In Focus

Warfarin therapy for atrial fibrillation in haemodialysis patients: mind the (evidence) gap

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Atrial Fibrillation (AFib) is the most frequent sustained arrhythmia in patients with kidney disease. Although the indications for anticoagulant therapy for AFib patients have become much refined during the last decade, there is clinical equipoise regarding the safety versus the effectiveness of warfarin in AFib patients undergoing chronic haemodialysis. Due to the complex nature of advanced kidney disease, which predisposes to both ischaemic stroke and bleeding [1], this condition poses concerns regarding warfarin effectiveness in stroke prevention as well as its safety as it may exacerbate the already high bleeding risk [2]. This equipoise is clearly reflected in the discordant recommendations from current guidelines: while the current American Heart Association/American College of Cardiology (AHA/ACC/HRS) guidelines [3] generally recommend the use of warfarin for primary stroke prevention in haemodialysis patients, the Kidney Disease Improving Global Outcomes (KDIGO) [4] advises against it because of the unknown net clinical benefit.

Several observational reports of AFib patients undergoing haemodialysis have associated warfarin use with an increased risk of bleeding, higher stroke risk or lack of stroke risk prevention [5–8]. These associations may not be entirely universal, but perhaps confined to special high-risk subpopulations, such as individuals above 75 years of age [7], or receiving high warfarin dosages [5] presumably denoting poor international normalized ratio (INR) control. A recent small report even observed a slightly faster aortic stiffness progression among warfarin users undergoing haemodialysis when compared with matched non-users [9]. Opposing these worrying reports, nevertheless, an equal number of studies favour warfarin use in this patient population, describing a significant association to both reduced mortality and stroke risk, without increased risk of bleeding [10–12]. Because the community-proven net clinical benefit of warfarin [13] seems preserved in individuals with moderate/advanced kidney disease [8, 10, 12, 14] or in kidney transplant recipients [15], we may conclude that the equipoise pertains to dialysis patients only. The haemodialysis procedure may indeed be a trigger for AFib, as monitoring with implantable cardioverter defibrillators showed that AFib occurred significantly more often on a dialysis day and especially during the haemodialysis session, persisting a few hours thereafter [16]. The absence of studies addressing this problem in peritoneal dialysis patients creates an important knowledge gap for this considerable renal replacement therapy segment.

The study by Genovesi et al. in this issue of Nephrology Dialysis Transplantation offers an interesting analysis of drug-associated outcomes from a prospectively collected, observational cohort. Such design poses an advantage over the retrospective data extraction of previous studies, together with collection of information on achieved INR during follow-up. Amongst 1529 patients treated at 10 Italian centres, there were 290 (19.0%) with an AFib diagnosis at inclusion. As many as 134 (46.2%) individuals were receiving warfarin, and ∼65% of them continued with this therapy for a median of 2 years. The investigators also recorded the occurrence of stroke events, thromboembolism, bleeding and death.

The high-risk profile of studied patients (CHADS-VASC score ≥2 in 97.8% in warfarin-treated versus 94.2% in non-warfarin-treated patients) clearly justifies an indication for warfarin according to current guideline recommendations. The authors found, however, neither a reduction nor an increased risk of ischaemic stroke in relation to warfarin therapy. Although it is reassuring that the mortality risk tended to be lower in the warfarin users, the low number of patients and
events calls, nonetheless, for caution in its interpretation. On the other hand, a very large proportion of patients were at a high risk of bleeding, and warfarin-treated patients experienced a 4-fold increased bleeding risk. Although alarming, disentangling the site and type of bleeding is essential. The lesser clinical relevance of certain bleedings may be acceptable and still justify warfarin use if an ischaemic stroke is prevented (net clinical benefit) [17, 18]. In this study, only two haemorrhagic strokes in warfarin-treated patients versus one in non-warfarin-treated patients were recorded, which again precludes the possibility to make strong statements regarding this important bleeding site. It would have been otherwise interesting to learn about the nature of the other bleedings recorded.

Of note, the study provides insight into how the bleeding risk could be tackled. For instance, individuals with a previous history of bleeding were more likely to bleed irrespective of warfarin use. This is a logical observation that reinforces the need of an individualized approach when prescribing warfarin. It is notable that despite monthly tests, the quality of achieved INR control was still suboptimal (median INR 54%, interquartile range 41–67%). Preceding studies have in fact reported the difficulty to achieve a desirable time in therapeutic range (TTR) (>70%) in haemodialysis patients [19–21], and it has been speculated that the equipoise of warfarin safety to effectiveness in this patient population may be explained by differences in INR control rather than by warfarin use per se [22–26]. In the study by Genovesi et al., the risk of bleeding increased in proportion to the worsening of TTR. This accords with an earlier retrospective study showing that no haemodialysis patient under sufficient oral anticoagulation experienced a stroke or a fatal bleeding event [19]. More recently, Kooiman et al. [27] observed that both less time spent within therapeutic range and high INR-variability were factors associated with increased risk of stroke and bleeding in warfarin-treated chronic kidney disease patients.

An unexpected finding in this report is the almost 2-fold increased risk of mortality associated with the use of antiplatelets. This result is confusing, and perhaps difficult to explain given that no increased risk of bleeding was linked to this therapy. A fifth of warfarin users (20.2%) and ∼70% of non-warfarin users were receiving an antiplatelet. The indication for antiplatelets is unknown for these patients, and may be related to the presence of ischaemic heart disease. Antiplatelets are shown to be inferior to warfarin in stroke prevention and to double the risk of bleeding [24, 28–30]. Thus, the combination of antiplatelets and warfarin is known and expected to particularly increase bleeding risk; whenever warfarin treatment is considered, the need for double anticoagulant use needs to be carefully considered.

The problem is that many nephrologists are not in equipoise and have decided with justification that anticoagulation is too risky for the large majority of haemodialysis patients. This justification is based on observational studies, limited by confounding by indication, patient selection bias and differences in practice patterns. The diverse definitions of bleeding events or the inability to accurately distinguish ischaemic from haemorrhagic strokes precludes from accurate study-to-study comparison, and altogether, it demands a careful and conservative interpretation of the evidence. The issue of whether to anticoagulate or not is far from resolved, and this prospective study teaches us that although AFib haemodialysis patients treated with warfarin are at high risk of bleeding, careful INR control may be a key factor to reduce such risk. The net clinical benefit of warfarin use in HD patients is not yet established, and the debate will only be resolved when a randomized controlled trial clarifies this conundrum. This is important, because the novel anticoagulants such as direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (edoxaban, apixaban and rivaroxaban) all have substantial kidney clearance and therefore prolonged half-lives in patients with chronic kidney disease. Haemodialysis patients with AFib are in need of anticoagulation therapy; however, for the time being, the decisions on whether or not to treat and which treatment to choose are left to the physician’s clinical judgment.

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CONFLICTS OF INTEREST STATEMENT

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(See related article by Genovesi et al. Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation. Nephrol Dial Transplant 2015; 30: 491–498.)

REFERENCES

Extracellular vesicles (EVs) are the generic term for nano-sized fragments surrounded by a lipid membrane that are routinely released by virtually all cell types into their surroundings. Within the cell, EVs are derived from the plasma membrane or from endosomal multivesicular bodies. They can be classified into microvesicles (microparticles), typically 100–1000 nm in diameter, released by plasma membrane shedding, and exosomes, 40–100 nm in diameter, generated by exocytosis of intracellular vesicles [1]. Exosomes are often identified using the markers CD63, CD9, CD81 and Hsp70.