Thromboembolism and antithrombotic therapy for heart failure in sinus rhythm

An Executive Summary of a joint Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis

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Summary

Chronic heart failure (HF) with either reduced or preserved left ventricular (LV) ejection fraction is common and remains an extremely serious disorder with a high mortality and morbidity. Many complications related to heart failure can be related to thrombosis. Epidemiological and pathophysiological data also link HF to an increased risk of thrombosis, leading to the clinical consequences of sudden death, stroke, systemic thromboembolism and/or venous thromboembolism. This executive summary of a joint consensus document of the Heart Failure Association (EHFA) of the European Society of Cardiology (ESC) and the ESC Working Group on Thrombosis reviews the published evidence, summarises ‘best practice’, and puts forward consensus statements that may help to define evidence gaps and assist management decisions in everyday clinical practice. In HF patients with atrial fibrillation, oral anticoagulation is clearly recommended, and the CHA2DS2-VASc and HAS-BLED scores should be used to determine the likely risk-benefit ratio (thromboembolism prevention versus risk of bleeding) of oral anticoagulation. In HF patients with reduced LV ejection fraction who are in sinus rhythm there is no evidence of an overall benefit of vitamin K antagonists (e.g. warfarin) on mortality, with risk of major bleeding. Whilst there is the potential for a reduction in ischaemic stroke, there is currently no compelling reason to routinely use warfarin for these patients. Risk factors associated with increased risk of thromboembolic events should be identified and decisions regarding use of anticoagulation individualised. Patient values and preferences are important determinants when balancing the risk of thromboembolism against bleeding risk. Novel oral anticoagulants that offer a different risk-benefit profile compared with warfarin may appear as an attractive therapeutic option, but this would need to be confirmed in clinical trials.

Keywords

Heart failure, sinus rhythm, thromboembolism, antithrombotic therapy, warfarin, aspirin

Introduction

Heart failure (HF) with either reduced or preserved ejection fraction (EF) is common and remains an extremely serious disorder with a high mortality and morbidity, despite significant advances in its management of this condition.

Venous thromboembolism (VTE), cardio-embolic stroke and sudden death occurs in about 30% of HF patients and may contribute to the high mortality and morbidity seen in HF. The incidence of ischaemic stroke has been reported to be 18 per 1,000 patients during the first year following HF diagnosis, increasing to 47 per 1,000 by the end of five years (1). Incident HF may be particu-
larly serious, as the risk of stroke and thromboembolism appears greatest in the initial period (<30 days) following diagnosis of HF, although the risk may still be evident up to six months later (2–4). Death in HF patients is attributed mainly to refractory HF or sudden cardiac death, and the latter commonly results from a new coronary (thrombotic) occlusion or arrhythmic events (5).

Given that HF is commonly associated with atrial fibrillation (AF), some patients may well have ‘silent’ paroxysms of AF – which may be an important mechanism of increased risk of stroke and thromboembolism in HF patients considered to be in sinus rhythm (6). Indeed, AF complicating HF significantly increases the risk of stroke by two- to three-fold. HF also predisposes to VTE, and is an important risk factor for in-hospital and 30-day mortality in patients who present with VTE (7, 8). Without thromboprophylaxis, venographically proven VTE may occur in 10% to 22% of hospitalised patients with HF (7, 8). Severe left ventricular (LV) dysfunction, clinical severity (New York Heart Association [NYHA] class III–IV), young age, and/or right ventricular dysfunction appear to enhance the VTE risk associated with HF (7, 8).

Whilst the complications of HF discussed above have a thrombosis-related pathophysiological basis and would theoretically require appropriate antithrombotic therapy, there remains debate over the actual potential benefit of using antithrombotic therapy in HF patients in sinus rhythm in clinical practice.

In recognising this problem, the Heart Failure Association (HFA) and the European Society of Cardiology (ESC) Working Group on Thrombosis convened a Task Force with the remit to review the published evidence and to propose a joint consensus on thromboembolic risk and antithrombotic therapy for HF patients in sinus rhythm, with a view to summarise ‘best practice’. Given the limited evidence in HF with preserved ejection fraction (HFrEF) this document will focus on HF patients with reduced ejection fraction (HFrEF). Reference to HFrEF will be made where appropriate, especially since many cohort studies do not differentiate between HFrEF and HFrEF. The present document is an executive summary of the full consensus document published in the European Journal of Heart Failure (9) which summarises the best available evidence and puts forward consensus statements that may help to define evidence gaps and assist management decisions in everyday clinical practice.

Literature searches were conducted in PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry). Data on studies before 1961 were retrieved through manual search of the primary publication. Searches were focused on English-language sources and studies in human subjects.

Pathophysiology

The increased rate of thrombotic complications in patients with HF does have a pathophysiological basis. For over 150 years, it has been acknowledged that thrombogenesis is precipitated by a combination of abnormal blood flow, abnormalities in the vessel wall and abnormalities in blood constituents commonly known as “Virchow’s triad” (10, 11).

In the setting of reduced LV EF, the dilated cardiac chambers and impaired systolic function both cause stasis of blood within the heart (10). Abnormalities in blood flow are more common in LV aneurysms, with areas of cardiac dyskinesia, and severe systolic dysfunction. In HF, flow abnormalities could perhaps be the major component of Virchow’s triad for thrombogenesis.

Abnormalities of the endocardial and endothelial (‘vessel’) wall are another component, but may simply reflect underlying comorbidities leading to cardiovascular events associated with plaque rupture and arterial thrombosis. Nonetheless, an impaired synthesis of endothelium-derived nitric oxide, which may promote monocyte and platelet adhesion to the endothelium, is observed in patients with HF (12). Endothelial damage/dysfunction is also detectable through the behaviour of specific biomarkers, such as von Willebrand factor, thrombomodulin or soluble E-selectin, which are found to be consistently elevated in HF patients (13–15). Abnormal levels of endothelial biomarkers have also been related to functional abnormalities, such as impaired flow-mediated dilation, in these patients (14, 15).

The third component of Virchow’s triad, abnormalities in blood constituents, has been observed in patients with HF. Indeed, a hypercoagulable state and platelet abnormalities with an increased tendency to form aggregates have been demonstrated (16, 17). Inflammatory cytokines and neuroendocrine abnormalities may also have a contributory role (18). For an overview of the pathophysiology of thrombosis in heart failure see Figure 1.

Epidemiology and size of the problem

Epidemiological cohort data

A significant proportion of patients presenting with stroke or peripheral thromboembolism have HF, specifically HFrEF or asymptomatic echocardiographic evidence of LV systolic dysfunction (LVSD). About 14% of patients with stroke have HF (19) and about 20% of stroke patients have some evidence of LVSD (EF ≤50%) (20). Data on thromboembolic risk in HF patients from large epidemiological studies to support this are limited, and many older studies do not differentiate between HFrEF and HFrEF. Also, many studies do not fully account for the risk of concomitant AF, and silent paroxysms of AF may occur frequently in HF patients.

What do epidemiological studies tell us? In one analysis of 516 deaths in a community long-term study comparing HF patients with depressed LV function versus those with preserved LV function, sudden death occurred in 21% versus 16%, respectively (21). In patients with depressed LV, new coronary occlusions (as reflected by myocardial infarction [MI]) resulted in a fairly small proportion of deaths according to poorly specified criteria during a 1.5 year follow up (21).

In the Rotterdam study of 7,546 participants ≥55 years of age followed for 10 years, the risk of ischaemic stroke increased more
than five-fold in the first month after diagnosis of HF compared with no HF diagnosis, even after adjustment for age and sex (adjusted hazard ratio [HR] 5.79, 95% confidence interval [CI] 2.15–15.62), although this risk was attenuated over time (age and sex adjusted HR 3.50, 95% CI 1.96–6.25) after 1–6 months, becoming non-significant after the first six months following diagnosis (0.83, 95% CI 0.53–1.29, after 0.5–6 years) (2). Adjustments for cardiovascular risk factors (including AF) modestly attenuated these HRs, and still demonstrated a risk of ischaemic stroke comparable to that of controls only after 0.5–6 years (age and sex adjusted HR 0.58, 95% CI 0.37–0.92). Thus, the risk of ischaemic stroke appears strongly increased shortly after the diagnosis of HF, returning to normal within six months after onset of HF (2).

Similar observations were noted in the Diet, Cancer, and Health study, where incident HF was a major risk factor for stroke, death, and the composite of ‘stroke and death,’ particularly in the initial 30 days following diagnosis (4). While lower than the 30-day risk, the increased risk for stroke and/or death did not return to normal even after six months following the initial diagnosis of incident HF. On multivariate analysis, previous stroke/transient ischaemic attack/thromboembolism was found to predict increased risk of stroke (adjusted HR 6.43, 95% CI 4.29–9.65), death (adjusted HR 2.01, 95% CI 1.57–2.57) and the composite of ‘stroke and death’ (adjusted HR 2.52, 95% CI 2.02–3.52). Of note, VKA treatment was independently associated with a lower risk of death (adjusted HR 0.46, 95% CI 0.28 to 0.74, p<0.001) and the combined endpoint of death or stroke (adjusted HR 0.64, 95% CI 0.43 to 0.96, p=0.003).

HF patients also have a high rate of stroke recurrence and mortality after stroke (22, 23), for example, in a population based study from Rochester, this risk was 20% in the first year and 45% after five years (12). In the Framingham Heart Study (24), the risk of stroke in HF patients was 4.1% and 2.8% per year for men and women, respectively, although concurrent AF was present in many patients.

There is also a clear association between HF and VTE, with a two-fold increased risk, and important implications for prognosis and death (25, 26).

**Case-control studies**

In the Northern Manhattan Study (NOMAS), a multiethnic population based case-control study of 270 patients with first ischaemic stroke and 288 matched controls, any degree of LV dysfunction was more frequent in stroke patients (24.1%) compared with controls (4.9%; p<0.0001) (20). Even a mild degree of LVSD (EF 41–50%) was still associated with an increased adjusted risk of ischaemic stroke.

Many publications from relatively small case-control or other observational studies from single centres and/or registries, with the inherent limitations of such studies, report wide variations in the incidence of arterial thromboembolism in HF, ranging from 1.4% to 12.5% (27–36) (Table 1). In one recent contemporary registry of 902 patients with HF, EF ≤35% and sinus rhythm, anticoagulation therapy use (in 26%) was not associated with significant differences in total mortality (14% versus 12.5%) or stroke (0.8% versus 0.9%) (37). There was a reduction in major cardiac events (cardiac death, heart transplantation, coronary revasculari-
sation, and cardiovascular hospitalisation (HR: 0.74; 95%CI 0.56–0.97; P=0.03) in patients receiving anticoagulation therapy. Bleeding data were not available. Also, many of these studies included a mixture of dilated cardiomyopathy and ischaemic HF.

The risk of stroke in HF patients may be related to the degree of LVSD, as seen in some retrospective studies (Table 1). Again, another limitation is that many of these studies included patients with AF, and thus the increase in the incidence of thromboembolic events could be more related to the inherent embolic risk in AF than in HF per se; conversely, anticoagulants given for AF with HF (apparent in varying proportions, as high as 57% [32]) could result in a considerably lower incidence of thromboembolic events than when given for HF without AF. Most of the studies did not specify thromboembolism as an endpoint and therefore the true incidence may be under-reported. Lastly, many studies did not differentiate between HFrEF and HFP EF.

### Post-hoc analyses of trial data

Although in a selective cohort with unclear definition of MI, autopsy findings from the Assessment of Treatment with Lisinopril and Survival (ATLAS) study adjudicated 33% of deaths classified as ‘sudden cardiac death’ to acute coronary findings (coronary thrombosis) whereas 37% of deaths originally classified as ‘progressive HF’ were reclassified as attributable to coronary thrombosis although few were classed as ‘definite acute MI’ (5).

The risk of thromboembolic events (stroke, pulmonary and peripheral thromboembolism) in patients with HF demonstrates little consistency in post-hoc analyses of large HF treatment trials of patients with HFrEF (38–45) (Table 2). In general, these post-hoc analyses have reported a somewhat lower stroke incidence when compared with relatively smaller prospective observational studies (see Table 1). In published HF trials, annual stroke rates between 1.1% and 4.6% have been reported, but almost all of these analyses included some patients with AF.

In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), the highest absolute incidence of cerebrovascular events was observed, at 4.6% per year; however, this trial included patients with severe HF with a high prevalence of concomitant AF (38). In an analysis of the Vasodilator-Heart Failure Trials (V-HeFT I and II) (39), the incidence of thromboembolic events in patients who were not receiving oral anticoagulation was 2.7% and 2.1% per year, respectively, in the V-HeFT I and II trials. However about 15% of the patients were in AF, although surprisingly this condition was not found to be independently associated with an increase rate of thromboembolism.

In a recent analysis of the SCD-HeFT trial (40) of patients with New York Heart Association (NYHA) class II and III HF without AF, the authors reported the incidence of thromboembolism (mostly strokes) by four years were 4.0%, with 2.6% in patients randomised to amiodarone, 3.2% in patients randomised to implantable cardioverter-defibrillator (ICD), and 6.0% in patients randomised to placebo (approx. rates of 0.7%, 0.8%, and 1.5% per year, respectively). By multivariable analysis, hypertension (p=0.021) and decreasing LVEF (HR 0.82, 95% CI 0.69 to 0.97) per 5% increase in EF) were significant predictors of thromboembolism. Interestingly, treatment with amiodarone or ICD was a significant predictor of thromboembolism-free survival (HR versus placebo, 0.57 [95% CI, 0.33 to 0.93] for ICD; 0.44 [95% CI, 0.24 to 0.80] for amiodarone) (40).

In an analysis of the Survival and Ventricular Enlargement (SAVE) Trial (41), the overall risk of stroke was 8.1% at five years. The risk of stroke was found to be twice as high in patients with EF <28%. Every 5% decrease in EF was associated with an 18% increase in stroke risk. Unfortunately, in this study, the authors did not exclude patients with AF and only reported stroke events.

Al-Kadra et al. (44) reviewed data on warfarin use in 6,797 patients enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) trial and found that the use of warfarin was independently associated with a significant reduction in all-cause mortality (adjusted HR 0.76, 95% CI 0.65 to 0.89, p=0.0006) and the risk of death or hospital admission for heart failure (HR 0.82, 95% CI 0.72 to 0.93, p=0.0002).

<table>
<thead>
<tr>
<th>Study/Trial</th>
<th>Patients (n)</th>
<th>Diagnosis</th>
<th>Follow up (months)</th>
<th>AF (%)</th>
<th>EF (%)</th>
<th>Anticoagulation (%)</th>
<th>Thromboembolic events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falk (27)</td>
<td>25</td>
<td>DCM</td>
<td>21</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>7.8</td>
</tr>
<tr>
<td>Blondheim (28)</td>
<td>79</td>
<td>DCM</td>
<td>32</td>
<td>NA</td>
<td>19–23</td>
<td>NA</td>
<td>2.1</td>
</tr>
<tr>
<td>Fuster (29)</td>
<td>106</td>
<td>DCM</td>
<td>132</td>
<td>23</td>
<td>NA</td>
<td>0</td>
<td>3.5</td>
</tr>
<tr>
<td>Gottdiener (30)</td>
<td>123</td>
<td>DCM/IC</td>
<td>24</td>
<td>NA</td>
<td>27</td>
<td>NA</td>
<td>5.7</td>
</tr>
<tr>
<td>Ciaccheri (31)</td>
<td>126</td>
<td>DCM</td>
<td>41</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>1.4</td>
</tr>
<tr>
<td>Sharma (32)</td>
<td>144</td>
<td>DCM/IC</td>
<td>30</td>
<td>NA</td>
<td>27</td>
<td>57</td>
<td>12.5</td>
</tr>
<tr>
<td>Diaz (33)</td>
<td>169</td>
<td>DCM</td>
<td>66</td>
<td>20</td>
<td>NA</td>
<td>0</td>
<td>5.6</td>
</tr>
<tr>
<td>Natterson (34)</td>
<td>224</td>
<td>DCM/IC</td>
<td>10</td>
<td>19</td>
<td>20</td>
<td>37</td>
<td>3.2</td>
</tr>
<tr>
<td>Katz (35)</td>
<td>264</td>
<td>DCM</td>
<td>14</td>
<td>13</td>
<td>27</td>
<td>13</td>
<td>1.7</td>
</tr>
<tr>
<td>Cioffi (36)</td>
<td>406</td>
<td>DCM/IC</td>
<td>16</td>
<td>16</td>
<td>23</td>
<td>48</td>
<td>1.7</td>
</tr>
</tbody>
</table>

DCM – dilated cardiomyopathy, IC – ischaemic cardiomyopathy, AF – atrial fibrillation, EF – left ventricular ejection fraction, NA – not available. The cumulative incidence of thromboembolism refers to the follow-up period of each study.

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**Table 1:** Thromboembolic events in observational case-control studies of patients with heart failure.
In a separate analysis from SOLVD (45), antiplatelet therapy use also significantly reduced mortality from all causes (adjusted HR 0.82, 95% CI 0.73 to 0.92, p < 0.0005) and reduced risk of death or hospital admission for HF (adjusted HR 0.81, 95% CI 0.74 to 0.89, p < 0.0001); however, the association between antiplatelet therapy use and survival was not observed in the enalapril group. In another retrospective analysis of the SOLVD trials (45), the annual rate of thromboembolic events was 2.4% in women and 1.8% in men (after excluding patients with AF). Lower EF was associated with higher thromboembolic event rates in women but not in men, and this difference was mainly related to an increment in pulmonary embolism events. Interestingly, women showed a 53% increased risk of thromboembolic events for every 10% impairment in EF.

Amongst the more recent trials in the post–MI period that included patients with LVSD, a post-hoc analysis of the VALIANT trial reported that the rate of stroke in the first 45 days was 0.94% (95% CI 0.78–1.09), whilst the cumulative rates were 2.33% (95% CI 2.08–2.58), 3.41% (95% CI 3.09–3.73), and 4.21% (95% CI 3.73–4.68) for the first, second, and third years, respectively (46). In the recent EMPHASIS-HF study, the stroke rate was 1.5–1.9%, taking into consideration the 21-month follow-up, the rate of stroke was around 1%/year (47). In the CORONA trial, where 92% were taking angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and 75% beta-blockers, non-fatal stroke incidence was 1.4–1.5% per annum, although 35% of these patients had AF and 23% were also receiving anticoagulation therapy (48).

Limited data on stroke rates in patients with HFpEF are available from post-hoc analyses from some large clinical trials (49, 50). These data suggest that risk of stroke (and also mortality due to stroke) may be similar. For example, the I-PRESERVE study (49) reported 147 stroke events in total, which gives an event rate of 0.8–0.9%/year; additionally, 9% of all deaths were due to stroke. Another example is CHARM-Preserved study, where the rate of fatal and non-fatal stroke was entirely unrelated to EF (EF<22% – 1.2%, 23–32 – 1.4%, 33–42 – 1.4%, 43–52 – 1.3%; >52% – 1.5%) (50).

Ongoing myocardial ischaemia may be a trigger in approximately 20% of cardiac arrest cases in hospitalised but stable patients with HF (51). This is reaffirmed by the ATLAS data discussed above, with acute (thrombotic) coronary findings at autopsy in many HF patients with sudden death (5). Recognised MI per se is rather uncommon in HF trials.

### Randomised controlled trials of antithrombotic therapy

Table 2A shows trials conducted before 1960 testing anticoagulants against no medication (52–54). These studies were performed in hospitalised patients with a high prevalence (up to 30%) of rheumatic valvular disease and AF. Randomisation methods were likely biased and methods used to monitor the patients, and to determine patient inclusion and exclusion were likely not as robust as in modern trials. Despite limitations, all three studies favored anticoagulant therapy in terms of a reduction in all-cause mortality and thromboembolic events (Table 3A). In the absence of accurate diagnostic imaging capabilities, most of the events were judged clinically or at autopsy, and as such, strokes were not always diagnosed. In terms of bleeding, although minor bleeding episodes were reported in the active treatment arm, no significant increase in major bleeding was reported for the anticoagulated patients.

Table 3B reports the contemporary randomised controlled trials of antithrombotic therapy in HF. Of these trials, Warfarin/Aspirin Study in Heart Failure (WASH) was a pilot for the Warfa-

Table 2: Examples of thromboembolism data in post-hoc analyses from major heart failure trials of HFrEF.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ref.</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>AF (%)</th>
<th>Anticoagulation use (%)</th>
<th>CVA (% per year)</th>
<th>Systemic TE events (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>38</td>
<td>253</td>
<td>73</td>
<td>50</td>
<td>34</td>
<td>4.6</td>
<td>NA</td>
</tr>
<tr>
<td>V-HeFT-I</td>
<td>39</td>
<td>642</td>
<td>44</td>
<td>15</td>
<td>19</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td>V-HeFT-II</td>
<td>39</td>
<td>840</td>
<td>53</td>
<td>15</td>
<td>21</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>PROMISE</td>
<td>43</td>
<td>1088</td>
<td>54</td>
<td>NA</td>
<td>30</td>
<td>3.5</td>
<td>NA</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>40</td>
<td>2114</td>
<td>44</td>
<td>0</td>
<td>46</td>
<td>2.6</td>
<td>1.0</td>
</tr>
<tr>
<td>SAVE*</td>
<td>41</td>
<td>2231</td>
<td>100</td>
<td>NA</td>
<td>28</td>
<td>1.5</td>
<td>NA</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>47</td>
<td>2737</td>
<td>21</td>
<td>31</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
</tr>
<tr>
<td>SOLVD</td>
<td>42</td>
<td>6797</td>
<td>79</td>
<td>6</td>
<td>28</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>VALIANT*</td>
<td>46</td>
<td>14703</td>
<td>25</td>
<td>13.6% of those with CVA vs. 6.3% without CVA</td>
<td>9.5%</td>
<td>2.33%</td>
<td>NA</td>
</tr>
</tbody>
</table>

*post-myocardial infarction trials in patients with LV systolic dysfunction. AF – atrial fibrillation; CVA – cerebrovascular accident; NA – not available. CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study; PROMISE: Prospective Randomized Milrinone Survival Evaluation; SAVE: Survival and Ventricular Enlarge-

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Table 3: Older randomised controlled trials, conducted >50 years ago (A) and contemporary randomised controlled trials of antithrombotic therapy in heart failure (B).

A

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Methods</th>
<th>Patients</th>
<th>n (followup)</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>In-hospital outcome rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson [52]</td>
<td>1950</td>
<td>Controlled/ prospective</td>
<td>Heart Failure</td>
<td>279</td>
<td>Dicoumarol</td>
<td>Death, pulmonary embolism, arterial embolism</td>
<td>Death: 8% with dicoumarol vs. 13% without</td>
</tr>
<tr>
<td>Harvey [53]</td>
<td>1950</td>
<td>Controlled prospective</td>
<td>Heart Failure</td>
<td>180</td>
<td>Dicoumarol</td>
<td>Death, pulmonary/arterial embolism, stroke, MI, thrombophlebitis</td>
<td>Death: 9% with dicoumarol vs. 17% without</td>
</tr>
<tr>
<td>Griffith [54]</td>
<td>1952</td>
<td>Controlled prospective</td>
<td>Heart Failure</td>
<td>603</td>
<td>Tromexan*, Dicoumarol +/- Depo-heparin or Sodium Heparin</td>
<td>Death, stroke, pulmonary and peripheral embolism</td>
<td>Thromboembolism: 2% with anticoagulant vs. 16% without</td>
</tr>
</tbody>
</table>

B

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Methods</th>
<th>Patients</th>
<th>n (followup)</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>WASH [55]</td>
<td>2004</td>
<td>Pilot RCT for WATCH</td>
<td>Heart failure (FF ≤35%)</td>
<td>279</td>
<td>(Mean follow-up 27 ± 1 months)</td>
<td>No med, aspirin (300 mg), Warfarin (target INR 2.5)</td>
<td>Death, non-fatal MI, non-fatal stroke.</td>
</tr>
<tr>
<td>HELAS [56]</td>
<td>2006</td>
<td>RCT</td>
<td>Heart failure (EF &lt;35%) NYHAII-IV/IV</td>
<td>197</td>
<td>(Mean follow-up 18.5 to 21.9 months dep. on group)</td>
<td>Warfarin (target INR2–3) vs. aspirin (325 mg) for ischaemic CM (115). Warfarin or placebo for dilated CM (82) –</td>
<td>Death, MI, periferal/pulmonary embolism, nonfatal stroke, re-hospitalisation (incl HF), exacerbation of HF</td>
</tr>
<tr>
<td>WATCH [57]</td>
<td>2010</td>
<td>Partially blind prospective RCT</td>
<td>LVEF ≤ 35%, Class II-IV/IV</td>
<td>1587</td>
<td>(Mean follow-up 21 months)</td>
<td>Warfarin (target INR 2–3.5) vs. aspirin (162 mg) vs. clopidogrel (75 mg)</td>
<td>All cause mortality, non-fatal MI, non-fatal stroke</td>
</tr>
<tr>
<td>WARCEF [58]</td>
<td>2012</td>
<td>Double blind prospective RCT</td>
<td>Heart failure (EF&lt;35%)</td>
<td>2305</td>
<td>(Mean follow-up 42.1 months)</td>
<td>Warfarin (target INR 2.5–3.5) vs. aspirin (325 mg)</td>
<td>First to occur of death, ischaemic stroke, or intracerebral haemorrhage.</td>
</tr>
</tbody>
</table>

HELAS, HEart failure Long-term Antithrombotic Study; WARCEF, Warfarin versus Aspirin in patients with Reduced Cardiac Ejection Fraction; WASH: warfarin/aspirin study in heart failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart failure.

rin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, and the subsequent WATCH and HEart failure Long-term Antithrombotic Study (HELAS) trials were stopped early due to slow recruitment rates. In the WASH study (55), 279 patients were randomised to receive warfarin, aspirin, or no antithrombotic therapy and followed up for a mean (± SD) of 27 (± 1) months, comparing the rate of all cause death, non-fatal MI and cerebrovascular accident (CVA). There was no difference in the primary endpoint among the three treatment groups. However, those receiving aspirin were more likely to be hospitalised. Minor bleeding was higher among those receiving warfarin and aspirin, although there were few major haemorrhagic events overall.

The HELAS (56) separated 197 patients according to the aetiology of their HF. The ischaemic cardiomyopathy group (n=115) was randomised to receive aspirin or warfarin, while the non-ischaemic cardiomyopathy group (n=82) was randomised to receive placebo or warfarin. Patients were followed up for a mean period of 18.5 to 21.9 months, depending on the group. No difference in the composite primary endpoint was observed. Major haemorrhage was seen among warfarin groups but not in other groups.
The WATCH trial (57), one of the largest published trials of antithrombotic therapy in HF patients to date, assessed the rate of death, non-fatal stroke, and non-fatal MI in 1,587 patients receiving aspirin, clopidogrel or warfarin, who were followed up for a mean duration of 1.9 years. Of note, there was no placebo arm to truly assess “efficacy” per se. There was no difference in the rate of the composite primary endpoint between treatment groups. However, the use of warfarin appeared to reduce the incidence of stroke compared with aspirin or clopidogrel. Major bleeding was higher with warfarin than with clopidogrel or aspirin. It was also noted that HF hospitalisations were significantly increased in patients receiving aspirin.

The Warfarin versus Aspirin in patients with Reduced Cardiac Ejection Fraction (WARCEF) study is the only completed modern trial to date, and compared the efficacy of aspirin or warfarin on the primary endpoint of the first to occur of death, ischemic stroke, or intracranial haemorrhage in HF patients in sinus rhythm (58). This study is unique among trials of antithrombotic therapy in HF in sinus rhythm in that it employed a double-blind, double-dummy study design. All patients took real warfarin or aspirin, and dummy warfarin or aspirin; however, there was no control arm receiving no antithrombotic therapy, which precludes quantification of the effect of warfarin (or aspirin) versus no treatment. All patients underwent international normalized ratio (INR) testing regularly and sham INRs were generated for those on dummy warfarin (target INR 2.5–3.0). In WARCEF, 2305 subjects (mean age 62 years, 80% male, mean EF 25%) were enrolled in 11 countries with final status known in 2,245 (97.4%) after a mean of 3.5 years follow-up.

The WARCEF trial (58) found no significant difference in the primary endpoint between the warfarin and aspirin groups (7.47% versus 7.93%/year, respectively; HR 0.93 [0.79–1.10], p=0.40). In a time-varying analysis, the hazard ratio changed over time, slightly favouring warfarin over aspirin by the fourth year of follow-up, but this finding was only marginally significant (p=0.046). For the main secondary outcome, which included primary end-point outcomes plus MI and HF hospitalisations, there was no difference between the groups. Warfarin was associated with a significant reduction in the rate of ischemic stroke throughout the follow-up period, when compared with aspirin (0.72% versus 1.36%/year, HR 0.52 [0.33–0.82], p=0.005). The rate of major haemorrhage was increased with warfarin compared with aspirin (1.78% versus 0.87%/year, p<0.001). Of note, the rates of intracerebral/intracranial haemorrhage did not differ significantly between the two treatment groups (0.27% versus 0.22%/year with warfarin and aspirin, respectively, p=0.82). In contrast to previous trials (i.e. WASH, WATCH), there was no evidence of increased HF hospitalisations in aspirin-treated patients (58). Thus, among patients with HFREF who were in sinus rhythm, there was no significant overall difference in the primary outcome of death, ischaemic stroke, or intracranial haemorrhage between warfarin and aspirin. The reduced risk of ischemic stroke with warfarin per se, was offset by an increased risk of major haemorrhage.

A subgroup analysis of WARCEF found that warfarin was associated with a 37% drop in risk of death, ischaemic stroke, or intracranial haemorrhage compared with aspirin in the younger (age <60) subgroup of patients [hazard ratio, HR 0.63 (0.48–0.84); p=0.001], in contrast to older subjects aged 60 and over (HR 1.09 (0.88–1.35); p=0.442) (106).

### Assessment and management issues

#### Clinical assessment/evaluation

Some HF groups at high thromboembolic risk merit specific clinical assessment and consideration for anticoagulation, although

<table>
<thead>
<tr>
<th>Table 4: What do published clinical guidelines say on the use of anticoagulation in heart failure patients in sinus rhythm? [59–62].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESC 2008 [59]</strong></td>
</tr>
<tr>
<td>OAC is recommended in patients with intracardiac thrombus detected by imaging or evidence of systemic thrombo-embolism (Class IC).</td>
</tr>
<tr>
<td><strong>ESC 2012 [60]</strong></td>
</tr>
<tr>
<td>Other than in patients with AF (both HF-REF and HF-PEF), these guidelines state that is no evidence that an OAC reduces mortality and morbidity compared with placebo or aspirin.</td>
</tr>
<tr>
<td><strong>ACC/AHA 2009 [61]</strong></td>
</tr>
</tbody>
</table>
| • OAC is mostly justified in those who have experienced a previous embolic event;  
• OAC should be considered in those with increased thromboembolic risk (e.g. amyloidosis or LV noncompaction) and in patients with familial dilated cardiomyopathy and a history of thromboembolism in first-degree relatives. |
| **HFSA 2010 [62]** |
| • OAC is recommended in patients with a history of systemic or pulmonary emboli including stroke or transient ischaemic attack;  
• OAC is recommended in patients with symptomatic or asymptomatic ischaemic cardiomyopathy and documented large anterior MI or recent MI with documented LV thrombus (for 3 months post-MI);  
• OAC should be considered in other cases of ischaemic/non-ischaemic cardiomyopathy with LV thrombus depending on the characteristics of the thrombus;  
• OAC may be considered in patients with dilated cardiomyopathy and LVEF ≤35%. |

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recommendations in previous clinical practice guidelines have varied in the level of detail (Table 4). In addition, anticoagulation may be considered for patients with right HF and pulmonary hypertension.

Assessment for underlying paroxysmal AF may be needed, given the close relation between AF burden and thromboembolism. Whilst direct studies in HF populations are lacking, one systematic review concluded that AF may be detected in one in 20 cases presenting with acute ischaemic stroke, especially with prolonged electrocardiogram (ECG) monitoring (e.g. 7-day Holter monitoring) (63). Thus, the harder one looks, the more likely one is likely to find AF.

Also, subclinical atrial tachyarrhythmias, without clinical AF, occur frequently in patients with pacemakers and can be associated with a significantly increased risk of ischaemic stroke or systemic thromboembolism (6). One ongoing multicenter, randomised trial of remote surveillance technology in patients (usually with reduced EF) with implanted dual-chamber cardiac resynchronisation therapy defibrillator (CRT-D) devices is testing the hypothesis that initiation and withdrawal of oral anticoagulant therapy guided by continuous ambulatory monitoring of the atrial ECG improves clinical outcomes by reducing the combined rate of stroke, systemic embolism, and major bleeding compared with conventional clinical management (64).

Evaluation of bleeding risk is also mandatory as HF patients have a significant risk of bleeding on warfarin, especially when INR control is erratic due to liver congestion. Although bleeding risk scores have been developed and validated mainly in AF populations, they may be also applicable to HF patients in sinus rhythm to evaluate the potential risks of anticoagulation (65). Using the well-validated HAS-BLED score (66) may be recommended in these patients with careful follow-up if anticoagulant is prescribed.

Additionally it should be remembered that there is often a ‘high risk’ period for bleeding, following initiation of oral anticoagulation (67). In elderly patients, the risk of major bleeding (and intracranial haemorrhage) with warfarin and aspirin may be similar (68). A recent systematic review and meta-analysis of randomised trials comparing warfarin and aspirin found a non-significant trend towards an increase in major bleeding risk in those randomised to warfarin (odds ratio [OR] 1.27; 95% CI 0.83–1.94) (69). The pooled ORs for intracranial haemorrhage in patients treated for warfarin versus aspirin was 1.64 (95% CI 0.71–3.78) and for extra-cranial major bleeding was 1.03 (95% CI 0.61–1.75) (69).

Detection/imaging of intracardiac thrombus

On transthoracic echocardiography (TTE) intracardiac thrombi appear as dense, echogenic, heterogeneous, convex masses, with distinct margins, sessile or pedunculated, near thin dyskinetic ventricular segments or in the atrial appendages. Differential diagnoses include vegetations, tumors, devices and artefacts, and intravenous agitated saline or other transpulmonary contrast can contribute to the imaging diagnosis. The age of the thrombus and whether it is endothelialised would influence its embolic potential, and imaging may not necessarily determine this.

In one series of 151 ischaemic stroke patients, transoesophageal echo (TOE) performed within one week of ischaemic stroke detected thrombus in approximately one fourth of cases (70). Those with either coronary artery disease, large strokes, AF, ECG evidence of ischaemia or LVSD were more likely to have intracardiac thrombus on TOE (70). The yield of TTE is considerably lower than that of TOE, as TTE may be limited by suboptimal images (especially in obese patients), restricted field (e.g. in visualising the apex or atria) and poor tissue characterisation; of note, TTE is inferior to TOE for exploring posterior structures such as the left atrial appendage. Ischaemic stroke patients with a negative TTE result may still show potential cardiac sources of emboli in 50% of cases by contrast TOE (71).

Compared with echocardiography, magnetic resonance (MR) imaging or ultrafast computed tomography (CT) offer wide fields, are less operator dependent, can be performed in morbidly obese patients, have high spatial and temporal resolution, and allow tissue characterisation (72, 73). In one series, gadolinium-enhanced MR detected ventricular thrombi in 12/57 (21%) patients with ischaemic cardiomyopathy or prior MI – less than half of which were seen by TTE; moreover, TTE gave false positive images in 3/57 (5%) patients (72). Thrombus on contrast enhanced MR was related to larger end-diastolic volumes, lower EF, and LV aneurysm (72).

Patient values and preferences, and quality of life issues

There are currently no studies, to our knowledge, which have examined patient preferences for antithrombotic therapy in patients with HF. However, we may extrapolate from studies of patient preferences for antithrombotic therapy in another chronic condition, that of AF (65) to identify issues that may be pertinent to HF patients.

Since poly-pharmacy is common among HF patients it is imperative that patients are aware of the purpose and effect of their medications to promote adherence. By promoting self-care, patients engage in the decision-making process and corroborate their preference for behaviours which will maintain physiological stability (symptom monitoring and treatment adherence) and their response to symptoms when they occur (74).

Regrettably, studies have demonstrated that 50–77% of HF patients lack adequate comprehension about their treatment (75). Lack of adherence has been associated with a higher mortality rate even in the well-controlled environment of a clinical trial (76). Increasing patients’ education about their health, termed ‘health literacy’ (77, 78), requires appropriate individualised counselling, but with respect to antithrombotic therapy particular attention needs to be paid to the medication regimen and concomitant drug therapy, the complexities of the dietary regimen (for vitamin K antagonists), and monitoring for potential haemorrhagic (and other
less common) side effects. Education of both the patient and their caregiver(s) would promote health literacy, although knowledge alone is not sufficient to induce the behavioural change necessary to establish and maintain self-care behaviours (79, 80).

Special situations – the role of aspirin in heart failure, bridging therapy, coronary interventions, presentation with acute coronary syndrome, devices (e.g. pacemakers, ICDs), cardiac transplant

Prospective studies of antiplatelet agents in patients with HF in sinus rhythm are limited, although information is available in certain subgroups of patients, including those with AF and post MI (81).

HF or moderate to severe LVSD are recognised as a risk factor for thromboembolism in patients with AF, and accordingly, most of the patients with this arrhythmia will require oral anticoagulation (82, 83). Aspirin reduces the risk of death in the acute and early post-MI phase, although the mortality benefits are less significant during long-term treatment (84).

There is no available prospective evidence from long-term studies to recommend routine aspirin use as thromboprophylaxis in patients with HF who are in sinus rhythm. A possible interaction between aspirin and the ACEi may reduce the efficacy of the latter drugs and may account for more hospital admissions in those taking aspirin compared with warfarin (81). However, these findings have not been confirmed in the WARCEF study – the largest trial directly comparing warfarin with aspirin in optimally treated HFpEF population in sinus rhythm (58). Thus, HF per se is not a condition to routinely recommend anticoagulation but anticoagulants may potentially be considered for patients with presence of intracardiac thrombus, prolonged immobility/bed rest, AF and previous systemic embolism or ischaemic stroke, as well as those with right heart failure and pulmonary hypertension (85).

In patients who require coronary angiography and are taking warfarin, common practice is to discontinue warfarin a few days prior to percutaneous coronary intervention (PCI) to allow peri-procedural INR levels to fall below therapeutic range (<2.0) and to start bridging therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), to cover the temporary discontinuation of oral anticoagulation, if the risk of thromboembolism is considered high (86). Recent recommendations suggest that uninterrupted anticoagulation with warfarin could replace heparin bridging in catheter interventions with a favorable balance between bleeding and thrombotic complications (86-88).

For HF patients requiring anticoagulation, options to reduce bleeding complications include shortening the duration of use of different antithrombotic drugs. Therefore, drug-eluting stents should be avoided or be strictly limited to specific clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc. (86-88). Patients who have chronic anticoagulation (usually with AF) presenting with an acute coronary syndrome and/or PCI/stenting represent a complex management problem, and have been reviewed in other consensus documents (86-88). Adding aspirin to warfarin in patients with stable vascular disease (whether coronary or peripheral artery disease) does not reduce the risk of stroke or vascular events (including MI), but substantially increases bleeding events (86-89).

It may be necessary to interrupt oral anticoagulant therapy for elective implantation or replacement of a pacemaker or an ICD, although smaller procedures can often be performed without such interruption. In patients with HF in sinus rhythm, based on extrapolation from the annual rate of thromboembolism in patients with non-valvular AF, anticoagulation may be interrupted temporarily for procedures that carry a risk of bleeding, such as ICD or pacemaker implantation, without substituting heparin. In patients at high thromboembolic risk (particularly those with prior stroke or transient ischaemic attack or systemic embolism), UFH or LMWH may be administered. It is possible that such operations can in part be performed without interruption of anticoagulation, as for vascular procedures.

In patients chronically anticoagulated with warfarin undergoing cardiac surgery, including heart transplantation, the risk of bleeding is likely to be increased when the INR is ≥1.5. Therefore, it is reasonable to reduce the INR to this level at the time of surgery. Several therapies are available for the reversal of oral anticoagulation, and these include oral or intravenous vitamin K, human fresh frozen plasma, prothrombin complex concentrates, and recombinant activated factor VII. Vitamin K alone is inappropriate if rapid normalisation of the INR is required, because the onset of action is 4–6 hours after intravenous administration and at least 24 hours after oral administration. Therefore, when rapid reversal of warfarin is needed, vitamin K at doses of 2.5 to 5 mg should be administered intravenously in conjunction with other faster therapies.

Mechanical circulatory support (MCS) use has increased over recent years, due to improvement of continuous-flow ventricular assist systems. After ventricular assist system implantation, a pro-thrombotic state has been observed, that is dependent on pump design and patient characteristics (90). Ventricular assist system confers an increased risk for stroke, with the reported incidence varying from 3%-47% (91). This hypercoagulable state commonly requires use of individualised antithrombotic therapy, based on a combination of oral anticoagulation and antiplatelet therapy.

Suggestions for future study

Role of oral anticoagulation (and antiplatelet therapy) for the reduction of stroke in HFpEF and sinus rhythm

The risk reduction for stroke by warfarin versus aspirin was very similar in the WATCH (57) (HR 0.58, 0.25–1.3) and WARCEF (HR 0.52, 0.33–0.82, p=0.005) (58) studies. However, stroke was only a
component of the primary endpoint in both studies, and neither showed a significant difference in the overall primary endpoint.

The effect of warfarin and aspirin on stroke in these two studies appears to be of similar magnitude to that seen in AF trials (83). However, this needs to be balanced against the risk of haemorrhage. A prespecified secondary analysis for the endpoint of stroke alone is planned for WARCEF, in addition to a pooled analysis of the WATCH and WARCEF data. These two studies may still not offer a definitive answer to the question of whether antithrombotic therapy lowers the risk of thromboembolism in HF patients in sinus rhythm, as stroke alone was not a primary endpoint in either trial. It will also be important to determine the effect of warfarin in preventing stroke recurrence in HF.

Until more evidence becomes available, clinical decisions to treat patients with HF in sinus rhythm with anticoagulants must be made on a patient by patient basis, balancing the individual benefits against the risks of treatment, especially among high-risk patients.

Alternative approaches that would probably be less useful would be to establish a prospective cohort study following patients with HF with and without warfarin for stroke events, as well as the establishment of a stroke registry in patients with HF and LV systolic dysfunction to compare stroke rates in larger numbers of HF patients with and without warfarin. One future large registry could prospectively evaluate the incidence of (silent or symptomatic) AF in HF patients in sinus rhythm.

There is also the perception that aspirin may be detrimental, and thus the Clopidogrel versus Aspirin in Chronic HEart failure (CACHE) trial [http://controlled-trials.com/ISRCTN13415258/] which is a randomised, open-label study, will compare the effects of aspirin and clopidogrel on outcomes in patients with chronic HF. This trial will test the hypothesis that when compared with clopidogrel, aspirin has an adverse effect on cardiovascular function in patients with HF including an increase in the symptoms of HF, reduced quality of life, an increase in hospitalisations and a higher mortality.

Studies to identify a high stroke risk subgroup in patients with HF in sinus rhythm

To justify anticoagulation with warfarin, there is a view that the stroke rates in HF patients must be high enough (3% to 5% per year) since warfarin carries a risk of serious haemorrhage and necessitates frequent blood tests to monitor the anticoagulation effect. However, the use of newer safer oral anticoagulants (92) that overcome the limitations of warfarin may shorten the ‘tipping point’ towards anticoagulation at stroke rates of ≥0.9%/year, at least in a Markov decision analysis model of patients with AF (93).

HF community studies have found low stroke rates, between 0.8% and 3.2% per year, and clinical studies also demonstrate similarly low annual stroke rates that may not justify routine anticoagulation in HF patients, even if warfarin has a stroke risk reduction effect similar to that in AF. A recent analysis of the REasons for Geographic and Racial Differences in Stroke (REGARDS) study was not able to define a subgroup of HF individuals with a rate of stroke high enough to warrant anticoagulation, as the stroke rates in HF were low (94).

Further studies are needed to identify high risk subgroups in patients with HF and to establish a risk stratification scheme in HF similar to the CHADS2 or CHA2DS2-VASc scores used in AF (83). Similarly, there are established bleeding risk assessment scores for AF receiving anticoagulation, and we would need data to assess if similar scores, such as the HAS-BLED score recommended for use in AF patients, would be of similar value in predicting HF patients at risk of bleeding in whom antithrombotic therapy (whether aspirin or anticoagulants) is being considered (83, 95).

Confirmation of a high stroke rate within 30 days of onset of HF or of acute stroke in patients with HF

There is increasing evidence that stroke risk during the first 30 days after HF onset may almost double the five year HF stroke risk with a persisting smaller effect up to six months (24). This may also be true for the acute period after a stroke (22, 23). These critical periods may be potential relative indications for anticoagulation in HF because of the higher stroke rates and further data are needed on stroke incidence in these situations to determine if anticoagulation would be justified.

Assessment of current warfarin use in HF patients

Baseline data on the use of warfarin from clinical HF studies suggest that up to 28% of HF patients in sinus rhythm are currently treated with warfarin (see above) (44, 45) but limited robust data exist. Since the indications for warfarin anticoagulation in HF in sinus rhythm are unclear it is important to establish which patients are currently being treated.

Confirmation of low or normal EF as a risk factor for stroke in HF

Many clinicians use low EF as an indication to anticoagulate HF or cardiomyopathy patients, but there are inconsistencies in the data supporting low EF as a risk factor for stroke in HF; such data come largely from case-control studies or secondary analyses of clinical trials (96). Further data to confirm the risk of stroke, and whether the risk increases with decreasing EF, are needed, as well as to assess any interaction between low EF, stroke rate, and aetiology of LV dysfunction (ischaemic versus non-ischaemic).

The majority of recent studies have focused on HFrEF. The impact of HF with normal or preserved EF on stroke and thromboembolism requires further attention as does patients with pre-
served LV function but who have right heart failure with pulmonary hypertension. One recent analysis in hospitalised patients with AF did not find an independent contribution of EF to stroke and thromboembolism risk (97), but additional data in patients with HF in sinus rhythm are required.

The role of new oral anticoagulants in HF patients

Currently, new oral anticoagulants are available as alternatives to warfarin: – these are in two broad classes, the oral direct thrombin inhibitors (e.g. dabigatran) and the oral factor Xa inhibitors (e.g. rivaroxaban, apixaban) (92).

For example, apixaban has been compared with aspirin in patients with non-valvular AF who have refused warfarin or been deemed unsuitable for warfarin in the AVERROES trial (98). The latter was stopped early due to a clear superiority of apixaban over aspirin for the prevention of stroke and thromboembolism, with no significant difference between apixaban and aspirin for major bleeding or intracranial haemorrhage. Apixaban was also better tolerated than aspirin in AVERROES. Although in this trial symptoms of HF were present in 40% of patients, only 5% had evidence of reduced LV EF (98). Preliminary results of the heart failure subgroup from the ARISTOTLE trial that compared apixaban against warfarin found that the AF patients with heart failure, LVSD, or had symptoms of HF. Although both studies recruited patients in non-valvular AF, subgroup analyses revealed that there were no significant interactions between treatment with rivaroxaban or dabigatran and the presence of symptomatic HF (100, 101).

One network meta-analysis and indirect comparison study for dabigatran in AF found that when compared with placebo, dabigatran etexilate 150 mg twice daily (bid) reduced the risk of any stroke (ischaemic and haemorrhagic) by 75%, ischaemic stroke by 77%, systemic embolism by 83% and mortality by 36%. Dabigatran etexilate 150 mg bid also significantly reduced the risk of any stroke compared with aspirin monotherapy by 63% and aspirin plus clopidogrel by 61% (102). In the absence of head-to-head trials in AF, the new oral anticoagulants have been studied in indirect comparison studies, which show no profound differences in efficacy endpoints between the different new drugs, but less major bleeding with dabigatran 110 mg bid and apixaban (103). It is uncertain whether any of these new oral anticoagulants would be superior to aspirin (or warfarin, or no antithrombotic agent) in patients with HF in sinus rhythm. Further clinical trials are indicated.

It is important to note that these new anticoagulant drugs are contraindicated in severe renal impairment (for dabigatran, creatinine clearance < 30 ml/minute; for rivaroxaban, creatinine clearance < 15 ml/minute), and renal dysfunction may be a concern in many patients with HF. There is also currently no antidote or established reversal method for the anticoagulant action of these new drugs (104, 105).

Consensus statements

- In HF, thromboembolic complications contribute to mortality and morbidity.
- Associated comorbidities such as AF, should be proactively looked for. In patients with AF, oral anticoagulation is recommended. The CHA2DS2-VASc and HAS-BLED scores should be used to determine the likely risk-benefit ratio (thromboembolism prevention versus risk of bleeding) of oral anticoagulation.
- If anticoagulation is used, the combination of an oral anticoagulant with an anti-platelet agent is not recommended in patients with chronic (> 12 months after an acute event) coronary or other arterial disease, because of a high risk of serious bleeding (especially intracranial haemorrhage) and the lack of clear benefit.
In the absence of a specific indication, such as documented coronary artery disease, aspirin should not be initiated. Given no overall benefit of warfarin on rates of death and stroke, with an increase in major bleeding – despite the potential for a reduction in ischaemic stroke – there is currently no compelling reason to routinely use warfarin for all HF patients in sinus rhythm.

Patient values and preferences are important determinants when balancing the risk of thromboembolism against bleeding. All antithrombotic drugs carry an intrinsic risk of bleeding complications and at this point, there is still uncertain benefit for their use in HF patients in sinus rhythm. Discussions regarding treatment options need to actively involve the patient, with consideration of their preferences when making antithrombotic treatment decisions.

Clinical trials are needed to see if the new oral anticoagulants (oral direct thrombin inhibitors, oral factor Xa inhibitors) that may offer a different risk-benefit profile compared with warfarin, could offer a reduction in ischaemic stroke with less risk of major bleeding.

Anticoagulation may potentially be considered by some clinicians in the following HF patient groups: HFrEF with previous thromboembolism (stroke, transient ischaemic attack, VTE), newly diagnosed intracardiac thrombus, and right heart failure with pulmonary hypertension but evidence is limited and more research is needed to ascertain the long-term risk-benefit ratio.

Registry data, to estimate the risk of stroke among contemporary HF patients and to identify relevant risk factors, may prove useful.

Conflicts of interest

G. Y. H. Lip (UK): Consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. P. Piotrponikowski (Poland): Consultancy for Bayer, Merck, Sanofi; speaker honoraria from Bayer, Sanofi, BMS/Pfizer, and Boehringer Ingelheim. S. D. Anker (Germany): Consultant for Bayer and currently con-ducting research sponsored by this company. Also a consultant for Janssen; received NIH grant support to perform parts of the WARCEF study in Europe. F. Andreotti (Italy): Consultant or speaker for AstraZeneca, Bayer, BMS/Pfizer, Eli Lilly and Daiichi-Sankyo. G. Filippatos (Greece): research grants and /or advisory boards for Alere, Nanosphere, Abbott Diagnostics, Bayer, Corthera, Vifor. S. Homma (USA): None declared. J. Morais (Portugal): None declared. P. Pullicino (UK): None declared. L. H. Rasmussen (Denmark): Speaker fees from AstraZeneca, BMS/Pfizer and Boehringer Ingelheim. F. Marin (Spain): Consultant or speaker fees from Bayer, Boehringer-Ingelheim, Menarini and Daiichi-Sankyo. Research Grants from Boston Scientific and Abbott. D. A. Lane (UK): On speakers bureau for Bayer, BMS/Pfizer, and Boehringer Ingelheim.

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