Biomarkers for atrial fibrillation and chronic kidney disease: what is the evidence?

Rungroj Krittayaphong[1], Komsing Methavigul[2]

[1]Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2]Department of Cardiology, Central Chest Institute of Thailand, Nonthaburi, Thailand

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Correspondence to:
Rungroj Krittayaphong, MD, Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand, phone: +66 241 961 04, e-mail: rungroj.kri@mahidol.ac.th

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Atrial fibrillation (AF) and chronic kidney disease (CKD) are a bad combination which leads to an increased risk of ischemic stroke and major bleeding [1]. Although CKD and biomarkers were not components of the CHA_2DS_2-VASc score, many studies have shown that CKD and certain biomarkers are independent risk factors for clinical outcomes in patients with AF [2–4]. The ABC (Age, Biomarkers, Clinical history) risk score [4] and impaired renal function [3] have been proposed and validated to have an incremental prognostic value compared to the CHA_2DS_2-VASc score. In fact, CKD has been listed in the prediction model for ischemic stroke, major bleeding, and death in the GARFIELD study [5].

Based on our current knowledge, several bleeding risk scores have been studied in patients with AF, such as HAS-BLED, ORBIT bleeding score, or ABC-bleeding scores [4, 6]. In the ABC-risk score, growth differentiation factor-15 (GDF-15) (a marker of oxidative stress), high-sensitivity cardiac troponin (cTn-hs) (a marker of myocardial injury), and cystatin C (a marker of renal dysfunction) were predictors of major bleeding events. The ABC-bleeding score using alternative biomarkers (hematocrit, cTnI-hs, cystatin C, or creatinine clearance) outperformed both the HAS-BLED and the ORBIT scores [4]. However, it has not been proven if these biomarkers could predict bleeding events in severe CKD.

Matusik et al. reported prospective data in 182 patients with AF and CKD stage 4 looking at the predictive value of many biomarkers such as GDF-15, cystatin-C, and cTnT-hs, and prothrombotic state parameters, i.e., plasma fibrin clot permeability (Ks) for ischemic stroke, clinically relevant bleeding and death [7]. The median CHA_2DS_2-VASc score was 3.0. Half of the patients were prescribed vitamin-K antagonist (VKA) while non-VKA oral anticoagulant (NOAC) was used in the other half. The results demonstrated that age and decreased plasma fibrin clot permeability (Ks) are predictors for ischemic stroke events (4.7% per year); growth differentiation factor-15 (GDF-15), cystatin C, high-sensitivity troponin T, and a history of bleeding are predictors of bleeding (7.1% per year), and only cystatin C is a predictor for death (6.5% per year). In this study, none of the other clinical parameters could be used as a prognostic marker. This study had limitations such as the small sample size and a relatively short follow-up time. Therefore, other clinical parameters that have been shown to be important prognostic markers could not be demonstrated in this study. However, the results of this study imply that biomarkers may have a more prominent prognostic value compared to many clinical data in patients with AF and severe CKD.

To date, the mechanisms underlying the role of GDF-15 and cystatin C in a bleeding risk assessment remains unclear. A previous study showed that elevated GDF-15 was associated with reduced endothelium-dependent vasodilatation in resistance vessels, plaque burdens, reduced left ventricular ejection fraction, coronary artery disease, and heart failure, all of them [8] were risk factors for major bleeding [9]. Heart failure is associated with an increased GDF-15 level and may increase the risk of bleeding from hepatic congestion and impaired coagulopathy resulted from vitamin K antagonist (VKA) [8]. Cystatin C is a marker of renal function and is used to calculate eGFR.

A previous study showed that the estimated glomerular filtration rate (eGFR) equation, based on combined creatinine and cystatin C, was more accurate than creatinine or cystatin C alone for calculating eGFR [10]. Elevated cystatin C is a marker of accurate renal dysfunction that is related to an increased bleeding risk according to the HAS-BLED and the ORBIT bleeding scores [6].

Oral anticoagulant (OAC) is usually required in patients with AF and CKD to decrease the risk of ischemic stroke [11]. Guidelines recommended NOAC over VKA for AF patients at increased risk of stroke [2]. Data are limited in patients with CKD. Major clinical trials comparing NOAC with VKA usually excluded patients with an eGFR less than 30 ml/min/1.73 m^2 [12]. Based on the observational data, guidelines recommended that some NOACs at a reduced dose, such as apixaban and rivaroxaban, could be used in patients with advanced CKD including those who required dialysis [2, 13].

Asian population had an increased risk of major bleeding compared to non-Asian patients with AF [14]. A prospective cohort study of AF in Thailand showed that CKD accounts for approximately 60% of AF cases [11] and is a predictor for ischemic stroke and major bleeding. NOAC had a trend towards reducing ischemic stroke and major bleeding compared to warfarin [11]. Analysis of clinical outcomes for patients with AF and CKD who were on warfarin demonstrated that high_time in the therapeutic range (TTR) is essential for the good effectiveness of anticoagulation [15]. However, the average TTR in this population was 54%, and only approximately one-third had a good TTR control [15].

The study by Matusik et al. [7] explored many biomarkers in patients with AF and CKD stage 4. Several questions remain open. The elevation of biomarker levels may begin early in the course of disease before clinical abnormalities. As such, a biomarker-based bleeding risk score is a better predictor than the clinical risk score [1, 4]. More studies are needed to verify whether the bleeding risk score e.g., the HAS-BLED, ORBIT bleeding score, including biomarkers such as GDF-15, cTnT-hs, and cystatin C, will be better predictors of clinical outcomes in AF patients with oral anticoagulant therapy. Whether the results of this study can be applied in patients with AF without CKD or those who require dialysis is unknown. Also, whether the results can be applied in patients without OAC, with VKA, or with NOACs remains uncertain. Even in patients with CKD stage 4, it also remains to be confirmed in a larger sample size cohort. Most importantly, it remains to be proven whether the implementation of a biomarker-based prediction model for patients with AF is cost-effective.

Article information

Conflict of interest: None declared.

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