Is risk-benefit of warfarin for atrial fibrillation with heart failure determined by heart failure severity?

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Until the last few years, vitamin K antagonists (VKAs) such as warfarin had been the cornerstone of anticoagulation for the reduction of stroke risk in patients with atrial fibrillation (AF). This therapy has been plagued by difficulty in keeping patients with a high time in therapeutic range (TTR), thereby potentially exposing patients to increased risk of bleeding or inadequate protection from stroke (1–5). Indeed, a recent European consensus document recommends a TTR of >70% to offer best efficacy and safety from VKAs (6). Difficulty in achieving a high TTR seems to be particularly problematic in patients with heart failure (HF), which forms part of a recent clinical score (SAMe-TT(R)) used to help predict the likelihood of poor TTRs and the increased risks of thromboembolism and bleeding consequent upon labile international normalised ratios (INRs) (7, 8).

Patients with heart failure (HF) and AF are at increased risk of stroke compared to the general population with AF, with HF being an accepted stroke risk factor (9) so anticoagulation is usually recommended. HF has a global prevalence of approximately 23 million people (10) and is the most common cause of hospitalisation in adults aged over 65 years in the developed world (11). Registry data suggests that 18 to 35% of patients with HF have AF (12) with the majority requiring anticoagulation. The Framingham study demonstrated that in patients with AF, development of HF was associated with a two- to three-fold increase in mortality but in those with HF, the development of AF (which occurred in 20% of the cohort), did not have a major impact on mortality (13). However, in the CHARM-HF study cohort, those with AF at baseline had a significantly higher cardiovascular mortality and more frequent HF hospitalisation (14), suggesting that AF does have an impact on prognosis in HF.

Patients with HF present a major challenge, and despite advances in medical and device therapy, there remains a high mortality (15, 16). In the recent EURObservational Research Programme Pilot survey on Atrial Fibrillation (EORP-AF), one-year mortality and morbidity remained high in AF patients with HF, whether HFrEF or HfPEF, despite a high prevalence of oral anticoagulant use (17). Nevertheless, patients are now surviving longer due to improved treatment, but are becoming more complex due to increased co-morbidities and advancing age, often requiring frequent hospitalisation (15, 16).

The increased co-morbidities were also well demonstrated in the study by Kim et al. in this issue of Thrombosis and Haemostasis (18). It is at this interface of HF and AF requiring anticoagulation that the paper by Kim et al. (18) provides some new insights. In 62,156 veterans with AF who received warfarin, 45% were reported as having HF. Those with HF were significantly older, and had more co-morbidities such as newly diagnosed cancer, chronic kidney disease, coronary heart disease, diabetes, psychiatric conditions and were on more medications. Patients with HF who received warfarin spent significantly less time in the therapeutic range (TTR) than those without HF. Much of this would be expected and has been previously demonstrated. The novel finding is that a score to measure HF severity was applied to those on warfarin and showed that as HF severity increased, TTR decreased. When analysed further, as HF severity increased, there was more time spent with the INR both above and below the therapeutic range (18). This bi-directional reduction in TTR might be expected to be associated with more thromboembolic events in the patients with HF, but in fact this was barely so. In contrast, major bleeding on warfarin was strongly related to HF severity.

The results of the study by Kim et al. (18) are intriguing. Although there was a trend towards increased ischaemic stroke as the HF severity increased, this was only evident for a dichotomous split into no markers of severity vs the three highest severity categories after adjusting for age, TTR or CHADS2 score. The fact that a low TTR with increasing HF severity in this population had a rather weak correlation with the risk of stroke is difficult to explain. One possibility may be that the markers available to categorise severity of HF may not have been adequate. Markers used included aspartate aminotransferase (AST), alkaline phosphatase, serum sodium, any receipt of metolazone, and any inpatient admission for HF exacerbation. AST is not usually abnormal in patients with heart failure alone, even in significant congestion. It usually rises in patients with other causes of liver disease, those with reduced hepatic perfusion (usually a late sign of poor prognosis) and may also rise as an adverse drug effect (e.g. statins). Hyponatraemia is a marker of poorer outcome in patients with heart failure and may be due to disease progression, but may also be due to injudicious use of diuretics or occur in patients not adhering to fluid restriction. Metolazone is no longer used in many countries as it has been associated with an
increased incidence of adverse outcomes. No correction was made for other major co-morbidities such as chronic lung disease, chronic renal impairment, prior coronary artery bypass grafting, etc. Better validated measures of HF severity such as left ventricular ejection fraction, N Terminal-B Type Natriuretic Peptide level, New York Heart Association functional classification (15, 16) may have shown a relationship with thromboembolic events, as has been demonstrated in patients with HF and AF who are not anticoagulated (5–9).

The really important and unique information from the study by Kim et al. was the ability of the HF severity score to predict an increased risk of bleeding during warfarin thromboprophylaxis for AF as HF severity increased (18). This appeared to persist even when corrected for age, sex, TTR, renal disease, prior stroke, alcohol, drugs, and hypertension. This effect of HF severity on bleeding is therefore not only partly explained by its relationship with TTR. The proposed HF severity risk score may therefore have most clinical utility in predicting bleeding risk in patients with HF who are to be commenced on warfarin.

The increased risk of bleeding may be due to concomitant medications, including anti-platelet medications, amiodarone, hepatic congestion or poor compliance with warfarin (19, 20, 21). These findings cannot yet be extrapolated to the NOACs, although the landmark trials using these agents did include significant numbers of patients with HF and found a similar number of bleeding events with NOACs and warfarin in patients with HF (22–24).

The SAMe-TT2R2 score has recently been found to be predictive of TTR and may be used in assessment of patient suitability for treatment with warfarin. This score includes presence of HF symptoms, a history of HF, and cardiomyopathy as potential co-morbidities contributing to higher scores which would predict a lower TTR (25). A recent guideline on anticoagulants in heart disease also included some caveats on warfarin prescription in HF with AF (6), because of increased risk of bleeding and lesser efficacy. The novel finding in the Kim et al. study (18), however, is that severity of HF adds additional information to just knowledge of its presence.

Although the management of HF has improved since 2008 when the patients were enrolled in the study by Kim et al. (18), with more widespread use of mineralocorticoid antagonists (including epleronene), ivabradine, omega-3 ethyl esters, iron infusions for patients with HF and iron deficiency and greater use of defibrillators and cardiac resynchronisation therapy (15, 16), it is uncertain whether these would alter the relationships shown in the study by Kim et al. It is also uncertain whether the relationship also holds for the NOACs, and this would be worthy of analysis now that there are significant numbers of patients with both HF and AF treated with these drugs.

HF and AF is a hazardous combination. There is an increased risk of stroke if not anticoagulated, sub-optimal TTR when anticoagulated with warfarin and a higher risk of bleeding, and it now appears, there is a large increase in risk of bleeding as HF severity increases. HF dramatically increases mortality of patients with AF particularly for those with severe HF who are caught between and rock and a hard place. Use warfarin and cause a massive bleed (20% were intracranial haemorrhages) or withhold and have a significant risk of stroke. Perhaps the net clinical benefit for those with severe HF may tip the balance against anticoagulation so that few will receive warfarin. It will be important to define whether this is also true for the NOACs.

Conflicts of interest
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References
1. Rose AJ, et al. Patient characteristics associated with oral anticoagulation control: results of the Veterans Affairs Study to Improve Anticoagu-