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IM - COMMENTARY

Real-world efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Francesco Violi[1] · **Daniele Pastori**[1]

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The INSIghT investigators performed a real-world prospective observational cohort study to investigate the safety and efficacy of non-vitamin K antagonist oral anticoagulants (NOACs) in 632 patients with atrial fibrillation (AF) according to the presence of chronic kidney disease (CKD), defined by a creatinine clearance (CrCl) < 60 ml/min [1]. Patients with CKD ($n = 219$) were at higher thromboembolic risk, as they were older, more likely to be women, hypertensive and diabetic. Among NOACs, apixaban was the most commonly used anticoagulant in CKD patients, followed by dabigatran and rivaroxaban. No patients on edoxaban were included.

At 2 years of follow-up, the rates of both thromboembolism and ISTH major bleeding events were 2.3% and 5.1%, respectively. The authors found no difference between patients with and without CKD (2.5 vs. 2.2% for thromboembolism and 5.0 vs. 5.2% for bleeding, respectively). A total of four intracranial hemorrhages occurred. However, the all-cause mortality incidence was higher in CKD patients (9.0 vs. 3.8%, $p = 0.010$).

Given the low number of events registered during the study, these results should be considered as hypothesis generating and no conclusive evidence can be drawn in relationship to the different performance of NOACs in CKD patients. However, some clinical considerations can be made.

The authors found no difference in thromboembolic and bleeding events rate in patients with and without CKD; this result is in contrast with previous findings showing that AF patients have an increased risk of CKD [2, 3] and that CKD increases both thromboembolic and bleeding risk in these patients [4]. Of note, most of the studies investigating the association between AF and CKD with clinical outcomes have been performed in patients taking warfarin, which is known to be associated with an accelerated decline of renal function [3, 5]. Recent findings suggested that NOACs can influence the variation of renal function by slowing the worsening of glomerular filtration rate, thereby potentially modifying the relationship between CKD and clinical adverse events in AF [6–8] (Fig. 1). Larger studies including AF patients with CKD are needed to investigate whether the exposure to NOACs may affect this association.

However, this real-world study seems to confirm previous evidence on the safety and efficacy of NOACs in AF patients with and without CKD [9, 10]. A previous meta-analysis also showed that NOACs are safer than VKAs in AF patients with worsening renal function [11]. However, the authors found some differences among NOACs; thus, in non-CKD patients, the 2-year ISTH-major bleeding rates were higher in rivaroxaban group (HR 2.9, 95% CI 1.1–7.3; $p = 0.047$), while in CKD patients, a significantly higher rate of thromboembolic events was observed in patients treated with rivaroxaban (HR 6.3, 95% CI 1.1–38.1; $p = 0.044$). Apixaban and dabigatran performed similarly with regard to both thromboembolism and bleeding in CKD patients. These results are in keeping with a previous analysis from the Truven MarketScan® Commercial & Medicare supplemental US claims database that included 45,361 AF patients starting oral anticoagulation [12]. Of these, 15,461 (34.1%) initiated warfarin, 7438 (16.4%) apixaban, 17,801 (39.2%) rivaroxaban, and 4661 (10.3%) dabigatran. Comparisons among NOACs showed that matched rivaroxaban patients had a higher risk of major bleeding (HR 1.82; 95% CI 1.36–2.43) compared to apixaban patients [12]. Similar findings were observed in 16,957 matched new rivaroxaban or dabigatran users, in whom rivaroxaban was associated with an increased risk of gastrointestinal bleeding (HR 1.28 95% CI 1.06–1.54, $p = 0.01$) [13].

✉ Daniele Pastori
daniele.pastori@uniroma1.it

[1] Department of Internal Medicine and Medical Specialties, I Clinica Medica, Atherothrombosis Center, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy

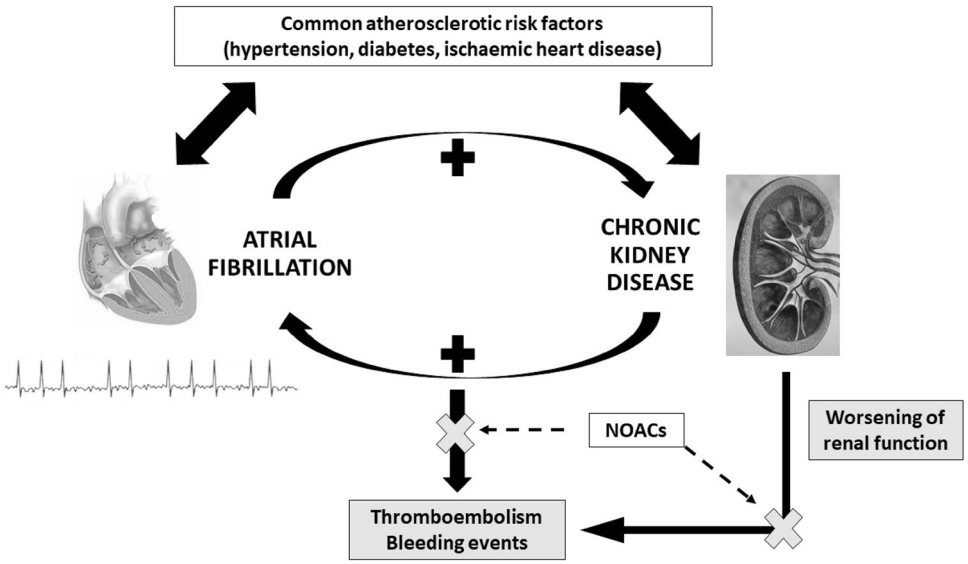

Fig. 1 Association between atrial fibrillation (AF) and chronic kidney disease (CKD) and potential effects of non-vitamin K antagonist oral anticoagulants (NOACs)

However, two recent studies investigated the efficacy and safety of apixaban and rivaroxaban in AF patients with very low glomerular filtration rate or undergoing hemodialysis, showing for both NOACs a better safety profile than warfarin [14, 15].

Another interesting finding of the study is the discontinuation rate of patients on NOACs. In 2008, the General Practice Research Database including 41,910 patients with permanent AF showed that only 60% had an uninterrupted treatment with warfarin at 2 years [16]. Moreover, the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) study showed that at 1 year 10.1% of 6110 patients stopped warfarin users was 10.1%, with 88.9% of reasons for discontinuation being patient rather than treatment-related [17]. In the present study by Godino et al. [1], the authors reported that about 20% of patients discontinued oral anticoagulation. Unfortunately, reasons for stopping anticoagulation therapy were not reported. This finding is in keeping with a recent large retrospective study in Italy which reported that at 1 year 25% of patients discontinued oral anticoagulation, with this proportion almost doubling at 2 years [18]. This issue is of particular clinical relevance as patients discontinuing oral anticoagulation disclose and excessive risk of ischaemic stroke and mortality [19].

Furthermore, in a study population that comprised 51,606 health-insured AF patients initiating warfarin ($n=21,468$, 41.6%), apixaban ($n=8832$, 17.1%), dabigatran ($n=3973$, 7.7%) or rivaroxaban ($n=17,333$, 33.6%), showed that after 1 year, 29.9% of warfarin and 29.5% of NOAC patients had discontinued oral anticoagulation [20].

These results suggest that despite a higher adherence to NOAC treatment compared to warfarin [21], a still high proportion of patients discontinues oral anticoagulant treatment also when prescribed on NOACs; strategies to reduce withdrawal from anticoagulation therapy are warranted.

In conclusion, patients with AF and CKD represent a high-risk subset of patients that would require a structured and careful monitoring. The use of NOACs in this population is increasing, and NOACs are becoming a safe alternative to warfarin also in patients with very low renal function.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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