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Apixaban in renal insufficiency: successful navigation between the Scylla and Charybdis

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This editorial refers to 'Efficacy of apixaban as compared with warfarin in relation to renal function in patients with a trial fibrillation: insights from the ARISTOTLE trial'†, by S.H. Hohnloser et al., on page 2821

A changing landscape of anticoagulation

Anticoagulation for stroke prevention in atrial fibrillation has traditionally been performed by vitamin K antagonists. Although effective under optimal conditions, the imminent risk of severe haemorrhage is a major cause for substantial underutilization of these drugs, even in patients at high risk of thrombo-embolic events. The recent introduction of the direct thrombin inhibitor dabigatran, as well as the oral factor Xa inhibitors rivaroxaban and apixaban (*Figure 1*) has resulted in a paradigm shift regarding the treatment of these patients. While large-scale clinical trials including Re-LY, ROCKET-AF, and ARISTOTLE have (essentially) all indicated superiority of the respective substance compared with warfarin in stroke prevention, these agents were equally shown to be superior with respect to bleeding events, especially major, life-threatening, and intracranial haemorrhage.[1–3] The initial enthusiasm associated with these novel agents was, however, dampened shortly after their introduction when reports of major haemorrhages surfaced, indicating that an unrestricted and injudicious use may put certain patients at an elevated risk for adverse events. Indeed, it quickly became clear that especially dabigatran, which is 80% renally cleared, has a significant potential for severe bleeding in patients with reduced renal function.

Anticoagulation in renal insufficiency: caught between the Scylla and Charybdis

Patients with renal insufficiency, however, are problematic for any kind of anticoagulant treatment due to the increased risk for both thrombo-embolic and bleeding events in this situation.[4] A recent cohort study once more identified reduced renal function as an independent predictor of cerebral ischaemic events, with a continuous increase in risk with decreasing kidney function.[5] This is even further potentiated in patients with end-stage renal disease as well as those on dialysis. In addition to the high prevalence of co-morbidities predisposing for thrombo-embolic complications such as hypertension, congestive heart failure, left atrial enlargement, and diabetes, the inflammatory state of chronic kidney disease as well as alterations of blood constituents and endothelial protein expression collectively result in a prothrombotic state.[6] At the same time, however, bleeding risk is equally increased in these patients, probably due to poorly or non-functional platelets, altered von Willebrand factor, and the presence of uraemic toxins.[4,6] As such, the treating physician is even more than normally caught between the Scylla and Charybdis when having to decide whether or not—and if yes, how—to anticoagulate patients with atrial fibrillation and renal insufficiency. With the rising incidence and prevalence of both diseases, this scenario is encountered with increasing frequency. Indeed, the co-prevalence of chronic kidney disease and atrial fibrillation is reported to be as high as 20%, and is likely to increase even further.[7] To make things even more confusing, several studies have suggested that use of vitamin K antagonists is even associated with an increased risk for stroke in the extreme case of end-stage renal disease patients.[8,9]

Apixaban in renal insufficiency

Hohnloser and colleagues have now reported the pre-specified subgroup analysis of the ARISTOTLE trial for patients with impaired renal function.[10] In the overall trial, apixaban was associated with a 22% reduction in stroke as well as a 31% reduction in major bleeding.[3] Importantly, a reduced dose of apixaban (2 × 2.5 mg instead of the usual 2 × 5 mg) was given to patients with two of the following criteria: age ≥ 80 years, weight ≤ 60 kg, and

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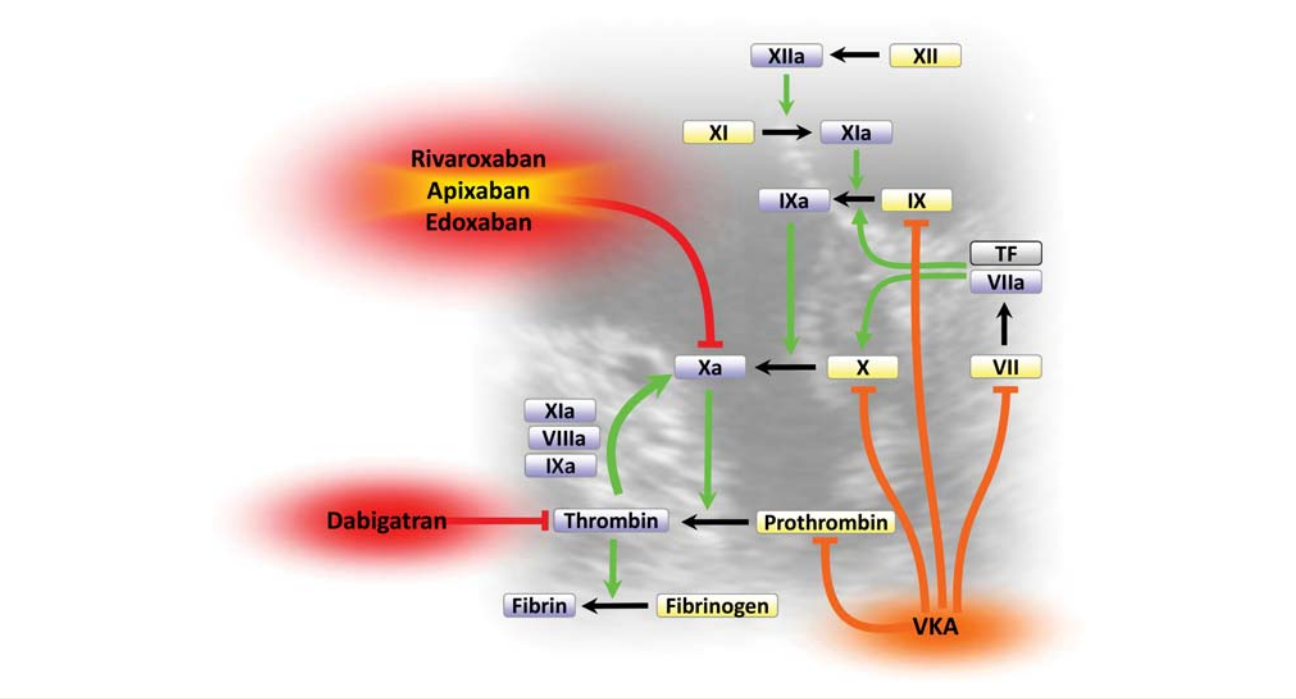

Figure 1. Point of action of novel oral anticoagulants in the coagulation cascade. See text for details. VKA, vitamin K antagonist. Adapted from Steffel and Braunwald.

serum creatinine $\geq$ 133 μmol/L (1.5 mg/dL). Baseline creatinine clearance was calculated according to the Cockcroft–Gault and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations as well as based on cystatin C measurements. When compared with warfarin, apixaban was superior in reducing stroke or systemic embolism, major bleeding, and mortality irrespective of kidney function. As already indicated in the primary publication, apixaban was associated with less major bleeding compared with warfarin across all categories of renal dysfunction, but this reduction was significantly greater in patients with an estimated glomerular filtration rate (eGFR) $\leq$ 50 mL/min (as determined by the Cockcroft–Gault equation of CKD-EPI, albeit not when based on cystatin C eGFR). The reason for the inconsistent effects with the (in practice much less frequently used) cystatin-based eGFR calculation is not clear, but may be related to confounding variables such as age. Importantly, the finding of a statistically significant greater reduction in major bleeding in patients with impaired renal function implies a particularly pronounced benefit of apixaban compared with warfarin in this patient population. Indeed, due to their iatrogenic nature, major bleeding events are the single most prevalent reason why proper anticoagulation is withheld in patients with atrial fibrillation, especially those with impaired renal function.

Implications for daily clinical practice

Should every patient with atrial fibrillation and renal insufficiency hence be anticoagulated with apixaban? How does apixaban compare with rivaroxaban and dabigatran in these patients? Unfortunately, comprehensive cross-trial comparisons with the other novel anticoagulants are impossible to perform given—among others—the different study designs, different patient populations, and (partly) different bleeding definitions. Since all three trials compared the respective novel agent with warfarin, it would be interesting to compare matched subsets of patients from each trial; such data, however, are not yet available. Chronic kidney disease certainly appears to be the 'Achilles heel' of dabigatran, as accumulation is likely to occur due to mainly renal elimination. Hence, in view of the available data, apixaban would probably be the preferred agent over dabigatran in these patients. For rivaroxaban, a solid and valid comparison is virtually impossible given the above-mentioned limitations. Data from large registries and from real-world use will provide additional evidence for further guidance. For the time being, the current data with apixaban certainly look very promising for patients with renal impairment.

The latter is particularly true for patients with moderately reduce renal function. It should be kept in mind, however, that only 1.5% of the included patients presented with an eGFR of $\leq$ 30 mL/min, and patients with a creatinine clearance $<$25 mL/min or a serum creatinine $>$2.5 mg/dL (221 μmol/L) were *a priori* excluded from the study.[3] The amount of data to support the use of apixaban in patients with severe renal insufficiency is hence scarce. The problem, of course, in these patients is the lack of alternatives, as vitamin K antagonist treatment is equally problematic in this situation and subject to inherent limitations and risks. Nevertheless, resorting to a familiar medication such as the latter in the treatment of these particularly challenging

patients is probably not the most unreasonable practice, especially until some familiarization has occurred during treatment of the many patients that otherwise qualify for apixaban. It should also be kept in mind that the results of Hohnloser *et al.* are based on baseline creatinine/GFR, whereas serial measurements are not provided. In contrast, in the real world and during longer treatment periods, renal function frequently worsens over time, especially in patients with various co-morbidities, necessitating individual adaptation of risk assessment and therapies.

A key factor for the successful use of the novel anticoagulants is their judicious application, especially in high-risk individuals. One of the most important aspects in this regard is to withstand the temptation to prescribe them in a 'fill and forget' manner, which is particularly true for patients with reduced renal function. As expected, and consistent with previous studies, Hohnloser *et al.* found a generally increased risk for events in these patients (stroke, major bleeding, all-cause mortality) as compared with those with normal kidney function. Hence, physicians are likely to see more events in their patients with renal dysfunction, independent of the way they are treated, just by virtue of them being at high risk for any kind of event. Data from the study of Hohnloser *et al.* provide reassurance that patients with moderately reduced renal function have a lower risk of major haemorrhage if treated with apixaban as compared with warfarin. Nevertheless, also with apixaban, regular follow-up of these high-risk patients, including early detection of renal function deterioration and adaptation of treatment, is crucial to successfully navigate between the Scylla and Charybdis.

In summary, this substudy of the ARISTOTLE trial provides solid evidence for the superiority of apixaban in patients with atrial fibrillation and chronic kidney disease. In the light of these data, apixaban appears to be a very appealing option for these individuals, potentially leading to a substantial increase in the numbers of appropriately anticoagulated patients. Judicious use and vigilant follow-up will be key to fully exploit the benefits of this therapy.

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