Renal function in patients with atrial fibrillation: From Virchow's triad to real-world practice

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DOI: 10.33963/v.phj.111175

Received:
February 12, 2026

Accepted:
February 12, 2026

Early publication date:
February 13, 2026

In atrial fibrillation (AF) thrombus formation is related to all 3 components of Virchow's triad (i.e., stasis, endothelial damage, and hypercoagulability). The structural, functional, and electrical changes occurring in the atria of patients with AF have recently been conceptualized as atrial cardiomyopathy [1, 2]. This condition promotes a high-risk prothrombotic state, with clots that may develop primarily within the left atrial appendage (Figure 1) [3].

Accordingly, patients with AF are exposed to a substantial risk of thromboembolism, which is currently estimated using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age [2 points], diabetes, previous stroke/transient ischemic attack [2 points], vascular disease, and sex category) or CHA_2DS_2-VA score [4, 5], alongside an intrinsic risk of bleeding that may be assessed through the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history of predisposition, labile international normalized ratio, old age, and drugs/alcohol) or DOAC (direct oral anticoagulants) scores [6, 7]. Within this delicate balance, oral anticoagulants (OACs) are indicated to prevent AF-related thromboembolic events, but their effectiveness critically depends on appropriate dose selection and long-term adherence. In real-world practice, however, fear of bleeding complications or the occurrence of bleeding events often leads to OAC discontinuation or prescription of reduced, inappropriate doses [5].

This issue is particularly important in patients with chronic kidney disease (CKD), a condition affecting a substantial proportion of the AF population and frequently complicating anticoagulant management. Beyond its impact on drug pharmacokinetics, CKD itself contributes to a prothrombotic state, potentially amplifying residual thromboembolic risk despite anticoagulation. Therefore, expanding evidence on left atrial thrombus (LAT) prevalence and OAC prescribing patterns in this vulnerable subgroup is of paramount clinical importance.

In this issue of the *Polish Heart Journal*, Gawałko et al. [8] report the results of a prospective observational study (LATTEE study) investigating the prevalence of LAT in patients with AF according to renal function, assessed by creatinine clearance (CrCl) using the Cockcroft–Gault formula, and across different anticoagulant regimens. Patients undergoing transesophageal echocardiography before cardioversion or catheter ablation for AF were enrolled. The primary endpoint was the presence of LAT detected by transesophageal echocardiography, and a cross-sectional analysis was performed to evaluate changes in LAT prevalence across different categories of renal function.

The authors included 2790 patients, of whom 310 (11%) had a CrCl <50 ml/min. They observed a marked increase in LAT prevalence with worsening renal function, rising from 6.7% in patients with CrCl ≥50 ml/min to 16% in those with CrCl 30–49 ml/min and 19% in patients with CrCl <30 ml/min. Notably, impaired renal function (CrCl <50 ml/min) remained independently associated with a higher odds of LAT even after adjustment

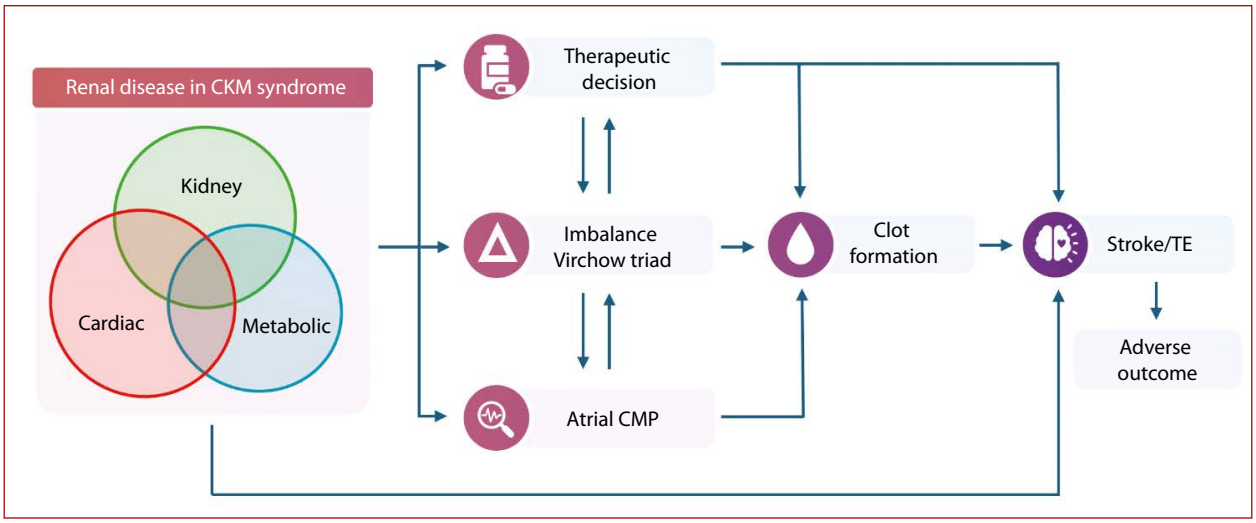

Figure 1. Renal dysfunction within cardio-kidney-metabolic syndrome: links between atrial cardiomyopathy, Virchow's triad, and thrombotic outcomes

Abbreviations: CMP, cardiomyopathy; CKM, cardio-kidney-metabolic; TE, thromboembolism

for common risk factors for AF patients (i.e., components of the CHA_2DS_2-VASc score) and baseline OAC use.

These findings are of great clinical interest and further underscore that renal function is a major determinant of outcomes in patients with AF. Epidemiological data have consistently shown an exponential increase in adverse events with progressive deterioration of renal function, regardless of the equation used to estimate kidney function [9]. An important aspect to consider, however, is that the study enrolled highly selected AF patients (e.g., those undergoing cardioversion or AF ablation). Hence, it is not surprising that the prevalence of patients with CrCl <50 ml/min in this cohort was approximately 10%, which may represent an underestimation as compared to an unselected cohort of AF patients. European real-world data suggest that CKD may be present in up to 30% of patients with AF [3, 9]. Consequently, the true burden of LAT in patients with AF and CKD may be even greater than that reported by Gawałko et al. [8].

It should also be acknowledged that although LAT was the primary endpoint of the study, renal dysfunction is likely to influence hard clinical outcomes as well. Indeed, previous observational studies have shown that renal function alone can predict composite outcomes including all-cause mortality and major adverse cardiovascular events with modest-to-good discriminatory performance [9]. This reinforces the concept that renal function remains one of the strongest mediators of risk in AF, particularly given its central role in guiding DOAC dosing strategies. In this context, the data provided by Gawałko et al. [8] are crucial to better contextualize the prevalence of one of the most feared complications in AF.

Another key finding of the study was that approximately 316 patients received inappropriate direct OAC dosing, among whom nearly 11% developed LAT, compared with 4.8% of patients receiving guideline-recommended doses [8]. These observations deserve careful interpretation in light of emerging evidence on clustering of comorbidities in AF. In recent years, the scientific literature has increasingly focused on the coexistence of conditions frequently accompanying AF, leading to the concept of cardio-kidney-metabolic disease. A recent observational study reported that the kidney domain is present in up to 33% of patients, although isolated kidney involvement occurred in only 1.6% [10]. In most cases, renal dysfunction clustered with cardiovascular and metabolic domains, with all 3 domains coexisting in approximately 21.4% of patients.

The increasing burden of cardio-kidney-metabolic conditions has a significant impact not only on clinical outcomes (with a stepwise increase in event rates as the number of affected domains rises), but also on the prescription of disease-modifying therapies in AF [10]. In observational studies renal disease was identified as one of the main drivers of direct OAC underuse or inappropriate dose reduction [10]. Therefore, the findings reported by the authors acquire even greater relevance in this complex clinical context. Given that renal function is a cornerstone determinant of direct OAC dosing, inappropriateness in this setting may directly translate into an increased risk of adverse events.

Altogether, these data highlight how renal disease, either alone or in combination with other common comorbidities in AF, can easily disrupt the balance of Virchow's triad (Figure 1). Within the framework of atrial cardiomyopathy, this imbalance may rapidly intensify the hypercoagulable state, ultimately leading to LAT formation, which in turn may act as a key mediator of worse outcomes in patients with AF and CKD (Figure 1). A holistic approach to any patient presenting with AF and patient-centered decision-making according to existing evidence are needed to minimize thromboembolic risk and improve patient outcomes.

Article information

Conflict of interest: None.

Declaration of artificial intelligence use: Nothing to disclose.

Funding: None.

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