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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Atrial Fibrillation and Thromboembolism in Patients With Chronic Kidney Disease

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ABSTRACT

A bidirectional relationship exists between atrial fibrillation (AF) and chronic renal disease. Patients with AF have a higher incidence of renal dysfunction, and the latter predisposes to incident AF. The coexistence of both conditions results in a higher risk for thromboembolic-related adverse events but a paradoxical increased hemorrhagic risk. Oral anticoagulants (both vitamin K antagonists [VKAs] and non-VKA oral anticoagulants [NOACs]) have been demonstrated to be effective in mild to moderate renal dysfunction. Patients with severe renal impairment were excluded from the non-VKA oral anticoagulant trials, so limited data are available. In end-stage renal failure, the net clinical benefit of VKAs in dialysis-dependent patients remains uncertain, although some evidence suggests that such patients may do well with high-quality anticoagulation control. Risk stratification and careful follow-up of such patients are necessary to ensure a net clinical benefit from thromboprophylaxis. (J Am Coll Cardiol 2016;68:1452–64) © 2016 by the American College of Cardiology Foundation.

Chronic kidney disease (CKD) is defined by Kidney Disease Improving Global Outcomes as a reduction in renal function with a reduction in glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or longer or with the presence of albuminuria (1,2). The scheme of CKD stages 1 to 5 is conventionally classified on the basis of GFR, ranging from CKD stage 1, which has preserved renal function (GFR >90 ml/min) to CKD stage 5, which has the worst renal function (GFR <15 ml/min). CKD has potential for gradual progression to end-stage renal disease (ESRD), which requires dialysis to correct the accompanying fluid and electrolyte imbalance.

The increasing incidence and prevalence of CKD are also associated with a parallel rise in incident atrial fibrillation (AF) (3–6). The main reason for this epidemiological coupling is the improving longevity in Western countries, resulting in a rapidly increasing elderly population, as well as a contemporary increase in the collective risk factors shared by both conditions, such as diabetes mellitus and hypertension.

Unsurprisingly, CKD and AF are not independent conditions, as several studies and national registries have highlighted the increased incidence of AF among those with worsening renal function (7–14). Indeed, the incidence of AF development can be as high as 12.1/1,000 patient-years in ESRD compared with 5.0/1,000 patient-years in controls (15). Likewise, a new diagnosis of AF not only heralds the progression of CKD but also hastens the development of ESRD (16–18). AF also leads to the progression of CKD, even among those with relatively "normal" renal function, with no detectable proteinuria on dipstick test at baseline (19). Thus, a bidirectional relationship exists between these 2 conditions.

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AF per se can result in increased risk of ischemic stroke and systemic thromboembolism and independently increased risk of cardiovascular death. However, the concurrent presence of both AF and CKD further exacerbates the stroke and mortality risks, with a 66% increase in relative risk of death (20–23). Hence, the presence of both of these conditions results in an increase in the propensity for thromboembolism-related adverse events (including stroke, systemic thromboembolism, myocardial infarction, and death) but a paradoxical increase in hemorrhagic risk.

Stroke/thromboembolism and bleeding risks can be assessed using clinical risk scores, such as the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack [TIA], or thromboembolism, vascular disease [prior myocardial infarction, peripheral arterial disease or aortic plaque], age 65–74 years, sex category [female]) and HAS-BLED (hypertension, abnormal renal/liver function, prior stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol) scores, to enable risk stratification of patients requiring thromboprophylaxis (24,25). Oral anticoagulants (both vitamin K antagonists [VKAs] and non-VKA oral anticoagulants [NOACs]) provide effective thromboprophylaxis in patients with mild to moderate renal dysfunction (creatinine clearance [CrCl] of 30 to 79 ml/min), in both clinical trials and observational studies (26,27). Patients with severe renal impairment (CrCl <25 to 30 ml/min) were excluded from the phase 3 randomized trials of NOACs, so limited trial data are available.

Initially, this review discusses the pathophysiological and clinical bases underlying the increased risk of thromboembolism and hemorrhage among AF patients with CKD. Second, we review the data for the use of oral anticoagulants for stroke prevention in AF across the spectrum of renal dysfunction.

SEARCH STRATEGY

A comprehensive search of published studies was performed using electronic bibliographic databases (i.e., PubMed, Medline, EMBASE, DARE, Cochrane database), scanning reference lists from included papers, and manual searching abstracts from national and international cardiovascular meetings. Search terms included: atrial fibrillation; chronic kidney disease; renal failure; antithrombotic treatment; vitamin K antagonist; dabigatran; rivaroxaban; apixaban; and edoxaban. Bibliographies of all selected papers and reviews were reviewed for other relevant papers. Finally, the supplements of major journals were searched manually to identify relevant abstracts that had not been published as peer-reviewed papers.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF THROMBOEMBOLISM IN CKD: A BRIEF OVERVIEW

PATHOPHYSIOLOGICAL INSIGHTS. AF confers a prothrombotic or hypercoagulable state through numerous pathophysiological pathways, fulfilling Virchow's triad for thrombogenesis, as shown by abnormalities in blood flow, in the vessel wall, and in blood constituents (28). The propensity of thrombus formation is further enhanced by the relationship between CKD and additional changes (29) in blood flow within the left atrium (and left atrial appendage), endothelial damage/dysfunction, or up-regulation of platelet and coagulation factors (**Table 1**).

In relation to changes in blood flow, worsening GFR in AF is associated with reduced left atrial appendage emptying velocity and formation of dense spontaneous echocardiographic contrast, indicative of significant blood stasis and increased thrombogenic risk (30,31). Second, CKD-related endothelial damage/dysfunction to the vessel wall may manifest directly as abnormal endothelial function (e.g., as assessed by flow-mediated dilation) or increased pulse-wave velocity (32–36), or indirectly, as elevated levels of endothelin and von Willebrand factor (33,37). Endothelial damage/dysfunction can also be reflected in intima-media thickening (38), which is predictive of a 10-fold increase in cardiovascular mortality in patients with ESRD (odds ratio: 10.20; 95% confidence interval [CI]: 3.67 to 28.3; $p < 0.0001$) (39,40).

Third, increased thrombogenesis in CKD is also related to an increase in platelet and coagulation abnormalities ("abnormal blood constituents") through several pathways, for example, increased procoagulant and inflammatory complexes (41–45), up-regulation of the tissue factor pathway and its interactions with platelets (46,47), reduction of antithrombin III and plasminogen-activator inhibitor (PAI)-1 levels (47,48), reduced von Willebrand factor degradation (49), and increased platelet aggregability (50).

CKD per se is also associated with various other factors contributing to an increased thromboembolic risk, for example, activation of the renin-angiotensin-aldosterone system (51), chronic inflammation (43), aortic or vascular calcification, and dysfunction of

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
b.i.d. = twice daily
CKD = chronic kidney disease
ESRD = end-stage renal disease
FDA = Food and Drug Administration
NOAC = non-vitamin K antagonist oral anticoagulant
TTR = time in therapeutic range
VKA = vitamin K antagonist