients with AHF. Amiodarone administered as an infusion is frequently used. However, even these patients also need to be monitored carefully, as amiodarone may cause hypotension which is caused by a combination of arterial vasodilation and negative inotropic effects. The former may be caused by the solvent. In patients with early AF recurrences after electrical cardioversion, repeat cardioversion some weeks after the acute event when optimal oral HF medication has been established can be effective.[266]

In patients with AHF, sustained ventricular tachycardia is poorly tolerated and should be immediately terminated by electrical cardioversion. Amiodaron may help to prevent recurrences. Patient with AHF and drug-refractory electrical storm (i.e. frequent recurrences of sustained ventricular tachycardia) and non-pharmacological treatment including CA is the therapy of choice.[267–270] After the acute phase of electrical storm, the treatment focus should shift towards maximizing heart failure therapy, performing revascularization, and preventing subsequent VAs.

The occurrence of symptomatic bradyarrhythmias also necessitates a rapid response. In addition to addressing aetiology factors, treatment with atropine or temporary transvenous pacing may become necessary. The administration of catecholamines, which may trigger VAs, should be avoided if possible.

In summary, in AHF, sustained tachyarrhythmias are often the cause of decompensation or poorly tolerated. Haemodynamic instability requires immediate cardioversion. In AHF associated with AF, intensified rate control using digitalis and amiodarone is often necessary.

Areas for future research

Although arrhythmias are extremely common in CHF, research to date has not given us a firm evidence base to guide many clinical management decisions. Uncertainties remain regarding how and when arrhythmias cause or exacerbate CHF, their precise role in the syndrome of HF-pEF and (despite many studies) the optimal management of the common arrhythmias that complicate the clinical course of either HF-pEF or HF-rEF.

Atrial fibrillation

As AF is the most common arrhythmia in HF, AF prevalence and its associated complications have been well studied in established HF. This evidence comes partially from large HF registries, but most extensively from the follow-up of patients recruited into large RCTs. However, these RCTs frequently exclude other co-morbidities and diagnoses, tend to have a restricted age range, and traditionally exclude children and women of child-bearing potential. In addition, HF-pEF is much less frequently studied despite being arguably even more associated with AF than HF-rEF. More community-based studies such as the Framingham study in the modern era that evaluate risk factors, the onset and natural history of AF and HF as they co- or separately develop for the first time, and the interaction between the two diagnoses would be extremely valuable. Related research would and should address interventions (including drugs, devices, and ablation therapies) to reduce the risk of AF onset, recurrence, or progression to more persistent forms and the effect of these therapies on the consequent progress of the HF syndromes, HF-rEF, and HF-pEF.

Larger comparative studies on the cost–benefit ratio of different antithrombotic options for established AF within the HF syndromes would be of interest, including the efficiacy and safety of NOACs. Also, there would be an economic and clinical value of defining those HF patients with AF who would do well with good quality anticoagulation after being initiated on a VKA (with a high TTR). These strategies could be based on clinical scores such as the SAMe-TT_2R_2 score, which has already been validated in various 'general' AF cohorts.[157,271]

As many HF patients have cardiac implantable devices, such as pacemakers and ICDs, that can detect asymptomatic AF, there is a need for studies that elucidate the burden of AF that is associated with thromboembolic complications and need for antithrombotic therapy, as well as for research in the setting of atrial high rate episodes other than confirmed AF detected by devices. Patients with implantable devices represent only a minority of all HF patients. Future studies with long-term arrhythmia monitoring with loop recorders might elucidate the true presence of AF in a larger HF population and identify subgroups of HF patients in need of continous monitoring for early detection of AF.

The optimal treatment modalities for controlling rate in AF and identification of optimal target ventricular rate ranges (at rest and during daily exercise) for both types of HF would also be valuable objectives for future research. The lack of benefit of rhythm over rate control in previous prospective trials reflects the need for identification of antiarrhythmic drugs with a better safety profile and/or a more efficient upstream therapy of the arrhythmogenic myocardial substrate in HF. Determining if there are identifiable subgroups of HF patients who would receive clinical benefit from rhythm control within episodic or recurrent AF would also be valuable, as would research into non-pharmacological strategies of rhythm and rate control, primary AF ablation and its role, CRT in AF-HF, and the role of AV node ablation.[272]

Ventricular tachyarrhythmias

Ventricular tachyarrhythmias are frequent in HF, especially in the presence of very low LVEF. The optimum management of VPBs and asymptomatic episodes of NSVT and their prognostic significance remain uncertain. Catheter ablation is usually reserved for adjunctive management of refractory life-threatening or symptomatic VAs. However, the role of early or even pre-emptive CA for ischaemic or non-ischaemic cardiomyopathy remains uncertain.

Furthermore, additional research on the burden of PVCs or VT that can lead to reduction in ventricular function or that indicates need for CA would help to address whether treating lesser degrees of VA with HF is beneficial. Studies on the role of ICD implantation or the wearable cardioverter defibrillator early after the diagnosis of HF would also address this gap period not covered by prior RCT. Despite international guidelines recommending the use of prophylactic ICD implantation in HF, the scientific evidence for this recommendation is weak in dilated cardiomyopathy, but an ongoing RCT may elucidate this. More evidence is also needed on the role of ICD in heart transplant recipients. A large registry revealed an incidence of 10% for SCD with allograft rejection and LVEF <40% as strong predictors.[273] Smaller retrospective reports report mixed efficiacy of ICDs in these patients,[274,275] and a larger prospective multicentre trial are needed.

The track record of antiarrhythmic drugs for SCD indications is suboptimal, so research is likely to focus on alternatives such as surgery, device, or biological therapies.

Bradyarrhythmias

Pacemakers for symptomatic bradyarrhythmias have clear indications in HF patients, as in the absence of HF, but if pacing is indicated, consideration should be given at the time of implant as to whether the addition of an ICD and/or CRT is worthwhile based on the patient's individual characteristics. Left ventricular pacing should be further explored in patients with bradycardia indication, but mildly to moderatly reduced LVEF. Research would be valuable to determine whether patients unable to tolerate beta-blockade due to drug-induced bradycardia would benefit sufficiently from prophylactic pacing to make this a worthwhile intervention to allow the use of adequate dose of beta-blockade.

Further research is likely to be necessary to determine the optimal locations and number of sites of atrial and ventricular pacing in patients whose need is restricted to the prevention of bradycardia so as to optimize long-term ventricular function and evolution of their clinical condition and HF status. At least for now, there appears to be ample evidence which suggests that one should avoid pacing the RV apex alone; biventricular pacing has been shown to be associated with improved outcomes in patients with AV block and LV dysfunction. However, further studies seem necessary to refine the patient population and confirm better outcomes and cost-effectiveness when compared with standard RV pacing devices.[254]

Biomarkers

Additionally, serum biomarkers such as brain natriuretic peptide (BNP), cystatin C, D-dimer, and others have been evaluated to predict thromboembolism in AF (and in case of BNP also to predict the presence of paroxysmal AF in the first place). While these factors have been shown to indicate an increased risk, their value in guiding clincial management remains to be established.

In a meta-analysis including 3543 patients from six studies, BNP was found to be predictive of SCD with a relative risk of 3.68 (CI 1.90–7.14; $P = 0.0001$), independent of LVEF. However, in these studies, the best cut-off point for BNP varied considerably (between >130 and >4500 pg/mL), probably related to the heterogeneity of the underlying patient cohorts.[276] On the other hand, very high BNP in the context of other co-morbidities may also indicate increased non-cardiac mortality and thus identify patients less likely to profit from ICD therapy.[277] Using blood urea nitrogen, together with the presence of AF, QRS width, NYHA, and age, Goldenberg *et al.*[278] found a U-shaped relationship between risk factors and reduction in mortality by ICD. Prospective studies are needed to evaluate the value of elevated BNP and other biomarkers to predict VA and SCD, and their role in the management of selected patient cohorts.

Consensus statements

In HF, cardiac remodelling and neurohumoral activation provide a substrate that increases the incidence of arrhythmias, potentially aggravates the impact of arrhythmias, and at the same time sets the stage for clinical management based on LV function.

1 General

- Despite the high prevalence of arrhythmias in HF, screening of asymptomatic HF patients aimed to detect VAs is not recommended. However, routine ECGs or at least regular pulse taking should be performed to detect and manage silent AF in this high-risk population.
- Sustained VA either symptomatic or not always warrant treatment.

2 Atrial fibrillation

- Most patients with HF (reduced or preserved EF) and AF will qualify for oral anticoagulation (either with VKAs or a NOAC) according to their CHA_2DS_2-VASc score and taking into account their bleeding risk (HAS-BLED score). Decision-making between a VKA and an NOAC can be helped by using the SAMe-TT_2R_2 score.
- Rate control of AF is non-inferior to rhythm control also in HF patients, but rhythm control should be attempted in patients with symptomatic AF episodes.
- Amiodarone is the drug of choice for rhythm control, whereas for rate control beta-blockers, digoxin, or their combination are recommended. Regular screening for side effects is necessary.
- In patients with acute HF, rate control seems to be the prefered teatment strategy. After the acute phase of HF, the indication for rhythm control should be re-evaluated.
- Beta-blockers should not be prescribed with the only aim of improving prognosis in patients with concomitant HF and AF. Catheter ablation may be considered for symptomatic patients with drug-refractory AF or in selected patients with favourable atrial anatomy. In patients with therapy-refractory AF symptoms or uncontrolled heart rate implantation of a biventricular pacemaker followed by AV node ablation ('pace and ablate') should be considered. Atrioventricular node ablation may also become necessary in HF patients on CRT therapy who develop permanent AF with ineffective biventricular pacing (fusion beats).

3 Bradycardias

- In case of symptomatic bradycardia of irreversible origin, according to pacing guidelines in HF patients (NYHA Class I–III), a CRT device should be considered to avoid RV pacing only.
- Heart failure with reduced ejection fraction patients with an AV block may profit from CRT pacing, but further evidence comparing standard (RV)- and CRT device implantation in these patients seems necessary for a generalized recommendation.

4 Ventricular arrhythmias

- Patients with documented sustained VAs mostly require an ICD after potentially reversible causes such as pronounced electrolyte disturbances or acute myocardial ischaemia have been excluded. In addition, escalation of beta-blockers and amiodarone may help to reduce arrhythmia incidence.
- Primary prophylaxis with an ICD or ICD-CRT is generally recommended in patients with severely reduced EF, except if HF symptoms are severe (at rest) without reasonable expectation for improvement or a life-expectancy of <1 year.
- Following acute MI, optimal medical therapy including beta-blockers needs to be established early to reduce the risk for arrhythmias.
- High-risk patients (low EF) should be re-evaluated after 4–6 weeks (or 3 months after revascularization) of optimal medical therapy before ICD implantation for primary prophylaxis is considered.
- Wearable defibrillators are currently evaluated for bridging this period in selected patients.

5 Post-MI HF and arrhythmias

- LV systolic dysfunction and HF remain common complications of acute MI.
- Patients with STEMI should be submitted to rapid reperfusion therapy, preferably with primary PCI or immediate

thrombolysis followed by PCI. Those who have suffered an MI have an increased risk of death and re-infarction for up to 1 year afterwards, with the majority of events occurring a few weeks after discharge.
- All patients should receive optimal medical therapy to bridge them for the first 4–6 weeks, until a re-assessment is made and for those who remain with low LVEF (35%) and NYHA Class II–III, an ICD with or without CRT, as appropriate, should be considered.
- Post-MI patients with angina, HF, or VAs are at extremely high risk and require immediate re-evaluation. Revascularization in case of recurrent amenable ischaemia, and/or early ICD implantation or wearable defibrillator, should be considered.
- All post-MI patients should be treated with a beta-blocker unless there is a specific contraindication.
- Patients with significant LV dysfunction should, in addition, be treated with an ACE inhibitor or an ARB and an MRA.
- Patients who have had a large anterior infarct are at risk of thromboembolism, VAs, and HF, and should be managed accordingly.

6 Cardiac resynchronization therapy and HF patients

- The evidence for a beneficial effect of CRT is strongest for patients in sinus rhythm with a QRS duration of ≥130 ms and LBBB QRS morphology (Class I/level A), or a QRS duration of ≥150 ms irrespective of QRS morphology (Class IIa/level A) in combination with an LVEF of ≤30%, who are expected to survive for >1 year with good functional status. Recently, the indications have been expanded to include NYHA Class II patients based on recent trials (see text above).
- A CRT-P or CRT-D device may also be considered in patients with permanent AF and NYHA functional Class III or ambulatory Class IV with a QRS duration of ≥120 ms and an LVEF of ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF worsening if:
  - The patient requires pacing because of an intrinsically slow ventricular rate.
  - The patient is pacemaker-dependent as a result of AV nodal ablation.
  - The patient's ventricular rate is ≤60 b.p.m. at rest and ≤90 b.p.m. on exercise.
- A CRT device may be considered in patients with an indication for conventional pacing, expected high frequency of ventricular pacing, no other indication for CRT, and expected to survive with good functional status for >1 year, if they are
  - NYHA functional Class III or IV with an LVEF of ≤35%, irrespective of QRS duration, to reduce the risk of worsening of HF, or
  - NYHA functional Class II with an LVEF of ≤35%, irrespective of QRS duration, to reduce the risk of HF worsening.

Conclusions

In summary, clinical management of HF needs to take into account the high risk of arrhythmias in these patients. Underlying structural heart disease limits the spectrum of antiarrhythmic drugs for symptomatic patients. Implantable cardioverter defibrillator therapy effectively reduces mortality in patients with severely reduced LVEF, but as only a minority of implanted patients will experience clinically relevant VAs, improved risk assessment for primary prophylaxis warrants further studies, including risk stratification in HF-pEF.

Supplementary material

Supplementary material is available at *Europace* online.

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References

1. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–46.
2. Lau YC, Lane DA, Lip GY. Atrial fibrillation and heart failure: a bad combination. *Am J Cardiol* 2014;**113**:1196–7.
3. Luu M, Stevenson WG, Stevenson LW, Baron K, Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation* 1989;**80**:1675–80.
4. Whitman IR, Feldman HI, Deo R. CKD and sudden cardiac death: epidemiology, mechanisms, and therapeutic approaches. *J Am Soc Nephrol* 2012;**23**:1929–39.
5. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M *et al.* The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123–33.
6. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J *et al.* EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013;**15**:808–17.
7. Rewiuk K, Wizner B, Fedyk-Lukasik M, Zdrojewski T, Opolski G, Dubiel J *et al.* Epidemiology and management of coexisting heart failure and atrial fibrillation in an outpatient setting. *Pol Arch Med Wewn* 2011;**121**:392–9.
8. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992;**327**:685–91.
9. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;**316**:1429–35.
10. Sanders P, Morton JB, Davidson NC, Spence SJ, Vohra JK, Sparks PB *et al.* Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation* 2003;**108**:1461–8.

11. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation* 1999;**100**:87–95.
12. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr *et al.* Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;**373**:739–45.
13. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. *Circulation* 1991;**84**:40–8.
14. Carson PE, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**(6 Suppl):VI102–10.
15. Natterson PD, Stevenson WG, Saxon LA, Middlekauff HR, Stevenson LW. Risk of arterial embolization in 224 patients awaiting cardiac transplantation. *Am Heart J* 1995;**129**:564–70.
16. Stevenson WG, Stevenson LW, Middlekauff HR, Fonarow GC, Hamilton MA, Woo MA *et al.* Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol* 1996;**28**:1458–63.
17. Cioffi G, Pozzoli M, Forni G, Franchini M, Opasich C, Cobelli F *et al.* Systemic thromboembolism in chronic heart failure. A prospective study in 406 patients. *Eur Heart J* 1996;**17**:1381–9.
18. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of left ventricular dysfunction. *J Am Coll Cardiol* 1998;**32**:695–703.
19. Mahoney P, Kimmel S, DeNofrio D, Wahl P, Loh E. Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. *Am J Cardiol* 1999;**83**:1544–7.
20. Mathew J, Hunsberger S, Fleg J, Mc Sherry F, Williford W, Yusuf S. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest* 2000;**118**:914–22.
21. Crijns HJ, Tjeerdsma G, de Kam PJ, Boomsma F, van Gelder IC, van den Berg MP *et al.* Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. *Eur Heart J* 2000;**21**:1238–45.
22. 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.
23. Ahmed A, Thornton P, Perry GJ, Allman RM, DeLong JF. Impact of atrial fibrillation on mortality and readmission in older adults hospitalized with heart failure. *Eur J Heart Fail* 2004;**6**:421–6.
24. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M *et al.* Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005;**26**:1303–8.
25. Pedersen OD, Sondergaard P, Nielsen T, Nielsen SJ, Nielsen ES, Falstie-Jensen N *et al.* Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. *Eur Heart J* 2006;**27**:2866–70.
26. 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.
27. Wojtkowska I, Sobkowicz B, Musial WJ, Kozuch M. Persistent atrial fibrillation as a prognostic factor of outcome in patients with advanced heart failure. *Kardiol Pol* 2006;**64**:777–83. discussion 784–5.
28. Pai RG and Varadarajan P. Prognostic significance of atrial fibrillation is a function of left ventricular ejection fraction. *Clin Cardiol* 2007;**30**:349–54.
29. Corell P, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail* 2007;**9**:258–65.
30. Rusinaru D, Leborgne L, Peltier M, Tribouilloy C. Effect of atrial fibrillation on long-term survival in patients hospitalised for heart failure with preserved ejection fraction. *Eur J Heart Fail* 2008;**10**:566–72.
31. Rivero-Ayerza M, Scholte Op Reimer W, Lenzen M, Theuns DA, Jordaens L, Komajda M *et al.* New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. *Eur Heart J* 2008;**29**:1618–24.
32. Sampson UK, Pfeffer MA, McMurray JJ, Lokhnygina Y, White HD, Solomon SD *et al.* Predictors of stroke in high-risk patients after acute myocardial infarction: insights from the VALIANT Trial. *Eur Heart J* 2007;**28**:685–91.
33. Santini M, Gasparini M, Landolina M, Lunati M, Proclemer A, Padeletti L *et al.* Device-detected atrial tachyarrhythmias predict adverse outcome in real-world patients with implantable biventricular defibrillators. *J Am Coll Cardiol* 2011;**57**:167–72.
34. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK *et al.* Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace* 2012;**14**:230–7.
35. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M *et al.* Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail* 2012;**5**:571–8.
36. Mentz RJ, Chung MJ, Gheorghiade M, Pang PS, Kwasny MJ, Ambrosy AP *et al.* Atrial fibrillation or flutter on initial electrocardiogram is associated with worse outcomes in patients admitted for worsening heart failure with reduced ejection fraction: findings from the EVEREST Trial. *Am Heart J* 2012;**164**:884–92. e2.
37. McManus DD, Hsu G, Sung SH, Saczynski JS, Smith DH, Magid DJ *et al.* Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. *J Am Heart Assoc* 2013;**2**:e005694.
38. Zakeri R, Borlaug BA, McNulty SE, Mohammed SF, Lewis GD, Semigran MJ *et al.* Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Circ Heart Fail* 2014;**7**:123–30.
39. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A *et al.* Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–85.
40. Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. *Heart* 2014;**100**:1506–10.
41. Agostoni P, Emdin M, Corra U, Veglia F, Magri D, Tedesco CC *et al.* Permanent atrial fibrillation affects exercise capacity in chronic heart failure patients. *Eur Heart J* 2008;**29**:2367–72.
42. Pullicino PM, Halperin JL, Thompson JL. Stroke in patients with heart failure and reduced left ventricular ejection fraction. *Neurology* 2000;**54**:288–94.
43. Vemmos K, Ntaios G, Savvari P, Vemmou AM, Koroboki E, Manios E *et al.* Stroke aetiology and predictors of outcome in patients with heart failure and acute stroke: a 10-year follow-up study. *Eur J Heart Fail* 2012;**14**:211–8.
44. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review *Thromb Haemost* 2013;**110**:213–22.
45. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J *et al.* Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;**111**:1167–76.
46. Potpara TS, Polovina MM, Marinkovic JM, Lip GY. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Int J Cardiol* 2013;**168**:4744–9.
47. Agarwal M, Apostolakis S, Lane DA, Lip GY. The impact of heart failure and left ventricular dysfunction in predicting stroke, thromboembolism, and mortality in atrial fibrillation patients: a systematic review. *Clin Ther* 2014;**36**:1135–44.
48. Jang SJ, Kim MS, Park HJ, Han S, Kang DH, Song JK *et al.* Impact of heart failure with normal ejection fraction on the occurrence of ischaemic stroke in patients with atrial fibrillation. *Heart* 2013;**99**:17–21.
49. 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.
50. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Lip GY. Predictors and prognostic implications of incident heart failure following the first diagnosis of atrial fibrillation in patients with structurally normal hearts: the Belgrade Atrial Fibrillation Study. *Eur J Heart Fail* 2013;**15**:415–24.
51. Gupta S and Figueredo VM. Tachycardia mediated cardiomyopathy: pathophysiology, mechanisms, clinical features and management. *Int J Cardiol* 2014;**172**:40–6.
52. Chen J, Johnson G, Hellkamp AS, Anderson J, Mark DB, Lee KL *et al.* Rapid-rate nonsustained ventricular tachycardia found on implantable cardioverter-defibrillator interrogation: relationship to outcomes in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). *J Am Coll Cardiol* 2013;**61**:2161–8.
53. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A *et al.* Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008;**118**:1080–111.
54. Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I *et al.* Circadian variation in the frequency of sudden cardiac death. *Circulation* 1987;**75**:131–8.
55. Podrid PJ, Fogel RI, Fuchs TT. Ventricular arrhythmia in congestive heart failure. *Am J Cardiol* 1992;**69**:82G–95G. discussion 95G–96G.

56. Cleland JG, Chattopadhyay S, Khand A, Houghton T, Kaye GC. Prevalence and incidence of arrhythmias and sudden death in heart failure. *Heart Fail Rev* 2002;**7**:229–42.
57. Liao YC, Hsieh YC, Hung CY, Huang JL, Lin CH, Wang KY *et al.* Statin therapy reduces the risk of ventricular arrhythmias, sudden cardiac death, and mortality in heart failure patients: a nationwide population-based cohort study. *Int J Cardiol* 2013;**168**:4805–7.
58. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M *et al.* Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J* 2002;**143**:398–405.
59. Packer DL, Prutkin JM, Hellkamp AS, Mitchell LB, Bernstein RC, Wood F *et al.* Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. *Circulation* 2009;**120**:2170–6.
60. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F *et al.* The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. *Eur J Heart Fail* 2000;**2**:123–32.
61. McMurray JJ, Carson PE, Komajda M, McKelvie R, Zile MR, Ptaszynska A *et al.* Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail* 2008;**10**:149–56.
62. Sweeney MO. Sudden death in heart failure associated with reduced left ventricular function: substrates, mechanisms, and evidence-based management, Part II. *Pacing Clin Electrophysiol* 2001;**24**:1002–22.
63. Whang W, Mittleman MA, Rich DQ, Wang PJ, Ruskin JN, Tofler GH *et al.* Heart failure and the risk of shocks in patients with implantable cardioverter defibrillators: results from the Triggers Of Ventricular Arrhythmias (TOVA) study. *Circulation* 2004;**109**:1386–91.
64. Adabag S, Smith LG, Anand IS, Berger AK, Luepker RV. Sudden cardiac death in heart failure patients with preserved ejection fraction. *J Card Fail* 2012;**18**:749–54.
65. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J *et al.* The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–45.
66. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW *et al.* Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation* 2006;**114**:397–403.
67. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ *et al.* Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;**362**:777–81.
68. Spirito P, Autore C, Formisano F, Assenza GE, Biagini E, Haas TS *et al.* Risk of sudden death and outcome in patients with hypertrophic cardiomyopathy with benign presentation and without risk factors. *Am J Cardiol* 2014;**113**:1550–5.
69. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P *et al.* 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–79.
70. Saoudi N, Cosio F, Waldo A, Chen SA, Iesaka Y, Lesh M *et al.* Classification of atrial flutter and regular atrial tachycardia according to electrophysiologic mechanism and anatomic bases: a statement from a joint expert group from the Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *J Cardiovasc Electrophysiol* 2001;**12**:852–66.
71. 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.
72. Dorian P, Philippon F, Thibault B, Kimber S, Sterns L, Greene M *et al.* Randomized controlled study of detection enhancements versus rate-only detection to prevent inappropriate therapy in a dual-chamber implantable cardioverter-defibrillator. *Heart Rhythm* 2004;**1**:540–7.
73. 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.
74. Bamimore A and Mounsey P. Ablation of atrial tachycardia and atrial flutter in heart failure. *Heart Fail Clin* 2013;**9**:501–14.
75. Gasparini M, Leclercq C, Lunati M, Landolina M, Auricchio A, Santini M *et al.* Cardiac resynchronization therapy in patients with atrial fibrillation: the CERTIFY study (Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry). *JACC Heart Fail* 2013;**1**:500–7.
76. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al.* 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
77. Adan V and Crown LA. Diagnosis and treatment of sick sinus syndrome. *Am Fam Physician* 2003;**67**:1725–32.
78. Witte KK, Cleland JG, Clark AL. Chronic heart failure, chronotropic incompetence, and the effects of beta blockade. *Heart* 2006;**92**:481–6.
79. Magri D, Corra U, Di Lenarda A, Cattadori G, Maruotti A, Iorio A *et al.* Cardiovascular mortality and chronotropic incompetence in systolic heart failure: the importance of a reappraisal of current cut-off criteria. *Eur J Heart Fail* 2014;**16**:201–9.
80. Bloch Thomsen PE, Jons C, Raatikainen MJ, Moerch Joergensen R, Hartikainen J, Virtanen V *et al.* Long-term recording of cardiac arrhythmias with an implantable cardiac monitor in patients with reduced ejection fraction after acute myocardial infarction: the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) study. *Circulation* 2010;**122**:1258–64.
81. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM *et al.* Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). *Eur Heart J* 2014;**35**:3155–79.
82. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ *et al.* Executive summary: heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 2014;**129**:399–410.
83. Ohlow MA, Geller JC, Richter S, Farah A, Muller S, Fuhrmann JT *et al.* Incidence and predictors of ventricular arrhythmias after ST-segment elevation myocardial infarction. *Am J Emerg Med* 2012;**30**:580–6.
84. Barron HV, Bowlby LJ, Breen T, Rogers WJ, Canto JG, Zhang Y *et al.* Use of reperfusion therapy for acute myocardial infarction in the United States: data from the National Registry of Myocardial Infarction 2. *Circulation* 1998;**97**:1150–6.
85. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20.
86. Heper G, Korkmaz ME, Kilic A. Reperfusion arrhythmias: are they only a marker of epicardial reperfusion or continuing myocardial ischemia after acute myocardial infarction? *Angiology* 2007;**58**:663–70.
87. Wu AH, Parsons L, Every NR, Bates ER, Second National Registry of Myocardial Infarction. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). *J Am Coll Cardiol* 2002;**40**:1389–94.
88. Pfeffer MA, Greaves SC, Arnold JM, Glynn RJ, LaMotte FS, Lee RT *et al.* Early versus delayed angiotensin-converting enzyme inhibition therapy in acute myocardial infarction. The healing and early afterload reducing therapy trial. *Circulation* 1997;**95**:2643–51.
89. Bunch TJ, May HT, Bair TL, Crandall BG, Weiss JP, Osborn JS *et al.* Trends in early and late mortality in patients undergoing coronary catheterization for myocardial infarction: implications on observation periods and risk factors to determine ICD candidacy. *Heart Rhythm* 2011;**8**:1460–6.
90. Adabag AS, Therneau TM, Gersh BJ, Weston SA, Roger VL. Sudden death after myocardial infarction. *JAMA* 2008;**300**:2022–9.
91. Ellis ER and Josephson ME. Heart failure and tachycardia-induced cardiomyopathy. *Curr Heart Fail Rep* 2013;**10**:296–306.
92. Fenelon G, Wijns W, Andries E, Brugada P. Tachycardiomyopathy: mechanisms and clinical implications. *Pacing Clin Electrophysiol* 1996;**19**:95–106.
93. 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.
94. Kanei Y, Friedman M, Ogawa N, Hanon S, Lam P, Schweitzer P. Frequent premature ventricular complexes originating from the right ventricular outflow tract are associated with left ventricular dysfunction. *Ann Noninvasive Electrocardiol* 2008;**13**:81–5.
95. Yokokawa M, Kim HM, Good E, Crawford T, Chugh A, Pelosi F Jr *et al.* Impact of QRS duration of frequent premature ventricular complexes on the development of cardiomyopathy. *Heart Rhythm* 2012;**9**:1460–4.
96. Deyell MW, Park KM, Han Y, Frankel DS, Dixit S, Cooper JM *et al.* Predictors of recovery of left ventricular dysfunction after ablation of frequent ventricular premature depolarizations. *Heart Rhythm* 2012;**9**:1465–72.

97. Sarrazin JF, Labounty T, Kuhne M, Crawford T, Armstrong WF, Desjardins B *et al.* Impact of radiofrequency ablation of frequent post-infarction premature ventricular complexes on left ventricular ejection fraction. *Heart Rhythm* 2009;**6**:1543–9.
98. Natale A, Zimerman L, Tomassoni G, Kearney M, Kent V, Brandon MJ *et al.* Impact on ventricular function and quality of life of transcatheter ablation of the atrioventricular junction in chronic atrial fibrillation with a normal ventricular response. *Am J Cardiol* 1996;**78**:1431–3.
99. Isbister GK and Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. *Br J Clin Pharmacol* 2013;**76**:48–57.
100. Pizzale S, Lemery R, Green MS, Gollob MH, Tang AS, Birnie DH. Frequency and predictors of tachycardia-induced cardiomyopathy in patients with persistent atrial flutter. *Can J Cardiol* 2009;**25**:469–72.
101. Aguinaga L, Primo J, Anguera I, Mont L, Valentino M, Brugada P *et al.* Long-term follow-up in patients with the permanent form of junctional reciprocating tachycardia treated with radiofrequency ablation. *Pacing Clin Electrophysiol* 1998;**21**(11 Pt 1):2073–8.
102. Zannad F, Huvelle E, Dickstein K, van Veldhuisen DJ, Stellbrink C, Kober L *et al.* Left bundle branch block as a risk factor for progression to heart failure. *Eur J Heart Fail* 2007;**9**:7–14.
103. Vaillant C, Martins RP, Donal E, Leclercq C, Thebault C, Behar N *et al.* Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. *J Am Coll Cardiol* 2013;**61**:1089–95.
104. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H *et al.* Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;**288**:3115–23.
105. 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.
106. Houmsse M, Tyler J, Kalbfleisch S. Supraventricular tachycardia causing heart failure. *Curr Opin Cardiol* 2011;**26**:261–9.
107. Butt M, Dwivedi G, Khair O, Lip GY. Obstructive sleep apnea and cardiovascular disease. *Int J Cardiol* 2010;**139**:7–16.
108. Chami HA, Devereux RB, Gottdiener JS, Mehra R, Roman MJ, Benjamin EJ *et al.* Left ventricular morphology and systolic function in sleep-disordered breathing: the Sleep Heart Health Study. *Circulation* 2008;**117**:2599–607.
109. Otto ME, Belohlavek M, Romero-Corral A, Gami AS, Gilman G, Svatikova A *et al.* Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. *Am J Cardiol* 2007;**99**:1298–302.
110. Javaheri S, Javaheri S, Javaheri A. Sleep apnea, heart failure, and pulmonary hypertension. *Curr Heart Fail Rep* 2013;**10**:315–20.
111. 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.
112. Neilan TG, Farhad H, Dodson JA, Shah RV, Abbasi SA, Bakker JP *et al.* Effect of sleep apnea and continuous positive airway pressure on cardiac structure and recurrence of atrial fibrillation. *J Am Heart Assoc* 2013;**2**:e000421.
113. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T *et al.* Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med* 2003;**348**:1233–41.
114. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D *et al.* Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). *Circulation* 2007;**115**:3173–80.
115. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J *et al.* Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005;**67**:2089–100.
116. Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG *et al.* Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011;**80**:572–86.
117. Roberts PR and Green D. Arrhythmias in chronic kidney disease. *Heart* 2011;**97**:766–73.
118. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA *et al.* Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;**367**:625–35.
119. Bonde AN, Lip GY, Kamper AL, Hansen PR, Lamberts M, Hommel K *et al.* Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a Nationwide Observational Cohort Study. *J Am Coll Cardiol* 2014;**64**:2471–82.
120. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J* 2015;**36**:297–306.
121. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. *Lancet* 1994;**343**:327–9.
122. Middlekauff HR, Stevenson WG, Saxon LA, Stevenson LW. Amiodarone and torsades de pointes in patients with advanced heart failure. *Am J Cardiol* 1995;**76**:499–502.
123. O'Callaghan PA and McGovern BA. Evolving role of sotalol in the management of ventricular tachyarrhythmias. *Am J Cardiol* 1996;**78**(4A):54–60.
124. Doval HC. Class III antiarrhythmic agents in cardiac failure: lessons from clinical trials with a focus on the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). *Am J Cardiol* 1999;**84**(9A):109R–14R.
125. Macdonald JE and Struthers AD. What is the optimal serum potassium level in cardiovascular patients? *J Am Coll Cardiol* 2004;**43**:155–61.
126. Brady WJ, DeBehnke DJ, Laundrie D. Prevalence, therapeutic response, and outcome of ventricular tachycardia in the out-of-hospital setting: a comparison of monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, and torsades de pointes. *Acad Emerg Med* 1999;**6**:609–17.
127. Varriale P and Leonardi M. Polymorphic ventricular tachycardia in the coronary care unit. *Heart Lung* 2006;**35**:283–9.
128. McNair WP, Sinagra G, Taylor MR, Di Lenarda A, Ferguson DA, Salcedo EE *et al.* SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. *J Am Coll Cardiol* 2011;**57**:2160–8.
129. Ziv O, Dizon J, Thosani A, Naka Y, Magnano AR, Garan H. Effects of left ventricular assist device therapy on ventricular arrhythmias. *J Am Coll Cardiol* 2005;**45**:1428–34.
130. Nakahara S, Chien C, Gelow J, Dalouk K, Henrikson CA, Mudd J *et al.* Ventricular arrhythmias after left ventricular assist device. *Circ Arrhythm Electrophysiol* 2013;**6**:648–54.
131. Pecha S, Wilke I, Bernhardt A, Hakmi S, Yildirim Y, Steven D *et al.* Clinical experience of combined HeartWare ventricular assist device and implantable cardioverter defibrillator therapy. *J Cardiovasc Electrophysiol* 2014;**25**:1109–14.
132. Oswald H, Schultz-Wildelau C, Gardiwal A, Lusebrink U, Konig T, Meyer A *et al.* Implantable defibrillator therapy for ventricular tachyarrhythmia in left ventricular assist device patients. *Eur J Heart Fail* 2010;**12**:593–9.
133. Boilson BA and Friedman PA. Role of implantable cardioverter-defibrillators in patients with continuous flow ventricular assist devices. *Circ Arrhythm Electrophysiol* 2013;**6**:663–5.
134. Hamzeh N, Steckman DA, Sauer WH, Judson MA. Pathophysiology and clinical management of cardiac sarcoidosis. *Nat Rev Cardiol* 2015;**12**:278–88.
135. 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. *Circulation* 2010;**121**:1533–41.
136. Tham YK, Bernardo BC, Ooi JY, Weeks KL, McMullen JR. Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets. *Arch Toxicol* 2015 [Epub ahead of print].
137. Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM *et al.* Decision making in advanced heart failure: a scientific statement from the American Heart Association. *Circulation* 2012;**125**:1928–52.
138. 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.
139. Lerma C, Gorelick A, Ghanem RN, Glass L, Huikuri HV. Patterns of ectopy leading to increased risk of fatal or near-fatal cardiac arrhythmia in patients with depressed left ventricular function after an acute myocardial infarction. *Europace* 2013;**15**:1304–12.
140. Guglin M, Chen R, Curtis AB. Sinus rhythm is associated with fewer heart failure symptoms: insights from the AFFIRM trial. *Heart Rhythm* 2010;**7**:596–601.
141. Baerman JM, Morady F, DiCarlo LA Jr, de Buitleir M. Differentiation of ventricular tachycardia from supraventricular tachycardia with aberration: value of the clinical history. *Ann Emerg Med* 1987;**16**:40–3.
142. Teerlink JR, Jalaluddin M, Anderson S, Kukin ML, Eichhorn EJ, Francis G *et al.* Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. PROMISE (Prospective Randomized Milrinone Survival Evaluation) Investigators. *Circulation* 2000;**101**:40–6.
143. Singh SN, Fisher SG, Carson PE, Fletcher RD. Prevalence and significance of nonsustained ventricular tachycardia in patients with premature ventricular contractions and heart failure treated with vasodilator therapy. Department of Veterans Affairs CHF STAT Investigators. *J Am Coll Cardiol* 1998;**32**:942–7.
144. Zecchin M, Di Lenarda A, Gregori D, Merlo M, Pivetta A, Vitrella G *et al.* Are nonsustained ventricular tachycardias predictive of major arrhythmias in patients with dilated cardiomyopathy on optimal medical treatment? *Pacing Clin Electrophysiol* 2008;**31**:290–9.

145. Wilkoff BL, Williamson BD, Stern RS, Moore SL, Lu F, Lee SW *et al.* Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. *J Am Coll Cardiol* 2008;**52**:541–50.
146. Lusebrink U, Duncker D, Hess M, Heinrichs I, Gardiwal A, Oswald H *et al.* Clinical relevance of slow ventricular tachycardia in heart failure patients with primary prophylactic implantable cardioverter defibrillator indication. *Europace* 2013;**15**:820–6.
147. Gasparini M, Proclemer A, Klersy C, Kloppe A, Lunati M, Ferrer JB *et al.* Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. *JAMA* 2013;**309**:1903–11.
148. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP *et al.* Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;**367**:2275–83.
149. Disertori M, Lombardi F, Barlera S, Maggioni AP, Favero C, Franzosi MG *et al.* Clinical characteristics of patients with asymptomatic recurrences of atrial fibrillation in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trial. *Am Heart J* 2011;**162**:382–9.
150. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A *et al.* Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–9.
151. Reiffel J, Verma A, Halperin JL, Gersh B, Tombul S, Carrithers J *et al.* Rationale and design of REVEAL AF: a prospective study of previously undiagnosed atrial fibrillation as documented by an insertable cardiac monitor in high-risk patients. *Am Heart J* 2014;**167**:22–7.
152. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**:803–69.
153. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**:1093–100.
154. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F *et al.* Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. *Thromb Haemost* 2013;**110**:1087–107.
155. Gallego P, Roldan V, Marin F, Romera M, Valdes M, Vicente V *et al.* Cessation of oral anticoagulation in relation to mortality and the risk of thrombotic events in patients with atrial fibrillation. *Thromb Haemost* 2013;**110**:1189–98.
156. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. *Chest* 2013;**144**:1555–63.
157. Fauchier L, Angoulvant D, Lip GY. The SAMe-TT_2R_2 score and quality of anticoagulation in atrial fibrillation: a simple aid to decision-making on who is suitable (or not) for vitamin K antagonists. *Europace* 2015;**17**:671–3.
158. Ferreira J, Ezekowitz MD, Connolly SJ, Brueckmann M, Fraessdorf M, Reilly PA *et al.* Dabigatran compared with warfarin in patients with atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. *Eur J Heart Fail* 2013;**15**:1053–61.
159. van Diepen S, Hellkamp AS, Patel MR, Becker RC, Breithardt G, Hacke W *et al.* Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. *Circ Heart Fail* 2013;**6**:740–7.
160. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J *et al.* Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail* 2013;**6**:451–60.
161. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J *et al.* European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;**15**:625–51.
162. Meier B, Blaauw Y, Khattab AA, Lewalter T, Sievert H, Tondo C *et al.* EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. *Europace* 2014;**16**:1397–416.
163. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL *et al.* Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004;**109**:1509–13.
164. Ionescu-Ittu R, Abrahamowicz M, Jackevicius CA, Essebag V, Eisenberg MJ, Wynant W *et al.* Comparative effectiveness of rhythm control vs rate control drug treatment effect on mortality in patients with atrial fibrillation. *Arch Intern Med* 2012;**172**:997–1004.
165. Talajic M, Khairy P, Levesque S, Connolly SJ, Dorian P, Dubuc M *et al.* Maintenance of sinus rhythm and survival in patients with heart failure and atrial fibrillation. *J Am Coll Cardiol* 2010;**55**:1796–802.
166. Tsadok MA, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH *et al.* Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. *Circulation* 2012; **126**:2680–7.
167. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E *et al.* Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function. *J Am Coll Cardiol* 2013;**62**:1990–7.
168. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H *et al.* Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–87.
169. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC *et al.* Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995;**333**:77–82.
170. Deedwania PC, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998;**98**:2574–9.
171. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F *et al.* Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* 2004;**351**:2373–83.
172. Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO *et al.* Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol* 2004;**43**:1004–9.
173. Tondo C, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A *et al.* Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. *Pacing Clin Electrophysiol* 2006;**29**:962–70.
174. Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E *et al.* Reversal of left ventricular dysfunction following ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2007;**18**:9–14.
175. Nademanee K, Schwab MC, Kosar EM, Karwecki M, Moran MD, Visessook N *et al.* Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:843–9.
176. Lutomsky BA, Rostock T, Koops A, Steven D, Mullerleile K, Servatius H *et al.* Catheter ablation of paroxysmal atrial fibrillation improves cardiac function: a prospective study on the impact of atrial fibrillation ablation on left ventricular function assessed by magnetic resonance imaging. *Europace* 2008;**10**:593–9.
177. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO *et al.* Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;**359**:1778–85.
178. De Potter T, Berruezo A, Mont L, Matiello M, Tamborero D, Santibanez C *et al.* Left ventricular systolic dysfunction by itself does not influence outcome of atrial fibrillation ablation. *Europace* 2010;**12**:24–9.
179. Cha YM, Wokhlu A, Asirvatham SJ, Shen WK, Friedman PA, Munger TM *et al.* Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. *Circ Arrhythm Electrophysiol* 2011;**4**:724–32.
180. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M *et al.* Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011;**97**:740–7.
181. Anselmino M, Grossi S, Scaglione M, Castagno D, Bianchi F, Senatore G *et al.* Long-term results of transcatheter atrial fibrillation ablation in patients with impaired left ventricular systolic function. *J Cardiovasc Electrophysiol* 2013;**24**:24–32.
182. Calvo N, Bisbal F, Guiu E, Ramos P, Nadal M, Tolosana JM *et al.* Impact of atrial fibrillation-induced tachycardiomyopathy in patients undergoing pulmonary vein isolation. *Int J Cardiol* 2013;**168**:4093–7.
183. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL *et al.* A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* 2013;**61**:1894–903.
184. Wilton SB, Fundytus A, Ghali WA, Veenhuyzen GD, Quinn FR, Mitchell LB *et al.* Meta-analysis of the effectiveness and safety of catheter ablation of atrial fibrillation in patients with versus without left ventricular systolic dysfunction. *Am J Cardiol* 2010;**106**:1284–91.
185. Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK *et al.* Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. *J Card Fail* 2011; **17**:964–70.

186. Anselmino M, Matta M, D'Ascenzo F, Bunch TJ, Schilling RJ, Hunter RJ *et al.* Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2014;**7**:1011–8.
187. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F *et al.* Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 2011;**57**:160–6.
188. Marrouche NF and Brachmann J. Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF)—study design. *Pacing Clin Electrophysiol* 2009;**32**:987–94.
189. Anselmino M, Scaglione M, Blandino A, Beninati S, Caponi D, Boffano C *et al.* Pulmonary veins branching pattern, assessed by magnetic resonance, does not affect transcatheter atrial fibrillation ablation outcome. *Acta Cardiol* 2010;**65**:665–74.
190. Berruezo A, Tamborero D, Mont L, Benito B, Tolosana JM, Sitges M *et al.* Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J* 2007;**28**:836–41.
191. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG *et al.* Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;**384**:2235–43.
192. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003;**42**:1944–51.
193. Mulder BA, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M *et al.* Lenient vs. strict rate control in patients with atrial fibrillation and heart failure: a post-hoc analysis of the RACE II study. *Eur J Heart Fail* 2013;**15**:1311–8.
194. Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D *et al.* Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**:2420–9.
195. Orlov MV, Gardin JM, Slawsky M, Bess RL, Cohen G, Bailey W *et al.* Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients with symptomatic atrial fibrillation after atrioventricular node ablation. *Am Heart J* 2010;**159**:264–70.
196. Stavrakis S, Garabelli P, Reynolds DW. Cardiac resynchronization therapy after atrioventricular junction ablation for symptomatic atrial fibrillation: a meta-analysis. *Europace* 2012;**14**:1490–7.
197. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T *et al.* EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Europace* 2014;**16**:1257–83.
198. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
199. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
200. Elizari MV, Martinez JM, Belziti C, Ciruzzi M, Perez de la Hoz R, Sinisi A *et al.* Morbidity and mortality following early administration of amiodarone in acute myocardial infarction. GEMICA study investigators, GEMA Group, Buenos Aires, Argentina. Grupo de Estudios Multicentricos en Argentina. *Eur Heart J* 2000;**21**:198–205.
201. 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.
202. Piepoli M, Villani GQ, Ponikowski P, Wright A, Flather MD, Coats AJ. Overview and meta-analysis of randomised trials of amiodarone in chronic heart failure. *Int J Cardiol* 1998;**66**:1–10.
203. Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. *Eur Heart J* 2009;**30**:1245–53.
204. Katritsis DG, Zareba W, Camm AJ. Nonsustained ventricular tachycardia. *J Am Coll Cardiol* 2012;**60**:1993–2004.
205. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF *et al.* Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival with oral d-Sotalol. *Lancet* 1996;**348**:7–12.
206. Kowey PR, Crijns HJ, Aliot EM, Capucci A, Kulakowski P, Radzik D *et al.* Efficacy and safety of celivarone, with amiodarone as calibrator, in patients with an implantable cardioverter-defibrillator for prevention of implantable cardioverter-defibrillator interventions or death: the ALPHEE study. *Circulation* 2011;**124**:2649–60.
207. Verrier RL, Pagotto VP, Kanas AF, Sobrado MF, Nearing BD, Zeng D *et al.* Low doses of ranolazine and dronedarone in combination exert potent protection against atrial fibrillation and vulnerability to ventricular arrhythmias during acute myocardial ischemia. *Heart Rhythm* 2013;**10**:121–7.
208. Verrier RL, Kumar K, Nieminen T, Belardinelli L. Mechanisms of ranolazine's dual protection against atrial and ventricular fibrillation. *Europace* 2013;**15**:317–24.
209. Doval HC, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G *et al.* Non-sustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA Investigators. *Circulation* 1996;**94**:3198–203.
210. Stein PK, Sanghavi D, Domitrovich PP, Mackey RA, Deedwania P. Ambulatory ECG-based T-wave alternans predicts sudden cardiac death in high-risk post-MI patients with left ventricular dysfunction in the EPHESUS study. *J Cardiovasc Electrophysiol* 2008;**19**:1037–42.
211. Rashba EJ, Estes NA, Wang P, Schaechter A, Howard A, Zareba W *et al.* Preserved heart rate variability identifies low-risk patients with nonischemic dilated cardiomyopathy: results from the DEFINITE trial. *Heart Rhythm* 2006; **3**:281–6.
212. Zeidan-Shwiri T, Yang Y, Lashevsky I, Kadmon E, Kagal D, Dick A *et al.* Magnetic resonance estimates of the extent and heterogeneity of scar tissue in ICD patients with ischemic cardiomyopathy predict ventricular arrhythmia. *Heart Rhythm* 2015;**12**:802–8.
213. Christensen TE, Kjaer A, Hasbak P. The clinical value of cardiac sympathetic imaging in heart failure. *Clin Physiol Funct Imaging* 2014;**34**:178–82.
214. Gorenek B, Blomstrom Lundqvist C, Brugada Terradellas J, Camm AJ, Hindricks G, Huber K *et al.* Cardiac arrhythmias in acute coronary syndromes: position paper from the joint EHRA, ACCA, and EAPCI task force. *Europace* 2014;**16**:1655–73.
215. Weir RA, McMurray JJ, Velazquez EJ. Epidemiology of heart failure and left ventricular systolic dysfunction after acute myocardial infarction: prevalence, clinical characteristics, and prognostic importance. *Am J Cardiol* 2006;**97**:13F–25F.
216. Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. *N Engl J Med* 2008;**359**:2245–53.
217. Makikallio TH, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP *et al.* Frequency of sudden cardiac death among acute myocardial infarction survivors with optimized medical and revascularization therapy. *Am J Cardiol* 2006;**97**:480–4.
218. Bougouin W, Marijon E, Puymirat E, Defaye P, Celermajer DS, Le Heuzey JY *et al.* Incidence of sudden cardiac death after ventricular fibrillation complicating acute myocardial infarction: a 5-year cause-of-death analysis of the FAST-MI 2005 registry. *Eur Heart J* 2014;**35**:116–22.
219. Carbucicchio C, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G *et al.* Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short- and long-term outcomes in a prospective single-center study. *Circulation* 2008;**117**:462–9.
220. Kozeluhova M, Peichl P, Cihak R, Wichterle D, Vancura V, Bytesnik J *et al.* Catheter ablation of electrical storm in patients with structural heart disease. *Europace* 2011;**13**:109–13.
221. Tan VH, Yap J, Hsu LF, Liew R. Catheter ablation of ventricular fibrillation triggers and electrical storm. *Europace* 2012;**14**:1687–95.
222. Exner D. Noninvasive risk stratification after myocardial infarction: rationale, current evidence and the need for definitive trials. *Can J Cardiol* 2009;**25**(Suppl A):21A–7A.
223. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA *et al.* ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**: 2569–619.
224. Kumar S, Sivagangabalan G, Zaman S, West EB, Narayan A, Thiagalingam A *et al.* Electrophysiology-guided defibrillator implantation early after ST-elevation myocardial infarction. *Heart Rhythm* 2010;**7**:1589–97.
225. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R *et al.* Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;**351**:2481–8.
226. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D *et al.* Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009;**361**:1427–36.
227. Raviele A, Bongiorni MG, Brignole M, Cappato R, Capucci A, Gaita F *et al.* Early EPS/ICD strategy in survivors of acute myocardial infarction with severe left ventricular dysfunction on optimal beta-blocker treatment. The BEta-blocker STrategy plus ICD trial. *Europace* 2005;**7**:327–37.
228. Pitt B, White H, Nicolau J, Martinez F, Gheorghiade M, Aschermann M *et al.* Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005;**46**:425–31.
229. Montalescot G, Pitt B, Lopez de Sa E, Hamm CW, Flather M, Verheugt F *et al.* Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. *Eur Heart J* 2014;**35**:2295–302.

230. Epstein AE, Abraham WT, Bianco NR, Kern KB, Mirro M, Rao SV *et al.* Wearable cardioverter-defibrillator use in patients perceived to be at high risk early post-myocardial infarction. *J Am Coll Cardiol* 2013;**62**:2000–7.
231. Bardy GH, Lee KL, Mark DB, Poole JE, Toff WD, Tonkin AM *et al.* Home use of automated external defibrillators for sudden cardiac arrest. *N Engl J Med* 2008;**358**:1793–804.
232. Shiga T, Hagiwara N, Ogawa H, Takagi A, Nagashima M, Yamauchi T *et al.* Sudden cardiac death and left ventricular ejection fraction during long-term follow-up after acute myocardial infarction in the primary percutaneous coronary intervention era: results from the HIJAMI-II registry. *Heart* 2009;**95**:216–20.
233. Mehta RH, Starr AZ, Lopes RD, Hochman JS, Widimsky P, Pieper KS *et al.* Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. *JAMA* 2009;**301**:1779–89.
234. Ottervanger JP, Ramdat Misier AR, Dambrink JH, de Boer MJ, Hoorntje JC, Gosselink AT *et al.* Mortality in patients with left ventricular ejection fraction ≤30% after primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiol* 2007;**100**:793–7.
235. Zaman S, Sivagangabalan G, Narayan A, Thiagalingam A, Ross DL, Kovoor P. Outcomes of early risk stratification and targeted implantable cardioverter-defibrillator implantation after ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Circulation* 2009;**120**:194–200.
236. 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.
237. Wilber DJ, Zareba W, Hall WJ, Brown MW, Lin AC, Andrews ML *et al.* Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004;**109**:1082–4.
238. Voller H, Kamke W, Klein HU, Block M, Reibis R, Treusch S *et al.*Clinical practice of defibrillator implantation after myocardial infarction: impact of implant time: results from the PreSCD II registry. *Europace* 2011;**13**:499–508.
239. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997;**337**:1576–83.
240. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;**102**:748–54.
241. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS *et al.* Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1297–302.
242. 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.
243. 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. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933–40.
244. 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.
245. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP *et al.* Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;**350**:2151–8.
246. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E *et al.* Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–53.
247. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B *et al.* Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003;**289**:2685–94.
248. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T *et al.* Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.
249. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49.
250. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C *et al.* Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–43.
251. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–38.
252. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S *et al.* Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–95.
253. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J *et al.* Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–405.
254. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L *et al.* Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;**368**:1585–93.
255. Refaat M, Chemaly E, Lebeche D, Gwathmey JK, Hajjar RJ. Ventricular arrhythmias after left ventricular assist device implantation. *Pacing Clin Electrophysiol* 2008;**31**:1246–52.
256. Andersen M, Videbaek R, Boesgaard S, Sander K, Hansen PB, Gustafsson F. Incidence of ventricular arrhythmias in patients on long-term support with a continuous-flow assist device (HeartMate II). *J Heart Lung Transplant* 2009;**28**:733–5.
257. Bedi M, Kormos R, Winowich S, McNamara DM, Mathier MA, Murali S. Ventricular arrhythmias during left ventricular assist device support. *Am J Cardiol* 2007;**99**:1151–3.
258. Enriquez AD, Calenda B, Miller MA, Anyanwu AC, Pinney SP. The role of implantable cardioverter-defibrillators in patients with continuous flow left ventricular assist devices. *Circ Arrhythm Electrophysiol* 2013;**6**:668–74.
259. Garan AR, Yuzefpolskaya M, Colombo PC, Morrow JP, Te-Frey R, Dano D *et al.* Ventricular arrhythmias and implantable cardioverter-defibrillator therapy in patients with continuous-flow left ventricular assist devices: need for primary prevention? *J Am Coll Cardiol* 2013;**61**:2542–50.
260. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT *et al.* Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;**149**:209–16.
261. Metra M, Cotter G, El-Khorazaty J, Davison BA, Milo O, Carubelli V *et al.* Acute heart failure in the elderly: differences in clinical characteristics, outcomes, and prognostic factors in the VERITAS study. *J Card Fail* 2015;**21**:179–88.
262. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC *et al.* The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;**24**:442–63.
263. Benza RL, Tallaj JA, Felker GM, Zabel KM, Kao W, Bourge RC *et al.* The impact of arrhythmias in acute heart failure. *J Card Fail* 2004;**10**:279–84.
264. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J *et al.* Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail* 2013;**1**:103–11.
265. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F *et al.* Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation* 2011;**123**:1587–93.
266. Boldt LH, Rolf S, Huemer M, Parwani AS, Luft FC, Dietz R *et al.* Optimal heart failure therapy and successful cardioversion in heart failure patients with atrial fibrillation. *Am Heart J* 2008;**155**:890–5.
267. Gatzoulis KA, Andrikopoulos GK, Apostolopoulos T, Sotiropoulos E, Zervopoulos G, Antoniou J *et al.* Electrical storm is an independent predictor of adverse long-term outcome in the era of implantable defibrillator therapy. *Europace* 2005;**7**:184–92.
268. Guerra F, Shkoza M, Scappini L, Flori M, Capucci A. Role of electrical storm as a mortality and morbidity risk factor and its clinical predictors: a meta-analysis. *Europace* 2014;**16**:347–53.
269. Hayashi M, Miyauchi Y, Murata H, Takahashi K, Tsuboi I, Uetake S *et al.* Urgent catheter ablation for sustained ventricular tachyarrhythmias in patients with acute heart failure decompensation. *Europace* 2014;**16**:92–100.
270. Guerra F, Flori M, Bonelli P, Patani F, Capucci A. Electrical storm and heart failure worsening in implantable cardiac defibrillator patients. *Europace* 2015;**17**:247–54.
271. Proietti M and Lip GY. Simple decision making between a vitamin K antagonist and non-vitamin K antagonist oral anticoagulant (NOACs): using the SAMe-TT_2R_2 score. *Eur Heart J Cardiovasc Pharmacother* [Epub ahead of print (4 March 2015)].
272. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS *et al.* Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;**2**:e004549.

273. Vakil K, Taimeh Z, Sharma A, Abidi KS, Colvin M, Luepker R *et al.* Incidence, predictors, and temporal trends of sudden cardiac death after heart transplantation. *Heart Rhythm* 2014;**11**:1684–90.
274. Marzoa-Rivas R, Perez-Alvarez L, Paniagua-Martin MJ, Ricoy-Martinez E, Flores-Rios X, Rodriguez-Fernandez JA *et al.* Sudden cardiac death of two heart transplant patients with correctly functioning implantable cardioverter defibrillators. *J Heart Lung Transplant* 2009;**28**:412–4.
275. Tsai VW, Cooper J, Garan H, Natale A, Ptaszek LM, Ellinor PT *et al.* The efficacy of implantable cardioverter-defibrillators in heart transplant recipients: results from a multicenter registry. *Circ Heart Fail* 2009;**2**:197–201.
276. Scott PA, Barry J, Roberts PR, Morgan JM. Brain natriuretic peptide for the prediction of sudden cardiac death and ventricular arrhythmias: a meta-analysis. *Eur J Heart Fail* 2009;**11**:958–66.
277. Zhang Y, Guallar E, Blasco-Colmenares E, Dalal D, Butcher B, Norgard S *et al.* Clinical and serum-based markers are associated with death within 1 year of de novo implant in primary prevention ICD recipients. *Heart Rhythm* 2015;**12**:360–6.
278. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H *et al.* Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008;**51**:288–96.