Oral anticoagulation in chronic kidney disease: A huge challenge

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The prevalence of chronic kidney disease (CKD) has doubled in the past 10 years related to the rise in obesity, diabetes and hypertension, becoming recognised as a silent epidemic (1). CKD is associated with an increased risk for cardiovascular morbidity and mortality, with the frequency of atrial fibrillation (AF) being especially high.

Indeed, AF is common in patients with CKD at different stages of severity (1–4). Both conditions share several pathophysiological and clinical risk factors, such as hypertension, diabetes mellitus and coronary heart disease (5). Thus, the prevalence of AF increases with decreasing glomerular filtration rate (6), and conversely, CKD increases the risk of thromboembolism in AF independently of other risk factors (7).

AF is the most common arrhythmia in clinical practice and associates a high morbidity and mortality due mainly to its five-fold increase in ischaemic stroke. The prevalence of AF increases with age, and age is also a risk factor for stroke, so the combination of age and AF means that stroke prevention in elderly AF patients is a huge challenge (8), added to the fact that CKD also increases with age. Oral anticoagulation reduces substantially the risk of stroke; however, elderly people are less likely to receive antithrombotic therapy, in spite of the net clinical benefit of oral anticoagulation in such patients (9, 10).

Renal impairment is an established bleeding risk factor in patients taking oral anticoagulation. Several studies have reported the association between CKD and a significantly increased risk for bleeding in anticoagulated patients with AF or venous thromboembolism (11–14). Thus, CKD has been included in the HAS-BLED bleeding score (15) which has been proposed in current AF clinical guidelines (16, 17), or other risk scores like the HEMORRHA,GES (18), or more recently, the ATRIA based bleeding risk score (19). In a similar way, the RIETE investigators have derived and validated a score to predict the risk of major bleeding for venous thromboembolism which also includes renal impairment (20).

In the June 2012 issue of Thrombosis and Haemostasis, the investigators of the EPICA study, reported that CKD is an independent risk factor for bleeding and that a wide proportion of aged patients taking oral anticoagulation had severe or moderate CKD independently of the method used for measuring glomerular filtration rate (21). Whilst the abbreviated MDRD (Modification of Diet in Renal Disease) formula is more accurate in estimating the glomerular filtration rate in elderly patients (22), it has recently been proposed that the Cockcroft-Gault formula is the better method to evaluate renal function in heart failure patients (where it was predictive of mortality), although the latter patients were about 10 years younger (23). In the study by Poli et al., the Cockcroft-Gault formula seemed to underestimate the incidence of severe CKD, as previously reported also, independent of the formula used to calculate, severe CKD patients (creatinine clearance less than 30 ml/minute) was associated with an independent increased risk of bleeding (21).

There is much renewed interest regarding to the evaluation of renal function in AF patients, as the new oral anticoagulants are contraindicated in patients with severe renal impairment (24), which could have implications for thromboprophylaxis. Indeed, the oral direct thrombin inhibitor dabigatran is highly excreted by the kidneys so there could be an increased risk of bleeding secondary to the accumulation of the drug (25). Indeed, patients with severe renal dysfunction were excluded from the recent clinical trials with new oral anticoagulants (26). Also, the management of warfarin therapy in severe CKD patients is difficult as they require lower warfarin dosages, spend less time on therapeutic range and are at risk of overanticoagulation (27).

Nonetheless, stroke risk is closely related to bleeding risk in AF patients (28), as many risk factors for stroke are also associated with a higher risk for anticoagulation associated haemorrhage (17). CKD does not only coexist with advancing age, but also with hypertension, diabetes, heart failure and vascular disease, which are included within current stroke risk stratification schemes such as the CHA2DS2-VASc score (29). Severe renal dysfunction is not included in neither of the two stroke risk stratification scores, but it has already been informally proposed in 2010 that it could be included in CHA2DS2-VASc score, with the little “c” letter indicating “chronic severe renal impairment” pending validation studies (3). Renal impairment is at least included in the HAS-BLED score, which also does have some modest predictive value for cardiovascular events and mortality, but less so compared to its predictiveness for major bleeding (where as a bleeding score, HAS-BLED performs as good as a multivariate analysis) (12).

Several studies agree that stroke risk stratification in severe CKD patients should be individualised which is essential to guide the selection of the most appropriate thromboprophylactic measures (30,
31). During the CHADS2 score validation, CKD was not considered even when the risk of stroke in unselected patients with end-stage CKD was up to 24% even without fulfilling all CHADS2 risk factors (e.g. a CHADS2 risk score of six displayed an annual stroke rate of 18%) (32). Although renal impairment is included in risk stratification schemes for bleeding, the published scores may still underestimate the risk of bleeding in end-stage kidney disease/haemodialysis patients (33), as the stratification schemes have not been validated in such patients.

Finally, renal function in AF patients may not remain static, so renal function should be monitored in AF patients, independent of the type of oral anticoagulation that we could have chosen. Respect to the new anticoagulants, the oral factor Xa inhibitors may have a better profile in CKD patients (34), whilst for warfarin this would need to be initiated at a lower dosage and monitored even more closely in patients with severe renal impairment compared with AF patients with normal kidney function (3).

What is the evidence here? In moderate CKD patients, warfarin significantly reduced the risk of stroke in such patients in the Stroke Prevention in Atrial Fibrillation trial (SPAF) but surprisingly, the INR adjusted warfarin cohort did not have higher bleeding rate compared to the (ineffective) fixed low dose warfarin cohort (35). This would support close international normalized ratio monitoring in these patients. Conversely, even mild kidney disease is associated with a higher risk for major bleeding as compared with normal-renal-function patients in patients with AF undergoing percutaneous coronary artery stenting (15), but this could probably be related to periprocedural events or adjunctive antithrombotic therapy (14). In any case, anticoagulation therapy is the most beneficial therapeutic decision for most AF patients, except for those who are ‘truly low risk’ for stroke, given the large net clinical benefit from anticoagulation (36).

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