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# Oral anticoagulant use for stroke prevention in atrial fibrillation patients with difficult scenarios

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ABSTRACT

Atrial fibrillation (AF) has become the most prevalent arrhythmia and it will increase the risk of ischemic stroke, heart failure, mortality, sudden cardiac death, myocardial infarction, and dementia. Stroke prevention with oral anticoagulant is crucial for management of AF patients. Vitamin K antagonist, which inhibits the clotting factors II, VII, IX and X, has been recommended for stroke prevention for decades. Non-Vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban and edoxaban are at least as effective as warfarin in reducing ischemic stroke with a lower rate of major bleeding. With the increasing prevalence of AF, prescription of the appropriate oral anticoagulants (OACs) according to patient's characteristics becomes a challenge. This review article aims to provide an overview of anticoagulant use in AF patients with difficult scenarios.



## 1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with a potential for blood stasis and increased risk of thrombus formation particularly in the left atrial appendage, resulting in hospitalizations, hemodynamic abnormalities, and thromboembolic events [1]. The current prevalence of AF is about 1% in the general population, increases with age [2], and is estimated to reach 4.01% in 2050 [3]. In 2011, the lifetime risk of AF was reported to be about 1 in 7 for subjects aged >20 years [3]. In comparison to patients without AF, AF increases the risk of ischemic stroke (adjusted hazard ratio [aHR] = 3.34), heart failure (aHR = 3.31), mortality (aHR = 2.61), sudden cardiac death (aHR = 1.83), myocardial infarction (aHR = 1.62) and dementia (aHR = 1.56) [3]. Oral anticoagulants (OACs) reduce the risk of ischemic stroke in patients with AF who have an additional stroke risk factor. Warfarin is a vitamin K antagonist that inhibits the synthesis of clotting factors II, VII, IX and X and has been used for prevention of ischemic stroke in patients with AF [4]. However, warfarin is prone to several drug and food interactions, which needs blood testing to maintain the international normalized ratio (INR) within the therapeutic range.

Non-Vitamin K antagonist oral anticoagulants (NOACs) directly target the specific clotting factor. The factor Xa inhibitors and direct factor IIa (thrombin) inhibitors have a more predictable anticoagulant effect, that does not require regular monitoring. Four large international phase III randomized controlled trials have demonstrated that compared with warfarin, these four NOACs are non-inferior or superior for prevention of stroke and systemic embolus and reduce the risk of intracranial hemorrhage [5–9]. Current guideline [1] suggests that anticoagulation should be considered for patients with AF with a CHA2DS2-VASc score of 1 or more for men or 2 or more for women. The HAS-BLED scoring system can be used to estimate the risk of bleeding with OACs. Nevertheless, OACs should not be withheld unless the risk of bleeding is unacceptably high.

With the increasing number of AF patients, prescription of the appropriate OACs according to patient's characteristics becomes a challenge. This review article aims to provide the evidence of warfarin and NOACs in AF patients with difficult scenarios and Tables 1 and 2 summarize those clinical studies.

## 2. Elderly patients

According to the ATRIA study [2], the prevalence of AF was 0.95% and it increases to 9.0% in persons aged 80 years or older from 0.1% among adults younger than 55 years. Symptomatic cerebral infarction was 2.4 times more common in older patients with paroxysmal AF than in older patients with sinus rhythm [10]. The risk of intracranial hemorrhage (ICH) in anticoagulated patients increases with advancing age [11], with mortality rates in excess of 50%, three times higher than

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**Table 1**
Evidence from clinical studies for efficacy and safety of OACs in difficult scenarios of patients with atrial fibrillation, part I.

| Scenarios | Clinical study | OAC | HR for ischemic stroke/systemic embolism (95% CI) | HR for major bleeding (95% CI) | HR for ICH (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Elderly (≥75 year-old) | Connolly SJ, 2009 [5] | Dabigatran 150 mg | ***0.67 (0.49–0.90)*** | 1.18 (0.98–1.42) | ***0.42 (0.25–0.70)*** | Compared with **warfarin**, Dabigatran 150 mg reduced Ischemic stroke. Both doses reduced risk of ICH. |
| | | Dabigatran 110 mg | 0.88 (0.66–1.17) | 1.01 (0.83–1.23) | ***0.37 (0.21–0.64)*** | |
| | Patel M, 2011 [7] | Rivaroxaban 20 mg | 0.80 (0.63–1.02) | 1.11 (0.92–1.34) | 0.80 (0.50–1.28) | Rivaroxaban had similar Safety and efficacy, compared with **warfarin** |
| | Granger CB, 2011 [8] | Apixaban | – | – | – | Apixaban had better efficacy and safety than **warfarin** in this subgroup |
| | Giugliano RP, 2013 [6] | Edoxaban | 0. 83 (0.66–1.04) | ***0.83 (0.70–0.99)*** | ***0.40 (0.26–0.62)*** | Edoxaban has better safety than **warfarin** |
| Very elderly (≥90 year-old) | Chao TF, 2018 [16] | NOACs | – | – | ***0.32 (0.10–0.97)*** | Compared with **warfarin**, NOACs were associated with a lower risk of ICH |
| CKD stage III (eGFR: 30–50 mL/min) | Connolly SJ, 2009 [5] | Dabigatran 150 mg | ***0.56 (0.37–0.85)*** | 1.01 (0.79–1.30) | ***0.31 (0.14–0.66)*** | Compared with **warfarin**, Dabigatran 150 mg reduced Ischemic stroke. Both doses reduced risk of ICH. |
| | | Dabigatran 110 mg | 0.85 (0.59–1.24) | 0.99 (0.77–1.28) | ***0.40 (0.20–0.80)*** | |
| | Patel M, 2011 [7] | Rivaroxaban 15 mg | 0.84 (0.57–1.23) | 0.95 (0.72–1.26) | 0.81 (0.41–1.60) | Rivaroxaban had similar Safety and efficacy, compared with **warfarin.** |
| | Granger CB, 2011 [8] | Apixaban | 0.79 (0.55–1.14) | ***0.50 (0.38–0.66)*** | – | Apixaban reduces major bleeding, compared with **warfarin.** |
| | Giugliano RP, 2013 [6] | Edoxaban (high dose arm) | 0.93 (0.67–1.30) | ***0.76 (0.58–0.98)*** | ***0.46 (0.26–0.82)*** | Edoxaban has lower rate of major bleeding and ICH than **warfarin.** |
| CKD stage IV (eGFR: 15–30 mL/min) | FDA label | Dabigatran 75 mg | – | – | – | Based on small pharmacokinetic and/or pharmacodynamic studies without clinical data. |
| | Patel M, 2011 [7] | Rivaroxaban 15 mg | – | – | – | Limited clinical data |
| | FDA label | Apixaban | – | – | – | Based on small pharmacokinetic and/or pharmacodynamic studies without clinical data. |
| ESRD | Siontis KC, 2018 [31] | Apixaban | 0.88 (0.69–1.12) | ***0.72 (0.59–0.87)*** | – | Compared with **warfarin**, Apixaban was associated with lower risks of major bleeding. |
| Previous ICH | Nielsen PB, 2015 [33] | NOACs & Warfarin | – | – | – | Compared with **no antithrombotic treatment**, OAC reduced ischemic stroke/all-cause mortality rates (HR = 0.55). |

CKD = chronic kidney disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = Hazard ratio; ICH = intracranial hemorrhage; NCB = net clinical benefit; NOAC = Non-Vitamin K antagonist oral anticoagulants; OAC = oral anticoagulants; PCI = percutaneous coronary intervention; RR = relative risk. Bold and italic values indicate statistically significant difference between two groups.

that of ischemic stroke. Thus, aging is a risk factor for ischemic stroke and ICH in patients with AF and attention should be paid to balance the risks of bleeding and thrombosis.

In the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial, which enrolled >7200 elderly patients (≥75 years), dabigatran 110 mg bid was associated with a similar risk in patients aged ≥75 years compared with warfarin [5]. However, a non-significant higher risk of major bleeding was observed in patients aged ≥75 years with dabigatran 150 mg bid. Both doses of Dabigatran had lower rates of ICH in this trial. One real-world study that included >47,000 AF patients also demonstrated the same results [12]. In elderly patients (≥75 years), dabigatran was associated with lower rates of ICH.

In a subgroup analysis of the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial [13], 6229 elderly AF patients taking warfarin or rivaroxaban were compared, and the results showed comparable efficacy and safety of rivaroxaban with warfarin in elderly patients. In a subgroup analysis of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study, the efficacy of apixaban in reducing the incidence of ischemic stroke was evident in elderly patients. The annual rate of ischemic stroke for apixaban and warfarin in patients was 1.6%/year vs. 2.2%/year, respectively, in patients ≥75 years. Similarly, the safety of apixaban was demonstrated with a rate of major bleeding of 3.3%/year vs. 5.2%/year in patients ≥75 years compared with warfarin [8]. In the ENGAGE AF-TIMI (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction) 48 trial, 8474 elderly patients (age ≥ 75 years) were enrolled, and after 2.8 years of follow-up, the rates of stroke event was similar with edoxaban versus warfarin, while major bleeding was significantly reduced with edoxaban [14].

Very elderly patients (age ≥ 90 years) are under-represented in RCTs, and even the largest prospective RCT in elderly subjects (BAFTA trial) only had modest numbers (approx. 10%) of subjects age ≥ 90 [15]. Overall, the BAFTA trial showed that warfarin was clearly superior to aspirin for reducing thromboembolism, with no significant difference in major bleeds or ICH between warfarin and aspirin. Recently, Chao TF et al. [16] investigated the risk of ischemic stroke and ICH of OAC treatment and found that the risk of ischemic stroke was similar between AF patients aged ≥90 years treated with warfarin or NOACs, but the risk of ICH was substantially lower with NOACs. Thus, OACs may still be considered as thromboprophylaxis for very elderly patients with NOACs being the more favorable choice.

Considering the enhanced risk of bleeding and related comorbidities in elderly patients, an individualized case-by-case approach should be chosen, instead of a generalized “one drug fits all” approach. For the