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The management of atrial fibrillation in heart failure: an expert panel consensus

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Abstract

Heart failure (HF) and atrial fibrillation (AF) often coexist, being closely interrelated as the one increases the prevalence and incidence and worsens the prognosis of the other. Their frequent coexistence raises several challenges, including under-diagnosis of HF with preserved ejection fraction in AF and of AF in HF, characterization and diagnosis of atrial cardiomyopathy, target and impact of rate control therapy on outcomes, optimal rhythm control strategy in the era of catheter ablation, HF-related thromboembolic risk and management of anticoagulation in patients with comorbidities, such as chronic kidney disease or transient renal function worsening, coronary artery disease or acute coronary syndromes, valvular or structural heart disease interventions and cancer. In the present document, derived by an expert panel meeting, we sought to focus on the above challenging issues, outlining the existing evidence and identifying gaps in knowledge that need to be addressed.

Keywords Heart failure · Atrial fibrillation · Rate control · Rhythm control · Direct oral anticoagulants · Non-vitamin K antagonist oral anticoagulants

Introduction

Heart failure (HF) and atrial fibrillation (AF) are both frequent, causing a significant health burden that is expected to increase due to population ageing and growing impact of cardiometabolic abnormalities and other increasingly prevalent risk factors. They have a general population prevalence of 2% each that climbs to 10% after the age of 65 [1, 2]. HF remains a syndrome with ominous prognosis, with an overall 50% mortality rate at 5 years, while being the most common cause of hospital admissions in the elderly and causing a significant financial burden mainly due to repeated hospitalizations [1, 3]. AF, on the other hand, is the most common sustained arrhythmia, associated with a 2- and 5-fold higher risk of death and stroke, respectively [2].

The two conditions are closely interrelated as each increases the prevalence and incidence and worsens the prognosis of the other. AF is present in at least one-third of HF patients, while HF increases the prevalence of AF up to 10-fold [4, 5]. Their frequent coexistence often raises diagnostic and therapeutic challenges. In the present manuscript, derived by an expert panel meeting, we sought to focus on the main challenging issues related to HF and AF co-treatment, outline the existing evidence and identify unmet needs and pertinent gaps in knowledge that need to be addressed.

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Epidemiology: AF begets and worsens HF and vice versa

Epidemiological studies show that AF is a common comorbidity in HF. It is prevalent in 24–44% of patients with acute HF [6], in one-third of those with chronic HF [4] and in more than half (57%) of those with new-onset HF [5]. In the two large American registries on acute HF, the ADHERE and OPTIMIZE-HF, on 105,388 and 48,612 patients, respectively, the prevalence of AF was 31% [7, 8]. In an analysis of the European Society of Cardiology (ESC) HF long-term registry on 14,964 patients with acute or chronic HF, the overall prevalence of AF was 30%, ranging from 27% in patients with reduced left ventricular ejection fraction (LVEF, HFrEF) to 39% in those with preserved EF (HFpEF); AF was strongly age-dependent, reaching 50% in patients older than 80 years [9]. The recent CHECK-AF registry on 8253 Dutch patients with HFrEF reported an AF prevalence of 25.6% [10]. AF incidence is nearly 10-fold higher in patients with prevalent HF compared with those without HF [5]. AF is further a precipitating factor for HF hospitalization, accounting for 19% of HF admissions [3].

On the other hand, HF is prevalent in 33%, 44% and 56% of ambulatory patients with paroxysmal, persistent and permanent AF, respectively [11], in more than one-third (37%) of those with new-onset AF [5], as well as in up to 50% of hospitalized AF patients [12]. Of note, HF was the primary reason for hospitalization in the majority of patients with a prior history of AF, whereas HF with preserved or mid-range LVEF (40% or higher) was twice as prevalent compared with HFrEF (EF < 40%) [12]. The incidence of HF, particularly HFpEF, is also increased by more than 2-fold in patients with prevalent AF compared with those without AF [5]. The presence of either HFpEF or HFrEF confers an increased risk of death in AF patients [5, 13], while AF also increases mortality in patients with either HFrEF or HFpEF [14, 15].

Pathophysiology: Is there a left atrial cardiomyopathy linking AF and HF?

Both AF and HF may predispose to each other by several mechanisms thus creating a vicious circle of interdependence, in which the one condition begets and worsens the other [16]. HF may lead to AF through increased filling pressures, diastolic dysfunction, mitral regurgitation and neurohormonal activation that increase atrial stretch and induce atrial fibrosis and remodelling [17]. AF in turn predisposes to HF due to rapid and irregular heart rate and loss of atrial kick that impair hemodynamic performance and cardiac output, tachycardia-induced cardiomyopathy and neurohormonal activation [18]. In addition, both conditions share common risk factors and pathogenetic mechanisms such as ageing, cardiometabolic abnormalities and systemic inflammation that predispose concurrently to AF and HF [19].

Over the past few years, the term "left atrial cardiomyopathy" or "left atrial disease" has been used to describe a condition of structural, functional and electrical atrial abnormalities that precede AF development and may further link AF with HF (Fig. 1) [20]. This condition is thought to be caused by the common risk factors and systemic conditions of AF and HF in combination with genetic predisposition. It is characterized by (i) electrical remodelling with action potential prolongation, calcium handling alterations and increased heterogeneity of refractoriness; (ii) mechanical dysfunction with impaired atrial deformation during reservoir, conduit and contraction phases; (iii) structural abnormalities with interstitial fibrosis, fibrofatty replacement, inflammatory infiltration and myocyte hypertrophy; (iv) systemic neurohormonal and inflammatory activation [21–23]. These abnormalities precede AF, while they may also occur early in the development of HF, as they seem to be coupled with corresponding changes in ventricular myocardium [24, 25]. Regardless of whether this condition should be framed as atrial cardiomyopathy or disease, it represents a window of opportunity for early intervention and thus prevention of AF and perhaps HFpEF. It remains however challenging how to identify its presence by existing diagnostic means. Sensitive diagnostic modalities such as atrial deformation imaging, magnetic resonance imaging and biomarkers may help in this regard.

Diagnosis of HF in AF and vice versa

Atrial fibrillation may hinder the diagnosis of HF, particularly when LVEF is preserved, as the two conditions share many diagnostic features, including symptoms, echocardiographic abnormalities (i.e. atrial enlargement) and increased levels of natriuretic peptides [26]. Actually, in recent HF trials, the applied natriuretic peptide cut-offs for the diagnosis of HF in the presence of AF are higher than those in the absence of AF; for example, in PARAGON-HF, a N-terminal beta-type natriuretic pro-peptide (NT-proBNP) higher than 900 pg/ml was required for the diagnosis of HFpEF in patients with AF versus only 300 pg/ml for those without AF [27]. Given the difficulties in diagnosing HFpEF in patients with AF, there is a potential risk that HFpEF remains underdiagnosed in these patients. It seems that the majority of AF patients with dyspnoea and high levels of natriuretic peptides also suffer from HF and should thus be regarded as having HF until proven otherwise [28]. Thus, patients with AF should meticulously investigated for the coexistence of HF. In this case, HF diagnosis may be facilitated by the appraisal of diastolic function indices and left atrial volume and strain, along with natriuretic peptides with AF-adjusted cut-offs (i.e. NT-proBNP > 660 or BNP > 240 pg/mL) [29]; the recently proposed HFA-PEFF

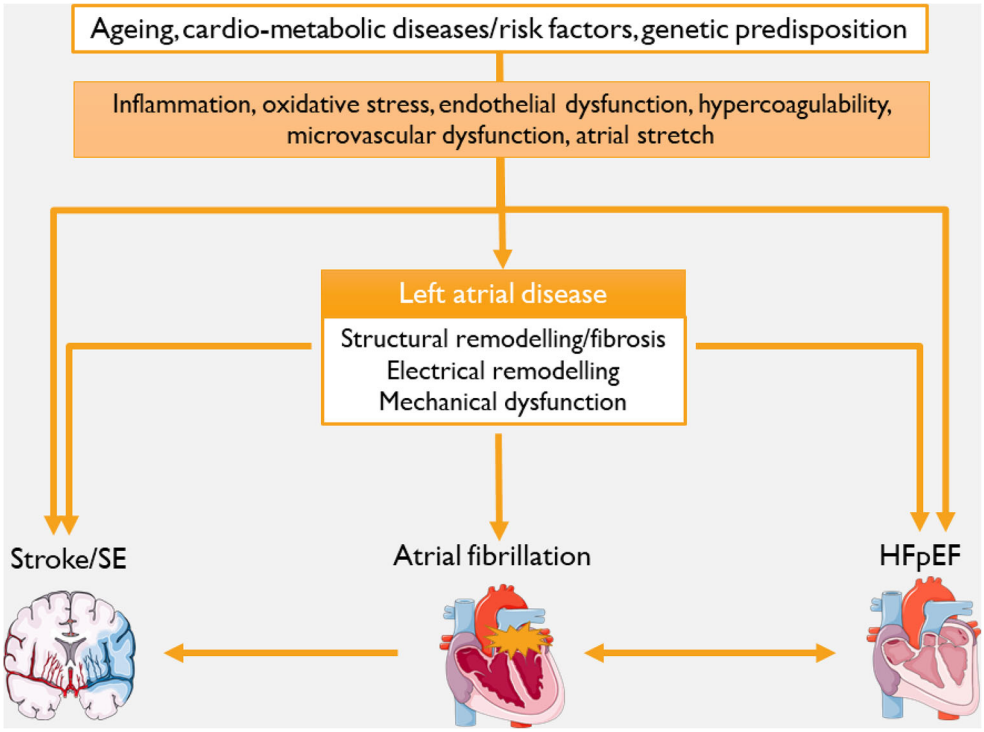

Fig. 1 Schematic representation of the atrial cardiomyopathy or atrial disease concept (SE, systemic embolism; HFpEF, heart failure with preserved left ventricular ejection fraction; created using artwork provided by Servier Medical Art, licenced under a Creative Commons Attribution 3.0 Unported Licence)

diagnostic algorithm by the Heart Failure Association of the European Society of Cardiology (ESC) may help in this regard [29].

On the other hand, AF may also be underdiagnosed in HF, as frequent episodes of silent or subclinical AF may occur in individuals at increased risk for AF [30]. Patients with a HF diagnosis should therefore be periodically checked for AF. Analysis of recorded arrhythmia events in the patients with implanted devices, as well as the novel technologies of wearable sensors, smart-watch and smart-phone applications may contribute considerably to AF diagnosis.

Management of arrhythmia: Rhythm and rate control strategies in the era of catheter ablation

Rate control

There is not a universally accepted target heart rate (HR) in AF with HF, as the recommended targets are arbitrary defined and differ among scientific bodies (Table 1). At the same time, in contrast to HF patients in sinus rhythm, the prognostic importance of HR in HF patients with AF has been questioned by meta-analysis evidence, having shown that HR does not affect prognosis and HR lowering with beta-blocker does not confer survival benefit in these patients [31, 32]. Until more solid evidence is available, targeting a HR lower than 100–110 bpm seems reasonable in HF with AF [33]. According to the latest European Heart Rhythm Association guidelines, therapeutic options for long-term rate control include diltiazem/verapamil, beta-blockers and digoxin in patients with preserved LVEF (40% or higher) and beta-blockers and digoxin for those with reduced LVEF (< 40%), initially as monotherapy, followed by two-drug combinations if required, while taking precautions to avoid bradycardia [34].

Rhythm control

Comparison between rate control and pharmacological rhythm control strategies in AF patients with HF before the era of radiofrequency catheter ablation showed no differences in outcomes, including mortality and stroke, according to one randomized trial (AF-CHF) and a meta-analysis of 25 studies [35]. In contrast, small studies comparing catheter ablation with pharmacological rate control in patients with AF and HFrEF showed that ablation was superior in improving HF symptoms, LVEF, peak oxygen consumption and quality of life [36–39]. In an open-label randomized trial on 203 patients with AF and HFrEF, the AATAC study, catheter ablation reduced significantly the risk of death and unplanned hospitalization compared with pharmacological rhythm control with amiodarone [40]. Catheter ablation was further proved to be superior to atrioventricular node ablation combined with biventricular pacing in improving exercise capacity, quality of life and LVEF in HFrEF according to the small PABA-HF trial [41]. The randomized CASTLE-AF trial in 363 patients with AF and HFrEF

Table 1 Recommended target heart rate in patients with atrial fibrillation with and without heart failure by different scientific bodies

	ESC-EHRA	ESC-HFA	ACC/AHA	CCS	NHFA/CSANZ
Atrial fibrillation	< 110	–	< 80 (IIa) < 110 (IIb, stable, pEF)	< 100	< 110
Atrial fibrillation and heart failure	< 110	60–100 (rest) < 110 (exercise)	–	< 110–115	60–100

ESC: European Society of Cardiology; *EHRA*: European Heart Rhythm Association; *ACC*: American College of Cardiology; *AHA*: American Heart Association; *CCS*: Canadian Cardiovascular Society; *NHFA*: National Heart Foundation of Australia; *CSANZ*: Cardiac Society of Australia and New Zealand; *pEF*: preserved left ventricular ejection fraction

demonstrated a significant reduction in the risk of all-cause death or hospitalization for HF at 60 months, compared with medical therapy (rhythm or rate control), but the study has been criticized particularly for the large number of patients screened for enrolment [42]. In this trial, the prognostic benefit of ablation was achieved without eliminating AF, but solely by achieving a significant reduction in patients' arrhythmia burden. These data point towards an alternative assessment of procedural outcome from categorical (success or failure) to continuous (percentage of time in sinus rhythm). In a pooled analysis of randomized data on 1112 patients comparing catheter ablation with any medical therapy, ablation was associated with lower rates of all-cause death and hospitalization, along with lower rates of AF recurrence and greater improvement in LVEF and quality of life, but similar rate of stroke [43]. The more recent CABANA trial that included only 15% of patients with HFrEF failed to show a benefit in the composite of all-cause death, disabling stroke, serious bleeding or arrest at 60 months, suffering from low event rate and significant crossover between arms [44]. A pre-specified subgroup analysis of the trial demonstrated a non-significant trend for primary endpoint reduction (HR 0.61) among AF patients with a history of HF as compared with neutral effect (HR 0.95) among those without HF. Therefore, in line with the CASTLE-AF results, these findings suggest that properly selected HF patients with AF may benefit from catheter ablation, with maximal benefit (super-responders) in those suffering from arrhythmia-induced cardiomyopathy [45].

Trials have suggested a number of factors that may identify potential responders to AF ablation among HF patients, including a non-ischemic aetiology, a LVEF of 35% or higher and a limited extent of left atrial fibrosis of 10% or less [39, 42, 46]. Additional factors that have been suggested although not supported by evidence include young age, recent AF onset, absence of significant left atrial dilatation or LV fibrosis and absence of comorbidities [47]. A number of ongoing studies (RAFT-AF NCT01420393, AMICA NCT00652522, CATCH-AF NCT02686749, CONTRA-AF NCT03062241) will hopefully shed some new light on this issue.

In general, a rhythm control strategy is preferable in patients with a reversible secondary cause of AF, an obvious precipitant or in those who remain symptomatic despite optimization of rate control and HF therapy [34].

Anticoagulation for thromboembolic prevention in HF with AF: A partially unmet need and room for improvement

The risk of thromboembolism in HF with AF

Heart failure is often regarded as a hypercoagulable state [48, 49]. It is an established thromboembolic risk factor in AF, adding 1 point in the CHA_2DS_2-VASc score. Indeed, a bulk of evidence shows that HF increases significantly the risk of stroke and systemic embolism in AF [50–52]. Importantly, paroxysmal AF, which is often misinterpreted as conferring a lower stroke risk, was associated with a greater risk for HF hospitalization and stroke compared with persistent or paroxysmal AF in a secondary analysis of PARADIGM-HF and ATMOSPHERE trials [53]. Further to AF type, the risk of stroke is also reported to be higher in the initial period following incident HF in patients with prevalent AF, especially during the first 30 days after HF diagnosis [54, 55].

Properly anticoagulated AF patients with HF, in contrast, seem to have comparable thromboembolic risk with those without HF. A meta-analysis of the four seminal trials on direct oral anticoagulants (DOAC) in AF showed that there was no difference in the rates of stroke or systemic embolism in anticoagulated patients with and without HF [13]. A secondary analysis of the ARISTOTLE trial also showed that the risk of stroke or systemic embolism did not differ in anticoagulated AF patients with or without either left ventricular systolic dysfunction or HFpEF [51]. Besides addressing the thromboembolic risk, anticoagulation therapy may improve the overall outcomes of patients with HF and AF. In a multi-centre study on 5105 hospitalized patients with HF and AF, the initiation of anticoagulation therapy at discharge was followed by a significantly lower adjusted rate of all-cause mortality at 1 and 3-year, without however an effect on all-cause re-admissions over the same time period [56].

At the same time, real-world evidence suggests that AF patients with HF seem to have a similar risk of bleeding, as

defined by a HAS-BLED score of 3 or higher, compared with AF patients without HF [57]. In addition, in the aforementioned meta-analysis of DOAC trials, anticoagulated patients with both AF and HF had actually reduced rates of intracranial haemorrhage and any bleeding compared with anticoagulated AF patients without HF [13].

Thromboembolic risk prediction in HF with AF

European guidelines recommend an oral anticoagulant (OAC) for AF patients with a CHA_2DS_2-VASc score of 1 or higher (unless 1 is due to female gender alone) [34]. Interestingly, the prediction of thromboembolic risk with CHA_2DS_2-VASc score in patients with HF may not be accurate. It has been shown that in patients with both HF and AF, the mean score increased significantly in parallel to LVEF, being 4.1 in patients with HFrEF, 4.5 in those with HFpEF and LVEF between 50 and 60% and 4.7 in those with HFpEF and LVEF >60%, while the annual incidence of stroke decreased with increasing LVEF, being significantly higher in patients with HFrEF [52]. As a result, HF patients with the highest LVEF had the lowest true incidence of stroke despite the highest CHA_2DS_2-VASc score, a finding that can be explained by the higher prevalence of advanced age and comorbidities in HFpEF patients. However, recent evidence from the NCDR PINNACLE-AF registry showed that HFpEF is probably under-appreciated as a risk factor in patients with AF, resulting in lower rates of anticoagulation [58].

The constellation of variables constituting CHA_2DS_2-VASc and other thromboembolic risk prediction scores are not only risk factors for stroke and systemic embolism but also risk factors for both HF and AF, not being necessarily related to the pathogenesis of thrombosis in AF. In this context, it has been suggested that additional factors that are probably more pathogenetically related to thromboembolism in AF should be used to predict thromboembolic risk, including atrial morphology and function and biomarkers [59].

Taken together, the evidence discussed in this paragraph suggests that it is reasonable to prescribe OAC in HF patients with AF, irrespective of the underlying systolic function, the thromboembolic risk score or the presence of other risk factors for thromboembolism [18].

Evidence on DOAC for thromboembolic prevention in HF with AF

In the four seminal studies of DOAC in AF, the prevalence of HF ranged between 19% and 64%, according to the different HF definitions used in the trials [60, 61]. Secondary analyses of these trials confirmed the efficacy and safety of DOAC in the subgroup of patients with HF.

A secondary analysis of the RE-LY trial on 4904 patients (27% of the total study population) with symptomatic HF, defined as a history of NYHA class symptoms of II or higher and previous HF hospitalization, showed that the efficacy and safety of dabigatran over warfarin was consistent among patients with and without HF as well as among those with reduced and preserved LVEF [50]. More specifically, compared with warfarin, dabigatran at 150 mg twice daily had superior efficacy for stroke prevention without an increase in major bleeding while dabigatran at 110 mg twice daily had similar efficacy for stroke prevention and less major bleeding; both doses reduced significantly the rate of intracranial haemorrhage [50]. Real-world evidence from the GLORIA-AF study on 4859 AF patients treated with dabigatran (including 32% with HF) showed that the incidence rates of stroke and major bleeding at 2 years were similarly low in patients with and without HF [57]. Accordingly, in a secondary analysis of the ARISTOTLE trial, the enhanced efficacy and safety of apixaban over warfarin was consistent in patients with and without HF across the LVEF spectrum [51].

Two meta-analyses of the aforementioned trials confirmed the above findings, having shown that the efficacy and safety of DOACs, as compared with warfarin, was consistent in patients with and without HF [13, 62]. It is worth to mention that in one of the meta-analyses, the risk of intracranial bleeding in particular was reduced by 57% by DOAC compared with warfarin in patients with both AF and HF [62].

In addition to the proven efficacy and safety of DOAC in patients with HF and AF, it should further be stressed that the presence of HF has been associated with reduced time in therapeutic range (TTR) in AF patients treated with VKA [63, 64]. Frequent hospitalizations and polypharmacy, which are common in HF, are also independent predictors of low TTR [65]. Low TTR may lead to even higher risk of thromboembolism or bleeding in these patients. DOAC are also very helpful in HF patients requiring device implantation, as their rapid on- and off-set action allows for a short window where the procedure can be carried out without the need for bridging therapy [66], although data from centres adopting this approach has shown variability in discontinuation timing [67]. Therefore, it is reasonable to suggest that DOAC are the preferable OAC in patients with HF and AF.

Impact of HF comorbidities on anticoagulation strategies

Chronic kidney disease

Chronic kidney disease is a frequent comorbidity in HF, while renal function worsening often accompanies HF decompensation [68]. Similarly, there is also a bidirectional relationship between AF and renal disease [69, 70]. In patients with AF and either moderate or mild renal dysfunction (creatinine clearance of 30–49 or 50–80 mL/min, respectively), meta-analysis data shows that DOAC are more efficacious and safer

compared with warfarin [71]. However, there is limited evidence for the use of DOAC in severe renal dysfunction with creatinine clearance < 30 mL/min, while DOAC are not indicated for patients with clearance < 15 mL/min in Europe. Of note, in DOAC studies in AF (RE-LY, ROCKET-AF, ARISTOTLE), the Cockcroft-Gault formula was used to estimate creatinine clearance.

Fluctuations of renal function may be frequent in HF and therefore the dose of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) should be adjusted according to creatinine clearance (Table 2) [60, 72]. For dabigatran, in contrast, there is no need to modify dosing, provided that clearance remains at 30 mL/min or above. The efficacy and safety of the drug has actually been shown to be consistent across the whole spectrum of renal function for clearance of 30 mL/min and above [73]. In addition, dabigatran and rivaroxaban have been shown to attenuate the renal function decline that has been attributed to warfarin-induced nephropathy [74–76].

Coronary artery disease and acute coronary syndromes

Coronary artery disease is the most common cause of HF and patients particularly with HFrEF often have a history of myocardial infarction. Patients with AF and recent (less than 1 year) acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) should receive a combination of antiplatelet agents and DOAC according to current recommendations [72, 77]. Double therapy with a DOAC and $P2Y_{12}$ inhibitor, omitting aspirin after few days post PCI, seems a reasonable choice, especially for patients with high bleeding and low thrombotic risk [78]. Patients with AF and chronic coronary syndromes or those with AF and ACS or PCI of more than 1 year before should be treated with a DOAC alone without the need for additional antiplatelet therapy [72, 77, 79]. The coexistence of HF in the above settings does not modify the choice or dosing of antithrombotic therapy.

Structural heart disease

Valvular heart disease (VHD) is a frequent comorbidity in HF and sometimes the cause of the syndrome. According to guideline recommendations, DOAC are contraindicated in patients with mechanical prosthetic valve or moderate-to-severe mitral valve stenosis and these patients should be anticoagulated with VKA. Evidence from the seminal DOAC trials in AF on dabigatran, rivaroxaban and apixaban shows that the efficacy and safety of DOAC compared with warfarin is consistent in patients with other forms of valvular heart disease [80–82]. Clinical evidence also suggests that DOAC are an effective and safe anticoagulation options for AF patients with bioprosthetic valves, prior surgical valve repair or transcatheter aortic valve replacement [83, 84].

Table 2 Recommended dosing of direct oral anticoagulants in patients with heart failure, atrial fibrillation and renal dysfunction (colour encoding: green, can be used safely; yellow, should be used with caution; red, is contraindicated; modified from Steffel et al., Eur Heart J 2018 [68] and Farmakis et al., Cardiology 2018 [56])

<table>
<tr><th>Creatinine clearance</th><th>Dabigatran 150 mg</th><th>Dabigatran 110 mg</th><th>Rivaroxaban</th><th>Apixaban</th><th>Edoxaban</th></tr>
<tr><td>≥95 mL/min</td><td rowspan="3">150 mg bid</td><td rowspan="3">110 mg bid[1]</td><td rowspan="2">20 mg od</td><td rowspan="3">5 mg bid[2]</td><td>60 mg od</td></tr>
<tr><td>50-94 mL/min</td><td>60 mg od[3]</td></tr>
<tr><td>30-49 mL/min</td><td>15 mg od</td><td>30 mg od</td></tr>
<tr><td>15-29 mL/min</td><td>-</td><td>-</td><td>15 mg od</td><td>2.5 mg bid</td><td>30 mg od</td></tr>
<tr><td><15 mL/min</td><td>-</td><td>-</td><td>-</td><td>-</td><td></td></tr>
</table>

bid: twice daily; *od*: once daily

[1] Preferable over 150 md bid if at least 1 of the following: age ≥ 80 years, concomitant verapamil, HAS-BLED ≥ 3

[2] Reduce to 2.5 mg bid if at least 2 of the following: age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL

[3] Reduce to 30 mg od if at least 1 of the following: weight ≤ 60 kg, concomitant cyclosporine, dronedarone, erythromycin, ketoconazole, or other potent P-glycoprotein inhibitor

As a result, the European Heart Rhythm Association (EHRA) states that DOACs can be used in AF patients with mild-to-moderate native valvular disease (except for mitral stenosis) and severe aortic stenosis [85]. EHRA further states that DOAC can also be used in AF patients with mitral valve repair (except for the first 3–6 months post-operatively), bioprosthetic valves (except for the first 3 months post-operatively) and transcatheter aortic valve implantation (TAVI, in combination with antiplatelet therapy during the first months according to local practices) [77, 85, 86]. However, a recent randomized study showed that addition of clopidogrel to OCA for the first 3 months post-TAVI increased the risk of bleeding compared with OAC monotherapy [87]. In patients with AF and secondary mitral regurgitation resulting from left ventricular remodelling in the context of HFrEF, who undergo repair of the valve with a transcatheter technique such as MitraClip, the suggested antithrombotic therapy includes a combination of an OAC and aspirin for at least the first 6 months after the intervention [77]. The coexistence of HF in the above settings does not modify the prescription of anticoagulation regimen. DOAC can also be used in patients with hypertrophic cardiomyopathy and AF that may also be a cause of HF [85]. There are scarce data on the use of DOAC in atrial arrhythmias associated with congenital heart disease [88].

Cancer

Cancer may often coexist in patients with HF and AF. On one hand, cancer shares several risk factors with HF and AF while both HF and AF may result from cancer therapy including classical chemotherapy, targeted therapies, radiotherapy and surgery [1, 89–91]. Overall, the management of AF in these patients follows the same principles as in patients without cancer. However, two additional parameters should be considered while making therapeutic decisions, the prognosis and life expectancy of cancer and the fact that cancer itself may often be associated with either a prothrombotic state or an increased bleeding tendency [89]. Regarding the choice of anticoagulation regimen, evidence from secondary analyses, meta-analyses and clinical studies have shown that DOAC are equally effective and safe for the prevention of stroke and systemic embolism in patients with cancer and therefore they constitute a viable therapeutic option [92–95]. On the other hand, cancer itself and the resulting polypharmacy and repeated hospital admissions have all been associated with reduced TTR in AF patients on VKA therapy [63, 65, 96]. The choice of anticoagulation regimen should further consider the potential drug-drug interactions with cancer therapy, which are numerous in the case of VKA.

Current status of anticoagulation in HF with AF

Global and local evidence shows that among patients with AF, the diagnosis of HF is associated with a lower chance of DOAC prescription over VKA. Evidence from the Global Anticoagulant Registry in the Filed-Atrial Fibrillation (GARFIELD-AF) on 24,137 patients receiving anticoagulation therapy showed that HF was among the factors favouring the prescription of VKAs over DOAC [OR, 0.81 (0.75–0.88)] [97]. Similarly, data from a survey on the management of AF in seven Balkan countries also showed that HF was negatively associated with DOAC use [OR, 0.65 (0.48–0.87)] [98].

In a Greek single-centre registry of patients hospitalized with AF, 13% of those with both AF and HF were not prescribed any OAC at discharge, with half of these patients being at high risk for stroke [12]. Data from this registry shows that HF, although was associated with an increased prescription of OAC, discouraged the use of DOAC over VKA. In another Greek multi-centre cross-sectional study in 603 patients hospitalized for either HF or AF, 43% of patients with both HF and AF were treated with DOAC and 33% with VKA, with the rest of patients being treated with either low molecular weight heparin or no anticoagulation [99].

Besides the lower than expected prescription rates of DOAC in patients with HF and AF, evidence from different surveys shows that HF is independently associated with inappropriate dose reductions of DOAC, despite the higher thromboembolic risk associated with the syndrome [100, 101]. Under-dosing of DOAC may jeopardize their efficacy. With the exception of dabigatran 110 mg twice daily that was studied in a significant number of patients ($n = 6015$, 49.7% of the total study population in RE-LY) [102], low doses of DOAC have not been adequately studied in the seminal studies in AF; rivaroxaban 15 mg once daily was studied in 1474 patients (20.7% of the total population in ROCKET-AF), edoxaban 30 mg once daily in 1784 patients (25.4% of the total population in ENGAGE-AF), while apixaban 2,5 mg twice daily only in 428 patients (4.7% of the total population in ARISTOTLE) [103–105].

Management of HF in the presence of AF

The management of HF in the presence of AF should generally follow the corresponding guideline recommendations that apply to the general HF population. However, the efficacy of some disease-modifying therapies may be altered in the presence of AF. As stressed above, previous meta-analyses indicated that beta-blockers may not have a prognostic impact on HFrEF patients with AF [31, 32]. A more recent meta-analysis that included HF patients across the whole LVEF spectrum, showed that in patients in sinus rhythm at baseline, beta-

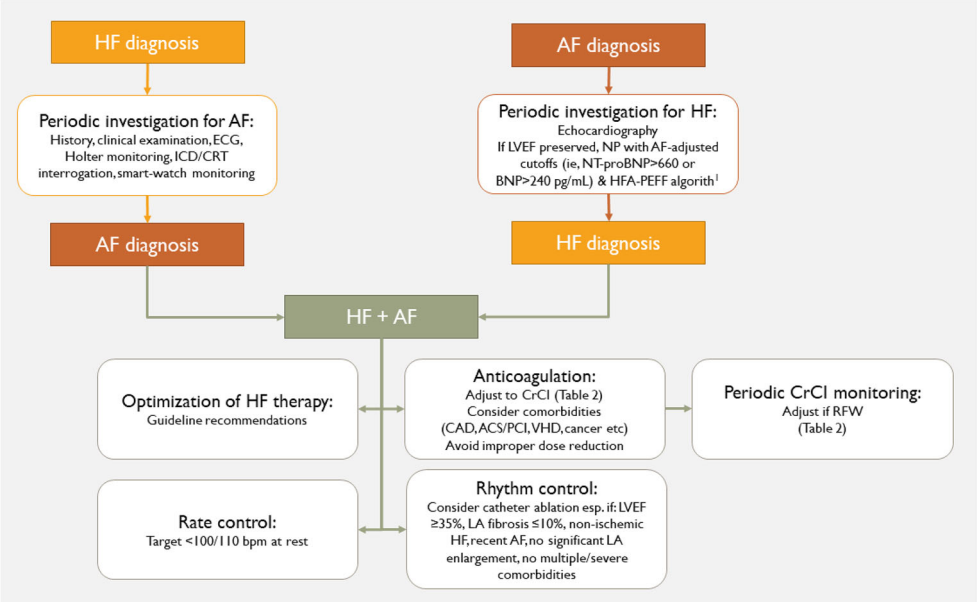

Fig. 2 A proposed overview of the management of patients with heart failure and atrial fibrillation. HF: heart failure; AF: atrial fibrillation; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal B-type natriuretic pro-peptide; BNP: B-type natriuretic peptide; CrCl: creatinine clearance; CAD: coronary artery disease; ACS: acute coronary syndromes; PCI: percutaneous coronary intervention; VHD: valvular heart disease; LA: left atrial. [1] Pieske et al., Eur Heart J 2019;40:3297–317 [102]

blockers improved LVEF and reduced all-cause and cardiovascular mortality in those with HFrEF and HFmrEF but not in those with HFpEF; in patients with AF at baseline, in contrast, although beta-blockers still improved LVEF in HFrEF and HFmrEF (but not in HFpEF), they did not have an impact on survival in any LVEF category [106]. In contrast, sacubitril/valsartan reduced the rates of cardiovascular death and HF hospitalization compared with enalapril consistently in HFrEF patients with and without AF in the context of the seminal PARADIG-HF trial [107]. Regarding sodium-glucose cotransporter-2 inhibitors (SGLT2i) that are currently under investigation as potential HF therapies, in a secondary analysis of the EMPA-REG OUTCOME trial that concerned type 2 diabetic patients with established cardiovascular disease, empagliflozin reduced significantly the risk of all-cause and cardiovascular mortality, HF hospitalization and new or worsening nephropathy consistently in patients with and without AF [108].

In terms of device therapy, not enough evidence is available on the effects of cardiac resynchronization therapy (CRT) in HFrEF patients with AF and other indications for this therapy (persisting symptoms despite optimal

Table 3 Open issues in the management of atrial fibrillation in patients with heart failure

Epidemiology	• True prevalence/incidence of HFpEF in patients with AF
	• True prevalence/incidence of AF in patients with HFpEF
Diagnosis	• Diagnostic criteria of HFpEF in patient with AF
	• Correct diagnosis of AF in patient with HF
	• Definition and diagnostic criteria of atrial disease/cardiomyopathy
	• Diagnostic criteria of AF in HF patients with devices
Rate control therapy	• Optimal heart rate target
	• Prognostic impact of heart rate lowering
	• Prognostic impact of beta-blocker therapy
Rhythm control therapy	• Optimal candidates for catheter ablation
	• Optimal ablation procedure (solely PVI vs. more extensive interventions)
	• Timing for referral for invasive management
	• Impact of alternative approaches such as AVN ablation with His bundle pacing
Antithrombotic therapy	• Optimal anticoagulation strategies in patients with comorbidities such as cancer or CKD
	• Anticoagulation in left atrial disease/cardiomyopathy
	• Anticoagulation in HF patients without AF
	• Correct dosing of DOAC in patient with AF and HF

HFpEF: heart failure with preserved left ventricular ejection fraction; *AF*: atrial fibrillation; *PVI*: pulmonary vein isolation; *AVN*: atrioventricular node; *CKD*: chronic kidney disease; *OAC*: oral anticoagulants; *DOAC*: direct oral anticoagulants

medical therapy, LVEF ≤35%, QRS duration ≥130 ms) [109]. Small studies comparing CRT with pharmacological therapy provided conflicting results in AF, while a subgroup analysis of the RAFT study comparing implantable cardioverter defibrillator (ICD) alone or with CRT (CRT-D) found no benefit from CRT addition, but the biventricular capture rate in the CRT-D arm was very low [110]. The ESC guidelines recommend the use of CRT in HFrEF patients with AF and the above indications with a IIaB recommendation provided there is a strategy to ensure high rates of biventricular capture or the patient is expected to return to sinus rhythm [109]. In contrast, CRT seems to be preferred over conventional right ventricular pacing in HFrEF patients with high-degree atrioventricular block requiring ventricular pacing or those undergoing atrioventricular node ablation for persistently high ventricular rate (> 110 bpm) despite pharmacological rate control [109]. In patients with ICD or CRT-D, inappropriate shocks triggered by AF may be an issue that can be managed by proper device programming ensuring shock triggering at higher ventricular rates and longer delay between detection and therapy delivery [111].

Conclusions, unmet needs and gaps in knowledge

A proposed management plan of patients with HF and AF is outlined in Fig. 2. As previously stressed, patients with a diagnosis of one of the two conditions should be meticulously and periodically investigated for the potential coexistence of the other. Patients with both HF and AF should be started on anticoagulation with a DOAC (unless contraindicated, as for creatinine clearance < 15 mL/min) and undergo optimization of HF therapy according to guideline recommendations [109].

Several issues concerning the association between HF and AF remain to be addressed (Table 3). In terms of epidemiology, as previously stated, it seems that HFpEF is underdiagnosed in patients with AF given the common symptoms, echocardiographic abnormalities and natriuretic peptide concentrations of the two conditions. The use of AF-specific natriuretic peptide cut-offs for the diagnosis of HF may help in this regard and have been adopted by recent trials involving patients with HFpEF. AF may also be underdiagnosed in HF, as clinically silent AF episodes seem to be frequent. Studies looking at the recordings of implantable cardioverter defibrillators and cardiac resynchronization devices in patients with HFrEF may help in establishing the true prevalence and incidence of AF in these patients.

Atrial disease or atrial myopathy seems an attractive entity nicely linking the pathophysiology of HF and AF, offering a window of opportunity for prevention; its definition and diagnosis, however, remain obscure. Advanced imaging modalities such as atrial deformation by speckle tracking and atrial tissue characterization with cardiac magnetic resonance and biomarkers targeting the local and systemic abnormalities related to the condition such as neurohormonal and inflammatory activation or fibrosis, provide the possibility for its better understanding and identification through properly designed mechanistic studies. Additional issues related to rhythm and rate control strategies have emerged in the era of catheter ablation and are listed in Table 3.

Available evidence shows that the prescription of anticoagulation therapy in HF patients with AF remains suboptimal, while there is a reluctance in the use of DOAC over VKA along with frequent inappropriate under-dosing of DOAC in these patients. Epidemiological studies and registries should provide detailed evidence on the type and dosing of anticoagulants and predictors of prescribing practices in populations with HF and AF in order to define the true unmet needs that should be targeted. This should be coupled with the better education of physicians to increase the implementation of guideline recommendations and address any relevant misinterpretations concerning anticoagulation therapy in patients with HF and AF.

Compliance with ethical standards

Conflict of interest DF: lecture honoraria and advisory board fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Menarini, Novartis, Orion Pharma and Roche Diagnostics; CC: honoraria from Boehringer Ingelheim and Novartis; G. Giamouzis: honoraria from Bayer, Boehringer Ingelheim and Pfizer; G. Giannakoulas: lecture honoraria and/or advisory boards from AstraZeneca, Bayer, Boehringer Ingelheim, ELPEN Pharmaceuticals, Genesis Pharma, Novartis, Pfizer, Roche and Servier; MH: honoraria from Astra Zeneca, Boehringer Ingelheim, Pfizer and Sanofi; KN: honoraria for participation in a clinical trial and contribution to advisory boards (all minor) from Boehringer Ingelheim; ST: lecture honoraria from Bayer, Boehringer Ingelheim and Pfizer; SX: lecture honoraria from Bayer, Boehringer Ingelheim, Merck, Novartis, Pfizer and Servier and advisory board fees from Boehringer Ingelheim, Novartis and Servier; AK: lectures honoraria and advisory board fees from Boehringer Ingelheim, Elpen, Genesis Pharma, Menarini, Novartis, Pfizer, Sanofi and Servier; JP: honoraria from Boehringer Ingelheim, Novartis, Pfizer, Roche Diagnostics and Servier.

References

1. Farmakis D, Stafylas P, Giamouzis G, Maniadakis N, Parissis J (2016) The medical and socioeconomic burden of heart failure: a comparative delineation with cancer. Int J Cardiol 203:279–281
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJL (2014) Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 129:837–847

3. Stafylas P, Farmakis D, Kourlaba G, Giamouzis G, Tsarouhas K, Maniadakis N, Parissis J (2017) The clinical and economic burden in Greece. Int J Cardiol 227:923–929
4. Komajda M, Anker SD, Cowie MR, Filippatos GS, Mengelle B, Ponikowski P, Tavazzi L, QUALIFY Investigators (2016) Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. Eur J Heart Fail 18:514–522
5. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ, Ho JE (2016) Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation. 133:484–492
6. Farmakis D, Parissis J, Papingiotis G, Filippatos G. (2018) Acute heart failure: epidemiology, classification, and pathophysiology. In Marco Tubaro, Pascal Vranckx, Susanna Price, and Christiaan Vrints (eds) The ESC textbook of intensive and acute cardiovascular care (2 ed.). Oxford University Press
7. Kociol RD, Hammill BG, Fonarow GC, Klaskala W, Mills RM, Hernandez AF, Curtis LH (2010) Generalizability and longitudinal outcomes of a national heart failure clinical registry: comparison of Acute Decompensated Heart Failure National Registry (ADHERE) and non-ADHERE Medicare beneficiaries. Am Heart J 160:885–892
8. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB, Investigators O-H, Coordinators (2008) Predictors of in-hospital mortality in patients hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol 52:347–356
9. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, De Mora MM, Polonski L, Silva-Cardoso J, Amir O, ESC-HFA HF long-term registry investigators (2018) Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. Eur Heart J 39:4277–4284
10. Veenis JF, Brunner-La Rocca HP, Linssen GCM, Smeele FJJ, Wouters NTAE, Westendorp PHM, Rademaker PC, Hemels MEW, Rienstra M, Hoes AW, Brugts JJ (2020) CHECK-HF investigators Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: the CHECK-HF registry. Int J Cardiol 308:60–66
11. Chiang CE, Naditch-Brûlé L, Murin J, Goethals M, Inoue H, O'Neill J, Silva-Cardoso J, Zharinov O, Gamra H, Alam S, Ponikowski P, Lewalter T, Rosenqvist M, Steg PG (2012) Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. Circ Arrhythm Electrophysiol 5:632–639
12. Kartas A, Samaras A, Vasdeki D, Dividis G, Fotos G, Paschou E, Forozidou E, Tsoukra P, Kotsi E, Goulas I, Efthimiadis G, Karvounis H, Tzikas A, Giannakoulas G (2019) Flaws in anticoagulation strategies in patients with atrial fibrillation at hospital discharge. J Cardiovasc Pharmacol Ther 24:225–232
13. Savarese G, Giugliano RP, Rosano GM, McMurray J, Magnani G, Filippatos G, Dellegrottaglie S, Lund LH, Trimarco B, Perrone-Filardi P (2016) Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation and heart failure: a meta-analysis. JACC Heart Fail 4:870–880
14. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L (2009) A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. Eur J Heart Fail 11:676–683
15. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D (2014) The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. Eur J Heart Fail 16:1317–1322
16. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M (2016) Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins. J Am Coll Cardiol 68: 2217–2228
17. Zhao L, Wang WYS, Yang X (2018) Anticoagulation in atrial fibrillation with heart failure. Heart Fail Rev 23:563–571
18. Verma A, Kalman JM, Callans DJ (2017) Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. Circulation. 135:1547–1563
19. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M (2014) Lone atrial fibrillation: does it exist? J Am Coll Cardiol 63:1715–1723
20. Guichard JB, Nattel S (2017) Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad? J Am Coll Cardiol 70:756–765
21. Heijman J, Voigt N, Nattel S, Dobrev D (2014) Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ Res 114:1483–1499
22. Schotten U, Dobrev D, Platonov PG, Kottkamp H, Hindricks G (2016) Current controversies in determining the main mechanisms of atrial fibrillation. J Intern Med 279:428–438
23. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, Rao SN, Blauer J, Fish EN, Dibella EV, Macleod RS, McGann C, Litwin SE, Marrouche NF (2010) Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. Circ Cardiovasc Imaging 3:231–239
24. Wijesurendra RS, Casadei B (2015) Atrial fibrillation: effects beyond the atrium? Cardiovasc Res 105:238–247
25. Brecht A, Oertelt-Prigione S, Seeland U, Rücke M, Hättasch R, Wagelöhner T, Regitz-Zagrosek V, Baumann G, Knebel F, Stangl V (2016) Left atrial function in preclinical diastolic dysfunction: two-dimensional speckle-tracking echocardiography-derived results from the BEFRI trial. J Am Soc Echocardiogr 29:750–758
26. Richards M, Di Somma S, Mueller C, Nowak R, Peacock WF, Ponikowski P, Mockel M, Hogan C, Wu AH, Clopton P, Filippatos GS, Anand I, Ng L, Daniels LB, Neath SX, Shah K, Christenson R, Hartmann O, Anker SD, Maisel A (2013) Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH study (Biomarkers in ACute Heart Failure). JACC Heart Fail 1:192–199
27. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, PARAGON-HF Investigators and Committees (2019) Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 381:1609–1620
28. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, Coats AJS, Metra M, Mebazaa A, Ruschitzka F, Lainscak M, Filippatos G, Seferovic PM, Meijers WC, Bayes-Genis A, Mueller T, Richards M, Januzzi JL Jr, Heart Failure Association of the European Society of Cardiology (2019) Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 21:715–731

29. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G (2019) How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 40:3297–3317
30. Wijesurendra RS, Casadei B (2017) Seek and ye shall find subclinical atrial fibrillation in high-risk elderly patients. Circulation. 136:1284–1287
31. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD (2014) Beta-Blockers in Heart Failure Collaborative Group. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet. 384:2235–2243
32. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, Packer M, Coats AJS, Manzano L, Böhm M, van Veldhuisen DJ, Andersson B, Wedel H, von Lueder TG, Rigby AS, Hjalmarson Å, Kjekshus J, Cleland JGF, Beta-blockers in Heart Failure Collaborative Group (2017) Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. J Am Coll Cardiol 69:2885–2896
33. Filippatos G, Farmakis D (2017) How to use beta-blockers in heart failure with reduced ejection fraction and atrial fibrillation. J Am Coll Cardiol 69:2897–2900
34. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K (2016) 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 18:1609–1678
35. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL, Atrial fibrillation and congestive heart failure investigators (2008) Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 358:2667–2677
36. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, McMurray JJ, Petrie MC (2011) Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. Heart. 97:740–747
37. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T (2013) A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol 61:1894–1903
38. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, Goromonzi F, Sawhney V, Duncan E, Page SP, Ullah W, Unsworth B, Mayet J, Dhinoja M, Earley MJ, Sporton S, Schilling RJ (2014) A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 7:31–38
39. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM (2017) Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. J Am Coll Cardiol 70:1949–1961
40. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M, Natale A (2016) Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 133:1637–1644
41. Khan MN, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haïssaguerre M, Natale A, PABA-CHF investigators (2008) Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med 359:1778–1785
42. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D, CASTLE-AF investigators (2018) Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 378:417–427
43. Chen S, Pürerfellner H, Meyer C, Acou WJ, Schratter A, Ling Z, Liu S, Yin Y, Martinek M, Kiuchi MG, Schmidt B, Chun KRJ. (2019) Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. Eur Heart J. ehz443
44. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL, CABANA Investigators (2019) Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA 321:1261–1274
45. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B (2015) Arrhythmia-induced cardiomyopathies: mechanisms, recognition, and management. J Am Coll Cardiol 66:1714–1728
46. Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK, Lekakis JP, Flevari P, Simeonidou E, Rallidis LS, Tsougos E, Hindricks G, Sommer P, Anastasiou-Nana M (2011) Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. J Card Fail 17:964–970
47. Richter S, Di Biase L, Hindricks G (2019) Atrial fibrillation ablation in heart failure. Eur Heart J 40:663–671
48. Filippatos G, Farmakis D (2019) A look back: the quest for thrombosis in heart failure continues after COMMANDER HF. Cardiovasc Res 115:e140–e142
49. Farmakis D, Filippatos G, Lainscak M, Parissis JT, Anker SD, Kremastinos DT (2008) Anticoagulants, antiplatelets, and statins in heart failure. Cardiol Clin 26(1):49–58
50. Ferreira J, Ezekowitz MD, Connolly SJ, Brueckmann M, Fraessdorf M, Reilly PA, Yusuf S, Wallentin L, RE-LY investigators (2013) Dabigatran compared with warfarin in patients with

Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM (2017) Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. J Am Coll Cardiol 70:1949–1961
40. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C,

atrial fibrillation and symptomatic heart failure: a subgroup analysis of the RE-LY trial. Eur J Heart Fail 15:1053–1061
51. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, Van Diepen S, Amerena J, Bartunek J, Commerford P, Oh BH, Harjola VP, Al-Khatib SM, Hanna M, Alexander JH, Lopes RD, Wojdyla DM, Wallentin L, Granger CB, ARISTOTLE committees and investigators (2013) Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. Circ Heart Fail 6: 451–460
52. Siller-Matula JM, Pecen L, Patti G, Lucerna M, Kirchhof P, Lesiak M, Huber K, FWA V, Lang IM, Renda G, Schnabel RB, Wachter R, Kotecha D, Sellal JM, Rohla M, Ricci F, De Caterina R, TEAM in AF group (2018) Heart failure subtypes and thromboembolic risk in patients with atrial fibrillation: the PREFER in AF - HF substudy. Int J Cardiol 265:141–147
53. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray JJV (2017) PARADIGM-HF and ATMOSPHERE investigators and committees type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 70:2490–2500
54. Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Ballman KV, Meverden RA, Roger VL (2006) Ischemic stroke after heart failure: a community-based study. Am Heart J 152:102–109
55. Adelborg K, Szépligeti S, Sundbøll J, Horváth-Puhó E, Henderson VW, Ording A, Pedersen L, Sørensen HT (2017) Risk of stroke in patients with heart failure: a population-based 30-year cohort study. Stroke. 48:1161–1168
56. Hernandez AF, Liang L, Fonarow GC, Hammill BG, Hammill SC, Heidenreich PA, Masoudi FA, Qualls LG, Al-Khatib SM, Piccini JP, Curtis LH (2014) Associations between anticoagulation therapy and risks of mortality and readmission among patients with heart failure and atrial fibrillation. Circ Cardiovasc Qual Outcomes 7:670–679
57. Dubner SJ, Huisman MV, Diener HC, Halperin JL, Rothman KJ, Ma CS, Bergler-Klein J, Zint K, Riou Franca L, Lu S, Teutsch C, Paquette M, GYH L, GLORIA-AF investigators (2018) P2887. Two-year outcomes of dabigatran etexilate treatment in patients with co-morbid heart failure and atrial fibrillation: the GLORIA-AF registry. Eur Heart J 39:ehy565.P2887
58. Contreras JP, Hong KN, Castillo J, Marzec LN, Hsu JC, Cannon CP, Yang S, Maddox TM (2019) Anticoagulation in patients with atrial fibrillation and heart failure: insights from the NCDR PINNACLE-AF registry. Clin Cardiol 42:339–345
59. Killu AM, Granger CB, Gersh BJ (2019) Risk stratification for stroke in atrial fibrillation: a critique. Eur Heart J 40:1294–1302
60. Farmakis D, Davlouros P, Giamouzis G, Giannakoulas G, Pipilis A, Tsivgoulis G, Parissis J (2018) Direct oral anticoagulants in nonvalvular atrial fibrillation: practical considerations on the choice of agent and dosing. Cardiology. 140:126–132
61. Isnard R, Bauer F, Cohen-Solal A, Damy T, Donal E, Galinier M, Hagège A, Jourdain P, Leclercq C, Sabatier R, Trochu JN, Cohen A (2016) Non-vitamin K antagonist oral anticoagulants and heart failure. Arch Cardiovasc Dis 109:641–650
62. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GY (2015) Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. Eur J Heart Fail 17:1192–1200
63. Nelson WW, Choi JC, Vanderpoel J, Damaraju CV, Wildgoose P, Fields LE, Schein JR (2013) Impact of co-morbidities and patient characteristics on international normalized ratio control over time in patients with nonvalvular atrial fibrillation. Am J Cardiol 112:509–512
64. Nelson WW, Desai S, Damaraju CV, Lu L, Fields LE, Wildgoose P, Schein JR (2015) International normalized ratio stability in warfarin-experienced patients with nonvalvular atrial fibrillation. Am J Cardiovasc Drugs 15:205–211
65. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR (2010) Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). J Thromb Haemost 8: 2182–2191
66. Brown LAE, Boos CJ (2017) Atrial fibrillation and heart failure: factors influencing the choice of oral anticoagulant. Int J Cardiol 227:863–868
67. Nascimento T, Birnie DH, Healey JS, Verma A, Joza J, Bernier ML, Essebag V (2014) Managing novel oral anticoagulants in patients with atrial fibrillation undergoing device surgery: Canadian survey. Can J Cardiol 30:231–236
68. Filippatos G, Farmakis D, Parissis J (2014) Renal dysfunction and heart failure: things are seldom what they seem. Eur Heart J 35: 416–418
69. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y (2009) Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J 158:629–636
70. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C (2012) Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 367:625–635
71. Del-Carpio Munoz F, Gharacholou SM, Munger TM, Friedman PA, Asirvatham SJ, Packer DL, Noseworthy PA (2016) Meta-analysis of renal function on the safety and efficacy of novel oral anticoagulants for atrial fibrillation. Am J Cardiol 117:69–75
72. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H, ESC scientific document group (2018) The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 39:1330–1393
73. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L (2014) Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 129:961–970
74. Böhm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, Schumacher H, Brueckmann M, Schirmer SH, Kratz MT, Yusuf S, Diener HC, Hijazi Z, Wallentin L (2015) Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. J Am Coll Cardiol 65:2481–2493
75. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, Noseworthy PA (2017) Renal outcomes in Anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 70:2621–2632
76. Brodsky SV, Nadasdy T, Rovin BH, Satoskar AA, Nadasdy GM, Wu HM, Bhatt UY, Hebert LA (2011) Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int 80:181–189
77. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigli M, Huber K, ESC Scientific Document Group (2019) 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm

Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace. 21:192–193

78. Cannon CP, Bhatt DL, Oldgren J, GYH L, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, Nordaby M, Kleine E, Harper R, Manassie J, Januzzi JL, Ten Berg JM, Steg PG, Hohnloser SH, RE-DUAL PCI Steering Committee and Investigators (2017) Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 377:1513–1524
79. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H (2019) AFIRE Investigators. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 381:1103–1113
80. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, Clemens A, Reilly PA, Connolly SJ, Yusuf S, Wallentin L (2016) Comparison of Dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy). Circulation. 134:589–598
81. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, Hankey GJ, Hacke W, Becker RC, Nessel CC, Mahaffey KW, Fox KA, Califf RM (2014) ROCKET AF Steering Committee & Investigators. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J 35:3377–3385
82. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, Pais P, Erol C, Diaz R, Bahit MC, Bartunek J, De Caterina R, Goto S, Ruzyllo W, Zhu J, Granger CB, Alexander JH (2015) Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation. 132:624–632
83. Russo V, Attena E, Mazzone C, Esposito F, Parisi V, Bancone C, Rago A, Nigro G, Sangiuolo R, D'Onofrio A, Nonvitamin K (2018) Antagonist oral anticoagulants use in patients with atrial fibrillation and bioprosthetic heart valves/prior surgical valve repair: a multicenter clinical practice experience. Semin Thromb Hemost 44:364–369
84. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wöhrle J (2017) Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. JACC Cardiovasc Interv 10:66–74
85. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P, ESC Scientific Document Group (2017) Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J 38:2137–2149
86. Iliodromitis E, Farmakis D (2018) Anti-thrombotic therapy after trans-catheter aortic valve implantation: time for refinement. Cardiology. 141:66–68
87. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, van der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Pin C, Yin DRPP, Swaans MJ, Rensing BJWM, van't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, Ten Berg JM (2020) Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med 382: 1696–1707
88. Yang H, Bouma BJ, Dimopoulos K, Khairy P, Ladouceur M, Niwa K, Greutmann M, Schwerzmann M, Egbe A, Scognamiglio G, Budts W, Veldtman G, Opotowsky AR, Broberg CS, Gumbiene L, Meijboom FJ, Rutz T, Post MC, Moe T, Lipczyńska M, Tsai SF, Chakrabarti S, Tobler D, Davidson W, Morissens M, van Dijk A, Buber J, Bouchardy J, Skoglund K, Christersson C, Kronvall T, Konings TC, Alonso-Gonzalez R, Mizuno A, Webb G, Laukyte M, Sieswerda GTJ, Shafer K, Aboulhosn J, Mulder BJM (2020) Non-vitamin K antagonist oral anticoagulants (NOACs) for thromboembolic prevention, are they safe in congenital heart disease? Results of a worldwide study. Int J Cardiol 299:123–130
89. Farmakis D, Parissis J, Filippatos G (2014) Insights into onco-cardiology: atrial fibrillation in cancer. J Am Coll Cardiol 63: 945–953
90. Farmakis D, Mantzourani M, Filippatos G (2018) Anthracycline-induced cardiomyopathy: secrets and lies. Eur J Heart Fail 20:907–909
91. Ameri P, Canepa M, Anker MS, Belenkov Y, Bergler-Klein J, Cohen-Solal A, Farmakis D, López-Fernández T, Lainscak M, Pudil R, Ruschitska F, Seferovic P, Filippatos G, Coats A, Suter T, Von Haehling S, Ciardiello F, de Boer RA, Lyon AR, Tocchetti CG (2018) Heart Failure Association Cardio-Oncology Study Group of the European Society of Cardiology. Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge. Eur J Heart Fail 20:879–887
92. Laube ES, Yu A, Gupta D, Miao Y, Samedy P, Wills J, Harnicar S, Soff GA, Mantha S (2017) Rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation and active cancer. Am J Cardiol 120:213–217
93. Melloni C, Dunning A, Granger CB, Thomas L, Khouri MG, Garcia DA, Hylek EM, Hanna M, Wallentin L, Gersh BJ, Douglas PS, Alexander JH, Lopes RD (2017) Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE trial. Am J Med 130:1440–1448
94. Fanola C, Ruff C, Murphy S, Jin J, Duggal A, Mercuri M, Antman E, Braunwald E, Giugliano R (2017) Efficacy and safety of edoxaban in patients with atrial fibrillation and active malignancy: an analysis of ENGAGE-AF TIMI 48 randomized clinical trial. J Am Coll Cardiol 69(11 Supplement):325
95. Shah S, Norby FL, Datta YH, Lutsey PL, MacLehose RF, Chen LY, Alonso A (2018) Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Adv 2:200–209
96. Lee YJ, Park JK, Uhm JS, Kim JY, Pak HN, Lee MH, Sung JH, Joung B (2016) Bleeding risk and major adverse events in patients with cancer on oral anticoagulation therapy. Int J Cardiol 203:372–378
97. Haas S, Camm AJ, Bassand JP, Angchaisuksiri P, Cools F, Corbalan R, Gibbs H, Jacobson B, Koretsune Y, Mantovani LG, Misselwitz F, Panchenko E, Ragy HI, Stepinska J, Turpie AG, Sawhney JP, Steffel J, Lim TW, Pieper KS, Virdone S, Verheugt FW, Kakkar AK, GARFIELD-AF Investigators (2019) Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: Results from GARFIELD-AF. Am Heart J 213:35–46
98. Potpara TS, Trendafilova E, Dan GA, Goda A, Kusljugic Z, Manola S, Music L, Gjini V, Pojskic B, Popescu MI, Georgescu CA, Dimitrova ES, Kamenova D, Ekmeciu U, Mrsic D, Nenezic A, Brusich S, Milanov S, Zeljkovic I, Lip GYH, BALKAN-AF Investigators (2017) The patterns of non-vitamin K antagonist oral anticoagulants (NOACs) use in patients with atrial fibrillation in

seven Balkan countries: a report from the BALKAN-AF survey. Adv Ther 34:2043–2057
99. Xintarakou A, Iliodromitis K, Tzeis S, Smyrnioudis N, Vogiatzis I, Manginas A, Lampropoulos S, Eleftheriadis I, Mantas I, Kafkas N, Gotsis A, Kogias I, Spanos A, Brika P, Andrikopoulos G, Koudounis G, Vardas P. (2019) Antithrombotic therapy in hospitalized patients with atrial fibrillation: results from a Panhellenic multicenter registry. 40th Panhellenic Congress of Cardiol, Abst. n. 191] [Greek]
100. McAlister FA, Garrison S, Kosowan L, Ezekowitz JA, Singer A (2018) Use of direct oral anticoagulants in Canadian primary care practice 2010–2015: a cohort study from the Canadian Primary Care Sentinel Surveillance Network. J Am Heart Assoc 7(3): e007603
101. Ono T, Ikemura N, Kimura T, Ueda I, Tanaka H, Tokuda H, Yajima N, Matsumura K, Suzuki M, Fukuda K, Kohsaka S, Takatsuki S (2019) Contemporary trend of reduced-dose non-vitamin K anticoagulants in Japanese patients with atrial fibrillation: a cross-sectional analysis of a multicenter outpatient registry. J Cardiol 73:14–21
102. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139–1151
103. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365:883–891
104. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369:2093–2104
105. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE Committees and Investigators (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365:981–992
106. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson Å, Wikstrand J, Kotecha D, Beta-blockers in Heart Failure Collaborative Group (2018) Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 39:26–35
107. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371:993–1004
108. Böhm M, Slawik J, Brueckmann M, Mattheus M, George JT, Ofstad AP, Inzucchi SE, Fitchett D, Anker SD, Marx N, Wanner C, Zinman B, Verma S (2020) Efficacy of empagliflozin on heart failure and renal outcomes in patients with atrial fibrillation: data from the EMPA-REG OUTCOME trial. Eur J Heart Fail 22: 126–135
109. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members; Document Reviewers (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18:891–975
110. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators (2010) Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 363: 2385–2395
111. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA 3rd, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W, MADIT-RIT Trial Investigators (2012) Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 367:2275–2283