Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation

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INTRODUCTION

Atrial fibrillation is the most common cardiac arrhythmia, and its prevalence increases with age, ranging from approximately 0.1%–0.16% in adults aged <49 years to 9%–17% in elderly people aged >80 years (1, 2). Atrial fibrillation is associated with substantial mortality and morbidity, including a five-fold increase in the risk of stroke (3, 4).

The incidence of stroke increases with age; indeed, age is included as a significant risk factor for thromboembolism in the commonly used CHA$_2$DS$_2$-VASc score (age between 65 and 74 years contributes 1 point and ≥75 years contributes 2 points) (5). Advanced age is also a risk factor for bleeding. Elderly patients (defined as those aged ≥75 years) are at a high risk of falling and usually have a low body mass index, altered body composition of muscle and fatty tissue, and age-related decline in renal function. Therefore, balancing risks and benefits of antithrombotic strategies in this population is crucial.

In light of the projected increase in the worldwide prevalence of atrial fibrillation in the near future, there is an urgent need for effective stroke preventive strategies, especially in the elderly (6, 7).

Oral anticoagulation represents the cornerstone of treatment to reduce the risk of cardioembolic stroke in patients with atrial fibrillation (class of recommendation I, level of evidence A) (8). Of note, a large meta-analysis by Hart et al. (9) showed that well-managed warfarin is associated with a 64% relative reduction in the risk of ischemic stroke compared with placebo or no treatment. On the other hand, antiplatelet therapy, being associated with a non-significant 19% relative risk reduction, is not recommended for the prevention of cardioembolic stroke in atrial fibrillation (class of recommendation III) (8).

Table 1 summarizes available data on clinical outcome of elderly patients with atrial fibrillation treated with different antithrombotic strategies [antiplatelet therapy, vitamin K antagonists, direct oral anticoagulants (DOACs)] (10-21).

Vitamin K antagonists

Previous historical studies have compared outcomes of patients with atrial fibrillation aged ≥75 years treated with anticoagulant versus antiplatelet agents. In particular, the randomized Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) trial, performed in the setting of primary care, demonstrated that the use of warfarin (target INR 2-3) compared with aspirin 75 mg daily resulted in a significant 52% relative reduction of the composite primary endpoint including stroke, systemic embolism, and
intracranial hemorrhage (yearly risk, 1.8% vs 3.8%; relative risk, 0.48; 95% CI, 0.28–0.80; p=0.003) (10). The occurrence of major bleeding complications in the warfarin and aspirin arms was similar (yearly risk, 1.9% vs. 2.0%; p=0.90), but the study may have been underpowered for the evaluation of safety outcome measures and the high percentage of crossovers in the warfarin arm (approximately 30%) might have led to an underestimation of the bleeding risk. A post-hoc analysis of the Stroke Prevention in Atrial Fibrilla-

Table 1. Main descriptors and results of studies specifically evaluating clinical outcome with different antithrombotic strategies in elderly/very elderly patients with atrial fibrillation

| Studies                   | Type            | N. patients | Age             | Treatment comparison | Follow-up (yrs) | Primary outcome | Results on primary outcome | Major bleeding |
|--------------------------|-----------------|-------------|-----------------|----------------------|-----------------|-----------------|---------------------------|----------------|
| **Antithrombotic strategies** |                 |             |                 |                      |                 |                 |                           |                |
| VKA vs. antiPLT          |                 |             |                 |                      |                 |                 |                           |                |
| BAFTA (10)              | CRT             | 973         | ≥75 yrs         | Warfarin vs. aspirin 75 mg | 2.7             | Stroke/SEE/ICH | RR 0.48 (0.28–0.80) | 1.9% yr vs. 2.0% yr  |
| WASPO (11)              | CRT             | 75          | ≥80 yrs         | Warfarin vs. aspirin 300 mg | 1               | Death, thromboembolism, serious bleeding, | 25% vs. 44% | P<0.11 |
| Wolf et al. (12)        | Retrospective   | 561         | ≥85 yrs         | VKA (36% of patients) vs. antiPLT (49%) vs. none (15%) vs. aspirin 325 mg | 1               | Stroke | OR with VKA: 0.53 (0.22–1.28) | - |
| Perera et al. (13)      | Prospective     | 207         | ≥70 yrs         | Warfarin (40%) vs. antiPLT (47%) vs. none (13%) | 6 months        | Stroke | 3.6% vs. 8.2% vs. 30.8% | 22.9% vs. 22.4% vs. 7.7% |
| SPAF II (14)            | Post-hoc from CRT | 385       | ≥75 yrs         | Warfarin (INR 2.4-4.5) vs. aspirin 325 mg | 2.7             | Stroke | 3.6% yr vs. 4.8% yr | P=0.29 |
| Patti et al. (15)       | Retrospective   | 505         | ≥85 yrs         | VKA (76% of patients) vs. antiPLT (15%) vs. none (7%) | 12 months       | Stroke/TIA/SEE | OR of VKA vs. antiPLT or no therapy 0.64 (0.24–1.69) | VKA vs. antiPLT or no therapy 4.0% yr vs. 4.2% yr |
| **NOAC vs Antiplatelet** |                 |             |                 |                      |                 |                 |                           |                |
| AVERROES (16)           | Post-hoc from CRT | 2.284     | ≥75 yrs         | Apixaban 5 mg vs. aspirin 81-324 mg | 1.1             | Stroke/SEE | ≥75 yrs: HR 0.33 (0.19-0.54) | ≥75 yrs: 2.6% yr vs. 2.2% yr |
|                         |                 |             |                 |                      |                 |                 | 85 yrs: HR 0.14 (0.02-0.48) | P=0.50 |
|                         |                 |             |                 |                      |                 |                 | ≥85 yrs: 4.7% yr vs. 4.9% yr | P=0.93 |
| **NOAC vs VKA**         |                 |             |                 |                      |                 |                 |                           |                |
| RE-LY (17)              | Post-hoc from CRT | 7.258     | ≥75 yrs         | Dabigatran 110 mg/150 mg vs. warfarin | Median 2.0      | Stroke/SEE | D110 vs. V: HR 0.88 (0.66-1.17) | D110 4.4% yr / D150 5.1% yr vs. V 4.4% yr |
|                         |                 |             |                 |                      |                 |                 | D150 vs. V: HR 0.67 (0.49-0.90) | D110 vs. V: P=0.89 |
|                         |                 |             |                 |                      |                 |                 | HR 0.80 (0.63-1.02) | D150 vs. V: P=0.07 |
|                         |                 |             |                 |                      |                 |                 | 4.9% yr vs. 4.4% yr | HR 1.11 (0.92-1.34) |
| ROCKET AF (18)          | Post-hoc from CRT | 6.229     | ≥75 yrs         | Rivaroxaban 20 mg vs. warfarin | 2               | Stroke/SEE | HR 0.71 (0.53-0.95) | 3.3%yr vs. 5.2 %yr |
|                         |                 |             |                 |                      |                 |                 | P=0.05 |                |
| ARISTOTLE (19)          | Post-hoc from CRT | 5.678     | ≥75 yrs         | Apixaban 5 mg vs. warfarin | 1.8             | Stroke/SEE | HR 0.83 (0.66-1.04) | 4.0% yr vs. 4.8% yr |
|                         |                 |             |                 |                      |                 |                 | P=0.05 |                |
| ENGAGE AF (20)          | Post-hoc from CRT | 8.474     | ≥75 yrs         | Edoxaban 60 mg vs. warfarin | 2.8             | Stroke/SEE | HR 0.83 (0.66-1.04) | 4.0% yr vs. 4.8% yr |
|                         |                 |             |                 |                      |                 |                 | P=0.05 |                |
| Graham et al. (21)      | Real world registry | 29.208   | 75-84 yrs and ≥85 yrs | Dabigatran vs. warfarin | -               | Ischemic stroke | -75-84 yrs: 12.7 vs. 13.7 per 1000 patients/yr: P<0.05 | -75-84 yrs: 4.4 vs. 10.9 per 1000 patients/yr: P<0.05 |
|                         |                 |             |                 |                      |                 |                 | ≥85 yrs: 16.0 vs. 23.5 per 1000 patients/yr: P=0.05 for men, P=0.05 for women | ≥85 yrs: 4.8 vs. 13.5 per 1000 patients/yr: P=0.05 for men, P=0.05 for women |

AntiPLT, antiplatelet; CRT, controlled randomized trial; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; RR, risk reduction; SEE, systemic embolic event; VKA, vitamin K antagonist
compared with warfarin. In addition, apixaban and edoxaban were at least equal efficacy, with lower rates of intracranial hemorrhage. Phase III randomized clinical trials have shown that DOACs have greater efficacy and safety (26). This risk was limited to extracranial bleeding; in fact, the risk of intracranial bleeding was lower with both doses of dabigatran regardless of age. A recent substudy of the RELY trial suggested that the effects of dabigatran on extracranial major bleeding are age-dependent, thereby supporting the use of dabigatran 110 mg twice daily in patients aged ≥80 years (28).

An analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study demonstrated that patients aged ≥75 years had higher stroke/systemic embolism (2.57% vs 2.05%/100 patient-years; p=0.0068) and major bleeding (4.63% vs 2.74%/100 patient-years; p<0.0001) rates than younger patients (18). However, the efficacy and safety of rivaroxaban relative to warfarin did not differ with age. Overall, there was no difference in the major bleeding rates between rivaroxaban and warfarin, whereas older patients in the rivaroxaban group had higher occurrence of the combined endpoint including major or clinically relevant non-major bleeding (interaction, p=0.009); however, this was restricted to extracranial bleeding and driven primarily by gastrointestinal bleeding, which was more frequent among elderly patients in the rivaroxaban than in the warfarin arm.

An analysis of the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) study included 39% of patients aged 65–74 years, 18% aged 75–79 years, and 13% aged ≥80 years. The use of apixaban was associated with less major bleeding, less total bleeding, and less intracranial hemorrhage regardless of age (19). As the risk of stroke, death, and major bleeding increased significantly with age and apixaban consistently prevented these events irrespective of age, the absolute benefits of apixaban were greater in the older population.

In the Effective Antiocoagulation with factor Xa next GENERation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) trial, 8,474 of the 21,105 participants were aged ≥75 years, the largest number of elderly patients enrolled in a randomized controlled trial of DOAC to date (20). The incidence of stroke/systemic embolism in patients aged ≥75 years was similar with edoxaban and warfarin, whereas major bleeding complications were significantly reduced with the use of edoxaban. In particular, the occurrence of intracranial hemorrhage increased only gradually with increasing age in the edoxaban group, whereas the elevation in the rates of intracranial hemorrhage was steeper with warfarin as age increased. As a result, the absolute risk difference in both major and intracranial bleeding in older populations was

DOACs

Since 2010, the regulatory approval of four DOACs, dabigatran, rivaroxaban, apixaban, and edoxaban, has provided an alternative to the use of warfarin for the prevention of cardioembolic stroke. Phase III randomized clinical trials have shown that DOACs have at least equal efficacy, with lower rates of intracranial hemorrhage compared with warfarin. In addition, apixaban and edoxaban were found to reduce major bleeding events in the overall trial population compared with warfarin (27). Despite the availability of these safer drug alternatives to warfarin, oral anticoagulation use remains suboptimal in elderly patients with atrial fibrillation.

An analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) trial found that among patients with atrial fibrillation aged ≥75 years, lower dabigatran dose (110 mg twice daily) was associated with major bleeding rates similar to warfarin (4.43% vs 4.37%; p=0.89; p for interaction<0.001), whereas higher dose (150 mg twice daily) showed a greater risk of major bleeding (5.10% vs 4.37% in the warfarin arm; p=0.07; p for interaction<0.001) (17). This risk was limited to extracranial bleeding; in fact, the risk of intracranial bleeding was lower with both doses of dabigatran regardless of age. A recent analysis of the RELY trial suggested that the effects of dabigatran on extracranial major bleeding are age-dependent, thereby supporting the use of dabigatran 110 mg twice daily in patients aged ≥80 years (28).

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greater for edoxaban than for warfarin; further subgroup analyses revealed that these benefits of edoxaban relative to warfarin were maintained in the setting of patients aged ≥80 and ≥85 years (20) and were prominent in the subgroup of patients at a high risk of fall (29). Of note, in the ENGAGE AF-TIMI 48 trial, (20) the risk of major bleeding markedly increased with increase in age, highlighting the need for safe anticoagulation treatment strategies.

Real-world data assessing the safety of DOACs in elderly patients indicated that over a mean of 2.6 years, the incidence of major bleeding while taking DOACs was 1.37 per 100 person-years (30). An increased risk of bleeding was associated with a decline in glomerular filtration rate compared with baseline. Therefore, the authors conclude that DOACs appear to be a safe type of anticoagulation in elderly patients with atrial fibrillation, but emphasize the need for regular monitoring of renal function. In a meta-analysis of randomized controlled trials comparing DOACs (rivaroxaban, apixaban, and dabigatran; insufficient data was available for edoxaban) with conventional therapy in patients aged ≥75 years, DOACs did not cause excessive bleeding and were associated with equal or greater efficacy than conventional therapy (31). However, data from phase III clinical trials on atrial fibrillation overall indicate that apixaban and edoxaban in elderly patients are associated with the highest reduction of extracranial bleeding events versus warfarin. In the ENGAGE AF-TIMI 48 and ARISTOTLE trials, the absolute major bleeding rates were consistently lower with DOAC than with warfarin across all age groups. The major limitation of individual studies on DOACs use in elderly patients are that they represent subgroup analyses, although pre-specified, of larger trials and had relatively low number of patients (2,436 patients were aged ≥80 years). In addition, elderly patients in clinical trials are generally relatively healthy and adhere to medication; conversely, discontinuation of and non-adherence to DOACs in the older populations are commonly reported in real-world studies (32, 33).

However, while there is a need for more real-world data, available evidence till date suggests that DOACs are effective alternatives to warfarin in elderly patients with atrial fibrillation with a better safety profile.

Conclusion

Treatment of elderly patients affected by atrial fibrillation presents numerous challenges; the most important is balancing the benefits of antithrombotic strategies against the possible increased risk of a potentially serious bleeding event, such as recurrent gastrointestinal bleed or intracerebral hemorrhage. In the past, the fear of bleeding has led to underuse of anticoagulation in older populations, but the introduction of DOACs may offer a safer alternative to warfarin, particularly in this setting of patients.

Conflict of interest: None declared.

GP: speaker/consultant/advisory board for Amgen, Sanofi, Bayer, Boehringer-Ingelheim, BMS-Pfizer, Daiichi Sankyo, Astra Zeneca, Sigma-Tau, Malesci, PIAM and MSD.

IC: none

Peer-review: Internally peer-reviewed.

Authorship contributions: Concept – I.C., G.P.; Design – I.C., G.P.; Supervision – I.C., G.P.; Fundings – I.C., G.P.; Materials – I.C., G.P.; Data collection &/or processing – I.C., G.P.; Analysis &/or interpretation – I.C., G.P.; Literature search – I.C., G.P.; Writing – I.C., G.P.; Critical review – I.C., G.P.

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