

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.

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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 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 symptoms⁸ 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 occurrence 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) $\leq 35\%$ 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 tolerated³⁹] 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 anaerobic 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 occur 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 enormously 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

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.

during sleep. There has been little primary epidemiological evidence on the prevalence of VA in the general CHF population (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 Cardíaca 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 failure 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

Bradycardia

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) Study⁸⁸ 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 ≤ 60 ml/min/1.73 m².¹¹⁵ 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 ratios 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 incrementally increases with a decreasing GFR, accounting for 25% of all-cause mortality in patients 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 re-entrant 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 torsades 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 SCD¹²² 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 arrhythmogenic 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 (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 dysfunction¹³⁷ (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 characterized 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,

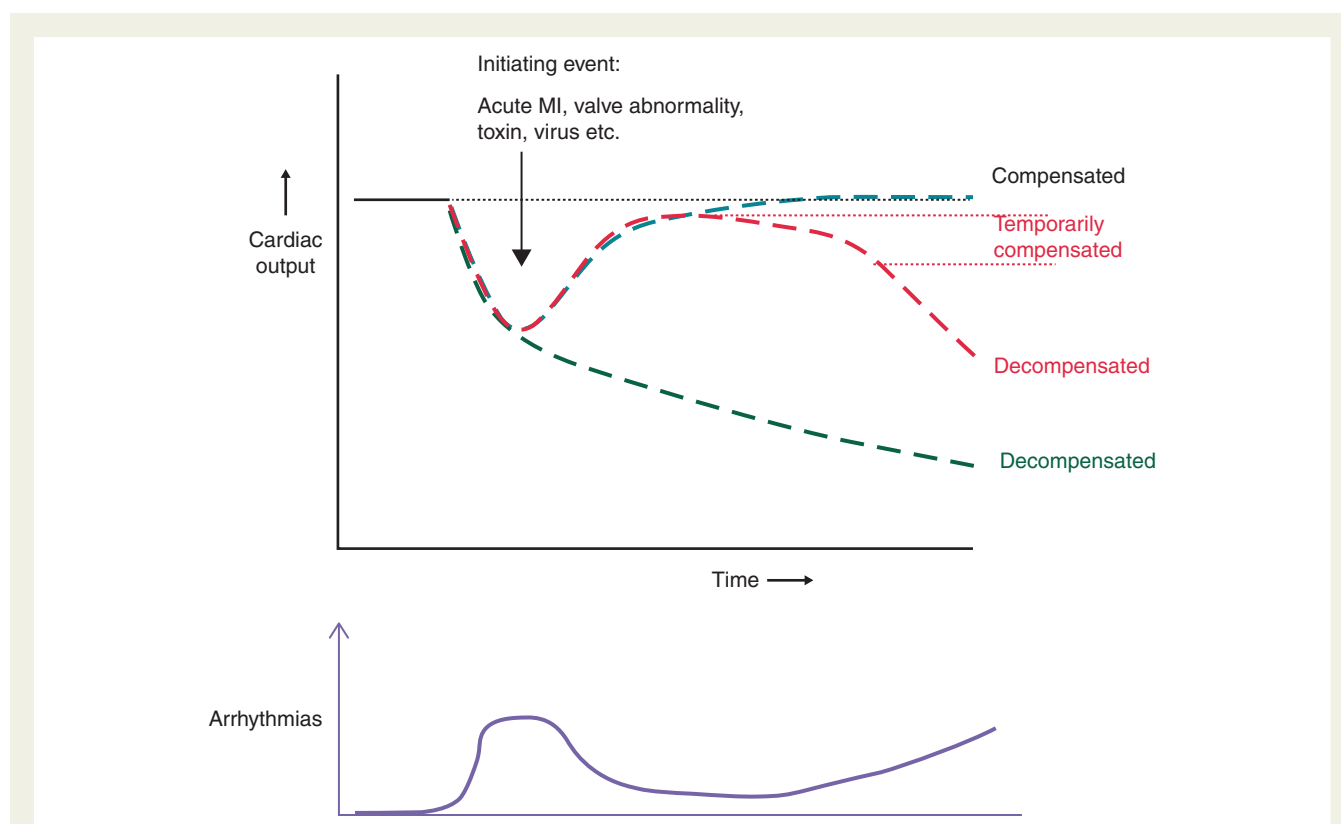


Figure 1 Arrhythmogenesis during the transition to chronic heart failure.

such as an increased late Na current and a reduced transient outward current (I_{to}). 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.

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.

Table 2 Rhythm monitoring in heart failure patients

Clinical condition	Aim for rhythm monitoring
No arrhythmia-related symptoms	
Stable HF patients with EF <35%	<ul style="list-style-type: none">• Screening for AF• No additional value for SCD risk
Stable HF patients with EF 35–50%	<ul style="list-style-type: none">• Screening for AF• Value for SCD prophylaxis not established
Stable HF patients with preserved EF	<ul style="list-style-type: none">• Screening for AF• Value for SCD prophylaxis not established
Post-myocardial infarction, EF <40%	<ul style="list-style-type: none">• Detect asymptomatic arrhythmias that may require therapy
Symptoms suspicious for arrhythmias	
Symptoms at rest	<ul style="list-style-type: none">• Correlate arrhythmia with symptoms
Symptoms during exercise	<ul style="list-style-type: none">• Correlate arrhythmia with symptoms
Syncope in patients with reduced EF or structural heart disease	<ul style="list-style-type: none">• Evaluate risk for SCD and sustained VT

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

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 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 smart-phone 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.

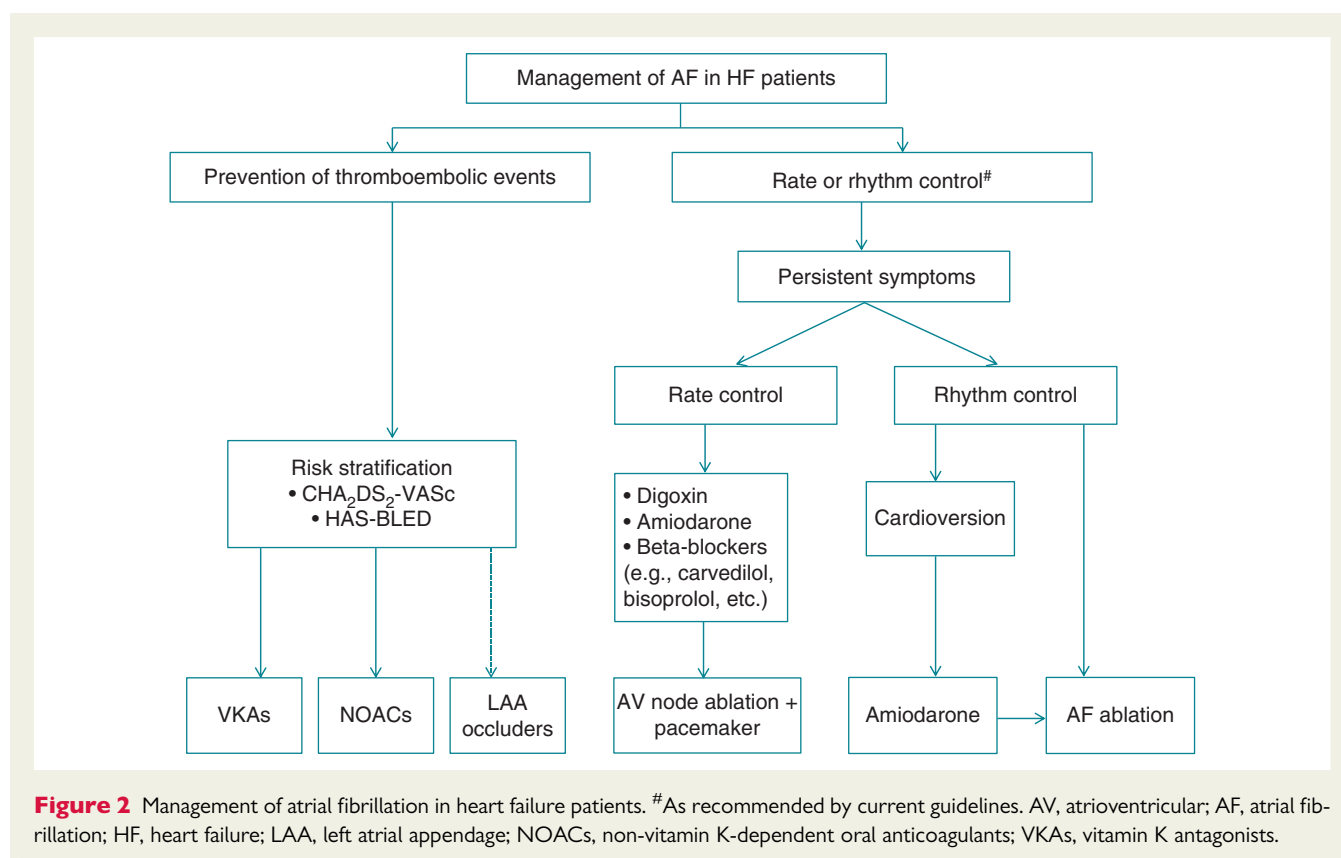
Management aspects

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 CHA₂DS₂-VASc score, to initially identify patients at truly low risk of stroke⁷⁶ 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 CHA₂DS₂-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 CHA₂DS₂-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-TT₂R₂ score that can help decision-making between those likely to do well on a VKA (SAME-TT₂R₂ score 0–2) and those unlikely to do well (SAME-TT₂R₂ 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 survival¹⁶⁴ 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 AN-ROMEDA (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

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

Author (year)	Study design	N	Summary of findings					Other parameters
			FU months	Success (single)	Redo	Success (final)	EF (%)	
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.

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}

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 AHA.¹⁹⁷ Risk stratification and management of patients with HF has been recently extensively reviewed.⁶⁹ Figure 3 and 4 show the management of ventricular tachycardias 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) study¹⁶⁹ 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

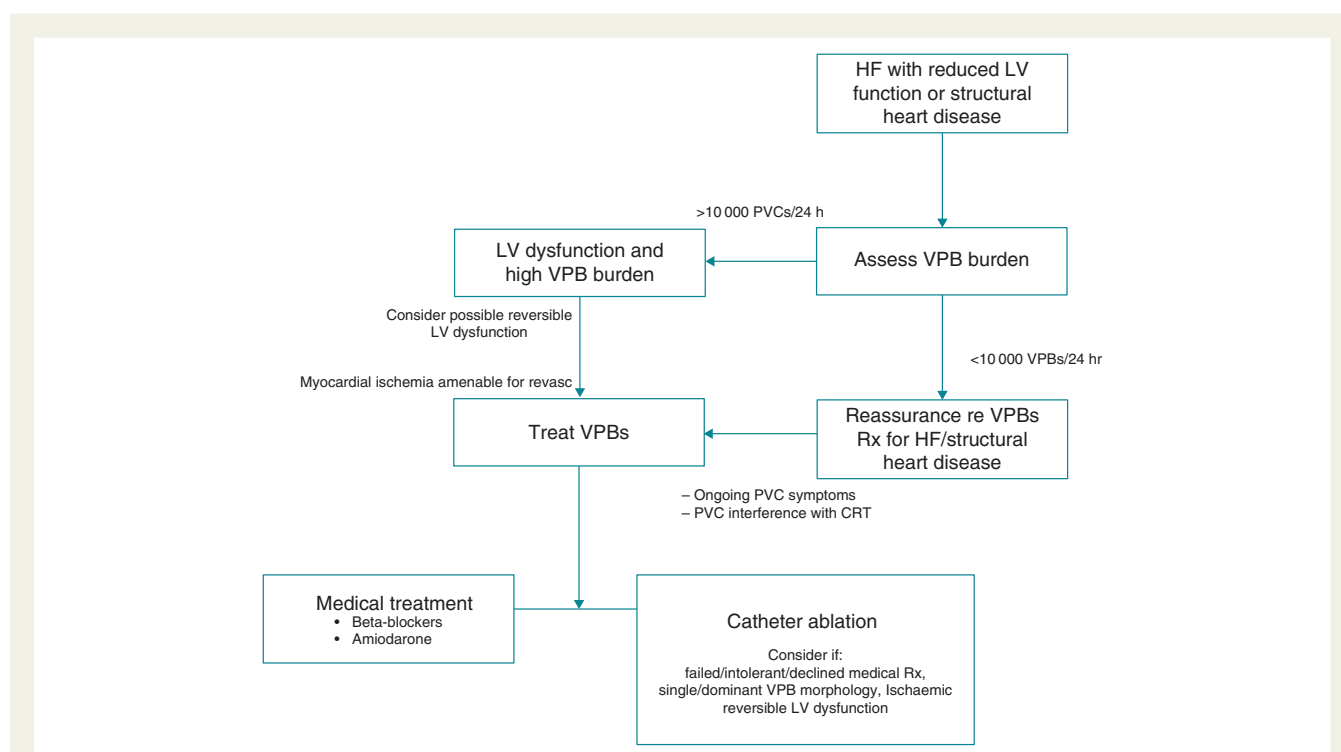


Figure 3 Management of ventricular premature beats in heart failure. Figure modified from Torp Pedersen et al.¹⁹⁶ HF, heart failure; LV, left ventricular; VPBs, ventricular premature beats.

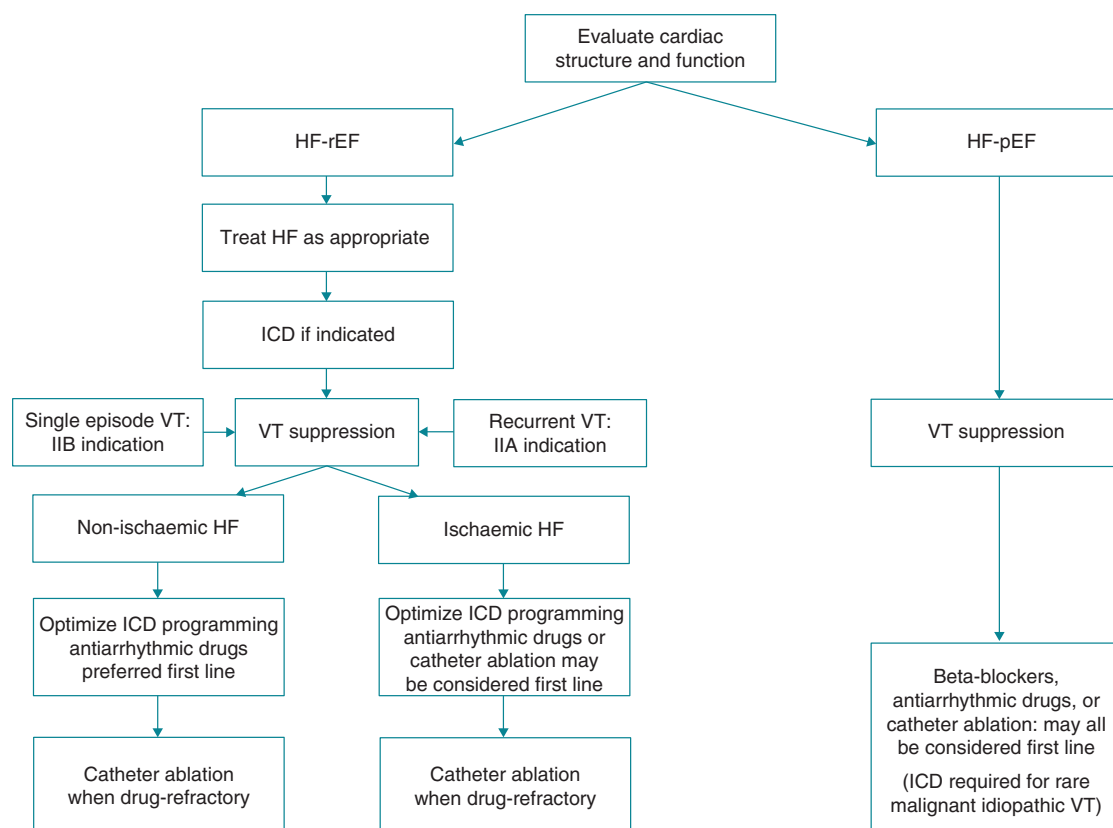


Figure 4 Evaluation and management of sustained monomorphic ventricular tachycardia. Figure modified from Torp Pedersen et al.¹⁹⁶ HF-rEF, heart failure with reduced ejection fraction; HF-pEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter defibrillator; HF, heart failure;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

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).

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 celivarone²⁰⁶ 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 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 $\leq 35\%$ 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 $\leq 40\%$ 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 Cardioverter-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 $\leq 40\%$ 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 CIDS²⁴¹) 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 $\leq 35\%$ 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 $\leq 35\%$, 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 $\leq 35\%$ 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 $\leq 30\%$ 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 $\leq 35\%$, 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 ($\leq 35\%$ NYHA Class II–III, in ischaemic cardiomyopathy with an LVEF of $\leq 30\%$, 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 routinely 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 be 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 deterioration. 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. Amiodarone 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 efficacy 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-TT₂R₂ 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 continuous 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 efficacy 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 moderately 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 clinical 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 CHA₂DS₂-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-TT₂R₂ 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 preferred treatment 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 $\leq 30\%$, 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 $\leq 35\%$, 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 $\leq 35\%$, irrespective of QRS duration, to reduce the risk of worsening of HF, or
 - NYHA functional Class II with an LVEF of $\leq 35\%$, 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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