

Editorial

Anticoagulation for Heart Failure Patients in Sinus Rhythm: Common in Clinical Practice But Still Not Evidence-based

Anticoagulación para pacientes con insuficiencia cardiaca en ritmo sinusal: habitual en la práctica clínica, pero aún no basada en la evidencia

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Heart failure (HF) remains a challenging medical problem with growing numbers of cases and dramatically increasing costs of medical care. Despite indisputable progress in the modern management of HF patients, morbidity and mortality are still unacceptably high, which fully justifies a search for novel therapies. In parallel, some drugs, already very well known, are commonly used in everyday practice despite a lack of evidence from large clinical trials, due to physicians' strong belief that they may simply work in HF patients. Oral anticoagulants (OAC) constitute one of the best examples of ancillary treatment of HF, and their use has a more than 60-year history. In the most recent European observational studies, OAC were used in 43% of all patients with stable chronic HF,¹ and in 39% of those discharged from hospital after an episode of decompensation.² In fact, the statement that "patients with congestive HF are prone to develop thromboembolic (TE) complications which increase the morbidity and mortality of the disease," made in 1950,³ forms a background for the first attempts to introduce OAC into the treatment of HF patients, but also sounds very timely today. Since then, we have accumulated strong evidence from epidemiological and pathophysiological studies linking HF syndrome to an increased risk of TE events seen in a broad clinical perspective as ischemic stroke, pulmonary embolism, other venous or arterial TE complications including acute myocardial infarction and sudden cardiac death.^{4,5}

The epidemiological studies rather uniformly confirm increased risk of stroke among HF patients compared with the general population and a recent meta-analysis of 26 studies reported the incidence of ischemic stroke was 18 per 1000 persons in the first year of HF diagnosis and increased to 47 per 1000 persons at 5 years.⁶ Other studies also seem to confirm particularly high risk of stroke in the early phase after HF diagnosis.⁴ It is estimated that HF ranks second as a cause of ischemic stroke, just after atrial fibrillation (AF), and is responsible for more than 60 000 strokes per year in the United States.⁴ According to actual etiological classification of ischemic stroke, symptomatic HF with

low left ventricular ejection fraction (LVEF), previous myocardial infarction with low LVEF, and dilated cardiomyopathy are considered as primary high risk sources of embolic stroke (with annual risk >2%).⁷ Stroke is always associated with an ominous outcome in these populations and HF also increases risk of venous TE complications. Deep venous thrombosis may be present in 10% to 20% of hospitalized patients with HF not receiving prophylaxis. Up to 10% of HF-related deaths are due to pulmonary embolism.⁸ Interestingly, many HF deaths initially classified as sudden and unexpected may be due to new coronary occlusion due to TE. In the ATLAS (*Assessment of Treatment with Lisinopril and Survival*) study, myocardial infarction confirmed at autopsy accounted for 40% of all sudden deaths.⁹ Although risk of TE complications is linked with severity of HF (in particular with impaired LVEF), recent analyses from clinical trials that recruited the whole spectrum of HF patients seem to show that the rate of stroke and stroke-related mortality may be independent of the magnitude of LVEF impairment.¹⁰ Whether patients with so-called HF with preserved LVEF are also at high risk for TE complications needs to be established in future studies.

Pathophysiology of increased risk of TE events in HF is traditionally linked with 3 elements comprising the "Virchow triad": abnormalities in blood flow, vessel wall, and blood constituents.⁵ Neuroendocrine activation typical of HF syndrome may also contribute to rheological abnormalities.⁵ Recently, high prevalence of anemia and iron deficiency has been described among patients with HF,¹¹ which may additionally predispose to thrombosis.¹² Among potential mechanisms underlying such an association the following may play an important role in HF syndrome: iron deficiency-related reactive thrombocytosis; elevated level of erythropoietin often present in anemic, iron-deficient, HF patients, which itself is associated with risk of thrombosis; increased platelet aggregation as a result of oxidative stress; and anemia-related hypercoagulable state.¹² Thus it is prudent to hypothesize that elevated risk of thrombosis may be an additional factor explaining high mortality and morbidity among iron-deficient HF patients and the beneficial effects of iron repletion in this population.¹³

It can be concluded that TE events, with an annual rate between 1% and 4%, should be viewed as a clinically relevant complication in HF patients, accounting for a substantial number of morbid events

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that may unfavorably affect patient outcome. Taking this into account, many physicians are tempted to initiate treatment with OAC in order to prevent such events, even though this is not well supported by the results from clinical trials.

According to the recent European Society of Cardiology (ESC) guidelines on HF management,¹⁴ OAC is recommended in HF patients with permanent, persistent, or paroxysmal AF without contraindications to anticoagulation. Similarly, new ESC guidelines on AF management consider the presence of HF with impaired LVEF as a risk factor for stroke and thromboembolism, and OAC therapy is generally indicated when AF is present.¹⁵ However, in the initial evaluation the CHA₂DS₂-VASc and HAS-BLED scores should always be used to establish the risk-benefit ratio of the decision whether to initiate OAC.¹⁵ On the other hand, in patients with sinus rhythm, the decision is often difficult and the guidelines recommend OAC only when intracardiac thrombus is present or there is evidence of systemic TE.¹⁴ In clinical practice, however, OAC are used much more often and between 10% and 30% of HF patients without AF are receiving this therapy.¹⁶ Due to potentially serious OAC-related complications and lack of conclusive data from clinical trials published so far, all attempts to investigate the problem of the efficacy of OAC are timely and clinically relevant.

The study by Avellana et al.¹⁷ is of particular interest here because it reports the real-life scenario seen in the everyday practice. The authors investigated a large cohort of unselected HF patients with impaired LVEF belonging to a well-organized research network and who were properly treated and carefully monitored. It appeared that among those with sinus rhythm and no conventional indications for OAC, 26% were receiving this therapy. Several findings deserve special attention.

Firstly, OAC prescription greatly varied between the centers participating in the registry (some virtually abandoned OAC; some used it in more than 50% of all cases), which again reflects variety of opinions among practicing physicians in the case of therapy not recommended by the ESC guidelines.

Secondly, those treated with OAC had slightly more advanced disease but surprisingly lower prevalence of hypertension and diabetes mellitus, well-recognized vascular factors traditionally linked with high risk of TE. This resulted in “paradoxically” lower CHA₂DS₂-VASc scores in patients receiving OAC and may well indicate that this score is still not a key for deciding whether to anticoagulate patients in clinical practice. On the other hand, it must be remembered that both scores currently recommended to justify the need for OAC (CHADS₂ and CHA₂DS₂-VASc) were initially developed for individuals with AF and have never been prospectively validated in HF patients in sinus rhythm. It may well be that for many physicians, a poorly contracting, dilated left ventricle, often with enlarged left atrium, coinciding with moderate to severe HF symptoms constitute stronger indications for anticoagulation than other well-established vascular factors. To this end, a recently published study by Pullicino et al.¹⁸ evaluated which of the vascular risk factors can identify a subgroup of HF patients without AF with a stroke rate high enough to justify OAC. History of stroke or transient ischemic attack, diabetes mellitus, and higher systolic blood pressure (but not a history of hypertension) were independently related to higher rate of stroke, but neither age nor sex appeared to be risk factors.¹⁸ A coincidence of HF with previous stroke/transient ischemic attack and diabetes mellitus carried 6 times the risk of stroke, but interestingly, the absolute stroke incidence in this subgroup was 2.4 per 100 patient-years, which in the opinion of the authors would not fully justify anticoagulation.¹⁸ Future studies are needed to prospectively identify risk factors for all TE complications in HF patients, in order to optimally determine a subgroup which may benefit from OAC.

Finally, and most importantly, in this study OAC seems not to have any favorable effect on mortality and morbidity. Although

anticoagulated patients had reduced risk of the combined endpoint of cardiac death, heart transplantation, coronary revascularization and cardiovascular admissions, the rate of mortality (including sudden death) and stroke was comparable in treated and untreated patients, (after using the propensity score as the adjustment covariate).¹⁷ The authors concluded, that their results do not support the need for routine use of OAC in HF patients with impaired LVEF in sinus rhythm with no other indications.¹⁷ These findings were in accordance with the previously published results of 3 randomized clinical trials—WASH (*Warfarin/Aspirin Study in Heart Failure*), WATCH (*Warfarin and Antiplatelet Therapy in Chronic Heart Failure*) and HELAS (*Efficacy of antithrombotic therapy in chronic heart failure*).^{19–21} All these studies did not report any favorable outcome effects of OAC in HF patients in sinus rhythm, but as they have been either small (WASH, HELAS) or terminated prematurely due to slow enrollment (WATCH),^{19–21} any definitive conclusion cannot be made. In this context, the results of the recently presented WARCEF (*Warfarin versus Aspirin in patients with Reduced Cardiac Ejection Fraction*) trial are particularly relevant and must be briefly discussed here.²²

The aim of the WARCEF study was to compare the efficacy of acid acetylsalicylic or warfarin on the primary combined endpoint of death, ischemic stroke or intracerebral hemorrhage in HF patients with LVEF below 35% and in sinus rhythm.²² The study used a double-blind, double-dummy design and all patients took warfarin or acid acetylsalicylic, to which dummy acid acetylsalicylic or warfarin was added. Acid acetylsalicylic was given in a daily dose of 325 mg and warfarin dose was adjusted in order to maintain international normalized ratio between 2–3.5. A total of 2305 patients (mean age 61 years, 80% male, majority in New York Heart Association functional class II and III, mean LVEF 25%) were enrolled and followed for a total of 4045 patient-years in the warfarin and 4033 patient-years in the acid acetylsalicylic group. Mean follow-up was 3.5 years, ranging from 1 year to 6 years. Importantly, patients received optimal pharmacotherapy, and almost all received angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and beta-blocker. There was no significant difference in the rate of primary endpoint between warfarin (7.47%/year) and acid acetylsalicylic (7.93%/year) (hazard ratio [HR]=0.93 [0.79–1.10]; $P=0.40$).²² However, an analysis of HR during the follow-up revealed a progressively increasing benefit from warfarin that became significant after 4 years. There was no difference in mortality between groups, whereas warfarin significantly decreased risk of ischaemic stroke (warfarin–0.72%/year vs acid acetylsalicylic–1.36%/year; HR=0.52 [0.33–0.82]; $P=0.005$). Rate of major haemorrhage was higher in those treated with warfarin, mainly due to gastrointestinal complications, and there was no significant difference in intracerebral or intracranial hemorrhages.²² In summary, it seems that the results of the WARCEF trial would not justify a broad recommendation of OAC as routine therapy for HF patients in sinus rhythm with severely impaired LVEF. However, it is prudent to expect that OAC may become particularly beneficial in some subgroups of HF patients, and therefore further analyses and reports from this seminal trial are eagerly awaited.

The introduction into clinical practice of 3 new OAC drugs (dabigatran, a direct thrombin inhibitor; rivaroxaban and apixaban, oral-activated factor X inhibitors), which have a favorable pharmacokinetic and safety profile and additionally do not require routine coagulation monitoring, seems to open a new era in the prevention of TE complications. Recently completed large randomized clinical trials have provided conclusive evidence that they are either noninferior (rivaroxaban) or even superior (dabigatran, apixaban) to warfarin in prevention of stroke and systemic embolism in patients with AF, with no excessive risk of major bleeding complications.²³ However, an experience with these new drugs in HF is still very limited and mainly restricted to

those with AF. In addition, they need to be cautiously used in patients with renal impairment (which may be particularly relevant in HF population) and until now no antidote is available. Even though these seem to be a really attractive alternative for traditional vitamin K antagonists, studies focusing on HF patients are warranted before any recommendation can be made.

The study by Avellana et al.¹⁷ is an important contribution to the clinically timely and relevant problem of how to prevent TE events in HF patients. There is no doubt that those with AF should receive OAC, but a solution for patients in sinus rhythm and without history of AF is much more complicated. In general, based on currently available data, routine use of OAC cannot be recommended, but the final decision should always be individualized after careful consideration of all the TE risk factors and benefits against the potential risk of such therapy.

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CONFLICTS OF INTEREST

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