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To accompany Harel et al

Editorial

Atrial Fibrillation and end-stage renal failure patients on dialysis: balancing the risks and benefits of stroke prevention.

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Large observational trials and meta-analysis have confirmed the benefit of oral anticoagulation therapy (OACs), with the Vitamin K Antagonists (VKAs eg. warfarin) for stroke prevention in atrial fibrillation (AF), even in patients with ≥1 stroke risk factors using the CHA_2DS_2VASc score[1]. Indeed, the net clinical benefit (NCB) is positive for OAC use compared to no antithrombotic therapy or aspirin, even with 1 stroke risk factor – while the NCB is neutral or negative for aspirin compared to no antithrombotic therapy[2]. The NCB is also higher as the CHA_2DS_2VASc score increases [3].

There are some exceptions to these 'general' statements. Patients with stage 5 chronic kidney disease (CKD) or end stage renal failure on dialysis have been excluded from randomised trials, and such patients might have multiple risk factors for stroke and thus, high CHA_2DS_2VASc score[4]. However, the balance between the risk and the benefits of oral anticoagulation (OAC) treatment for prevention of embolic events is less clear.

Most stroke risk stratification approaches in AF have excluded patients with severe renal impairment and thus the benefit of OAC in patients with AF and normal renal function cannot be extrapolated to patients with AF in end stage renal failure (ESRF). The latter are high risk for thrombosis-related complications such as stroke, systemic thromboembolism, mortality and myocardial infarction, but paradoxically, these patients are also at risk of serious bleeding[4].

Many factors have been implicated to promote thrombogenicity along with the haemorrhagic tendency in AF patients with ESRF on renal replacement therapy (ie. haemodialysis or peritoneal dialysis). Abnormal renal function affects anticoagulation control[5], and unsurprisingly, the management of such patients is extremely delicate[6]. CKD per se is associated with higher prevalence of AF and the numbers of dialysis patients are increasing[7], the management dilemma for the optimal use of OAC in such patients is even more pressing.

In the current issue of the *Canadian Journal of Cardiology* Harel et al[8] provide a systematic review and meta-analysis regarding the safety and efficacy of Vitamin K antagonists (VKAs) for the prevention of ischaemic stroke in AF patients with end stage renal failure receiving dialysis (haemodiaysis and peritoneal dialysis). The total number of participants was 20,398 of whom 4,779 (23%) were receiving warfarin. The primary outcome was defined as ischemic stroke or systemic thromboembolism, and secondary outcomes included intracranial haemorrhage (ICH), gastrointestinal bleeding (GIB) and all-cause mortality.

In the absence of any randomised control trials, 14 observational trials were included. There was a significant heterogeneity among the included studies regarding outcomes. For example, although transient ischaemic attack (TIA) is considered in most of the studies as a type of ischaemic stroke, in some this endpoint was not recorded. Also, the definition of bleeding varied from study to study. Additionally, the authors were unable to perform meta-regression analysis due to paucity of available data for the majority of baseline characteristics apart from age. Despite the several limitations of this meta-analysis and systematic review, several high quality observational studies were included. The overall conclusion was that VKAs are not associated with any statistically significant difference in ischaemic stroke or ICH. There were more haemorrhagic events in the VKA group but that did not influence all cause mortality.

There are no RCTs to support OAC therapy with VKAs for dialysis patients with AF. Among these patients are there subgroups with characteristics that might benefit from VKAs? An individualised approach, with careful assessment of the risks of ischaemic stroke against the risks of bleeding, will help management of patients who will benefit from OAC.

There are important limitations to the metaanalysis by Harel et al. All the observational trials that conclude a non-beneficial role of VKA in patients with AF on dialysis did not report on quality of anticoagulation control, as reflected by time in therapeutic range (TTR). On the contrary, 2 studies[9,10] that demonstrated a reduced risk of thromboembolic events without a significant increase in haemorrhagic events in AF patients on dialysis have reported on the TTR. In these studies, the TTR was maintained in a reasonable level (54-60% or higher) and that was reflected in the findings. On the other hand, patients with poor OAC control have more bleeding and thromboembolic episodes [11].

Many participants in the observational trials that were included in the meta-analysis by Harel et al, were also on antiplatelet drugs. The concomitant use of antiplatelet drugs, NSAIDs and VKAs cumulatively increases the risk of bleeding. In the cases that triple or double antithrombotic therapy (VKA with aspirin and/or clopidogrel) is necessary, for example, following acute coronary syndromes, the optimal TTR should be above 70% to minimise bleeding complications. It is unclear why the antiplatetelet drugs were prescribed for these patients in the studies that were used in the systematic review by Harel et al[8].

Exposure to medications that can induce or enhance a bleeding diathesis, as well as excess alcohol intake, are additional modifiable risk factors for haemorrhagic events. Use of the HAS-BLED score is helpful to identify patients at high risk of bleeding who can be flagged

up for more regular review and followup, and to draw attention to the modifiable bleeding factors[12 13]. The HAS-BLED score has been validated in patients on no antithrombotic therapy, aspirin and anticoagulants (warfarin and non-warfarin), as well as in AF and non-AF cohorts – thus would be applicable for all stages of the patient pathway.

An observational study from Denmark [14] collected data from nationwide registries for patients with AF and CKD, and found that warfarin was associated with a significantly decreased risk of all-cause mortality (HR: 0.85, 95% CI: 0.72 to 0.99) in patients with end stage renal failure on dialysis. On the contrary, aspirin plus warfarin did not show any benefit. Fewer negative events, such as stroke or major haemorrhage, were observed in AF patients with high risk of stroke on peritoneal dialysis compared to patients with similar features but on haemodialysis.

In another observational study on patients with peritoneal dialysis and AF, warfarin was associated with significantly reduced risk of ischaemic stroke without increasing the risk of intracranial haemorrhage[15]. These findings suggest that the modality of dialysis is also important and might influence outcomes in these patients.

For now, the VKAs appear to be the only OAC therapy with at least some studies to show clinical benefit for patients with AF and ESRF on dialysis. The Non-Vitamin K oral anticoagulants (NOACs) have been increasingly adopted for stroke prevention therapy in patients with non-valvular AF, given their increasing evidence of effectiveness and safety from trials and 'real world' use[16 17,18]. The NOACs have a degree of renal excretion, and the absence of large trials in AF patients with creatinine clearance<25-30 ml/min makes clinicians doubt their use in ESRF. Indeed, one study that assessed the outcomes of patients on haemodialysis with AF treated with dabigatran or rivaroxaban, found their use highly discouraging[19]. Apixaban has less renal excretion in its elimination pathway, compared to the other licenced NOACs, and in the USA label approved by the FDA, apixaban 5mg bid may be considered in AF patients undergoing haemodialysis even in the absence of trial outcome data.

In conclusion, Harel et al[8] provide a comprehensive systematic review and meta-analysis focused on the benefit-risk ratio of warfarin in patients with AF on dialysis, which not surprisingly, has similar findings with other previous meta-analysis of the same subject. A well organised randomised control trial avoiding the heterogeneity pitfalls identified by the Harel et al would provide more precise evidence about the risk and benefit ratio of OAC in

dialysis (i.e haemodialysis vs peritoneal) patients with AF. For now, patients on dialysis with high risk of stroke (CHA_2DS_2VASc score ≥ 2) should be assessed individually and treated with warfarin with good TTR, unless there is a recent history of intracranial bleed or other major bleed[4]. The HAS-BLED score should also be routinely used to identify patients with high risk of bleeding who can be monitored and followed up more closely, and to address modifiable factors which contribute to bleeding. Patient education, counselling and treatment adherence are also essential aspects of management[20].

Figure 1 provides a suggested approach for the management of such AF patients with end stage renal disease on dialysis who are being considered for thromboprophylaxis.

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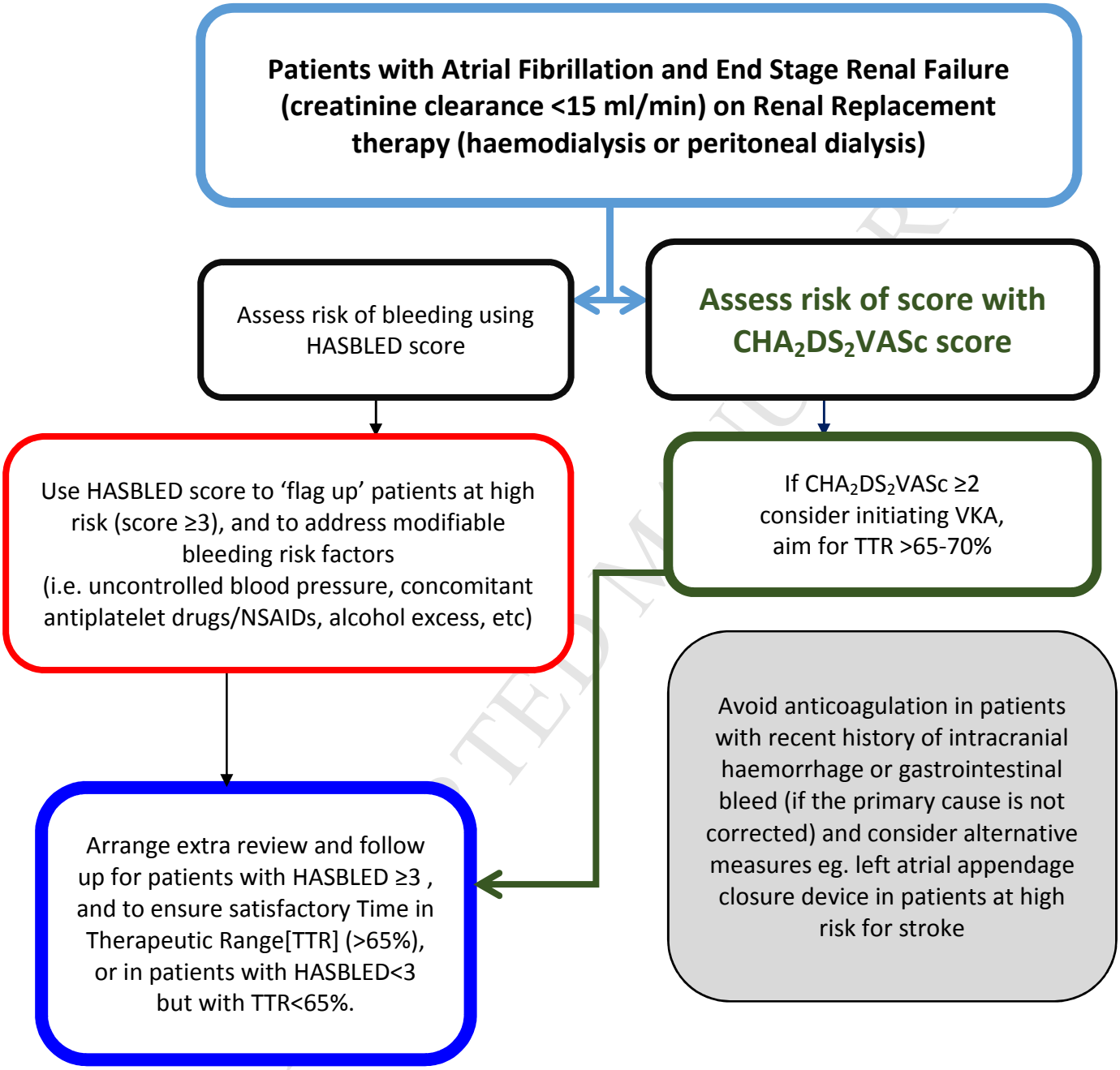
Figure 1. Suggested management approach for using oral anticoagulation therapy in patients with Atrial fibrillation and end stage renal failure



Abbreviations: CHA_2DS_2VASc : C, congestive heart failure, H, hypertension, A_2,age at least 75 years (x2), D, diabetes, S_2, previous stroke, TIA, or systemic embolism, (x2) V, vascular disease, A, age 65 through 74 years, Sc, sex category female sex. HAS-BLED: H, Hypertension, A, Abnormal renal and liver function, S, Stroke, B, Bleeding tendency, L, Labile INRs, E, Elderly, D, Drugs.