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The safety and efficacy of non-vitamin K antagonist oral anticoagulants in atrial fibrillation in the elderly

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ABSTRACT

Atrial fibrillation (AF) is the most common arrhythmia and its prevalence increases with age. Age also increases the risk of thromboembolism related to AF. As a result, elderly patients are at increased risk of AF-related stroke compared to younger patients. Age, however, also increases the risk of bleeding, including that of intracranial haemorrhage, an important cause of death and disability. Elderly patients with AF are, therefore, often undertreated due to the fear of bleeding complications, although recent data suggest an even greater net clinical benefit for anticoagulation in general in the elderly, even the very elderly, compared with younger patients. The non-vitamin K antagonist oral anticoagulants (NOACs), such as dabigatran, rivaroxaban, apixaban and edoxaban, have become popular alternatives to vitamin K antagonists (VKAs) for anticoagulation in AF. The improved safety profile of NOACs may enable treatment of elderly patients that were previously untreated, further improving on this net clinical benefit. However, a number of factors, including renal impairment and multiple comorbidities, may elicit in elderly patients concerns with NOACs that are not seen in younger patients. Recent clinical data suggest that the use of NOACs offers a safer alternative to VKAs. However, on the basis of current evidence, it is not possible to simply recommend one NOAC over another in elderly adults. A personalised approach is recommended, accounting for individual patient factors.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice [1,2]. AF is associated with substantial mortality and morbidity, and is a significant risk factor for stroke, increasing the risk fivefold [3,4]. As a result, elderly patients (defined as patients having age ≥ 75 years) are at increased risk of stroke compared to younger patients. In the Framingham Study, 23.5% of strokes in individuals aged 80 and older were attributable to AF [5]. Of note, there is a progressive ageing of the population in developed countries, where the worldwide prevalence of AF is projected to increase significantly in the future [6,7], emphasising the need for effective treatment strategies in the elderly.

Advancing age, however, also increases the risk of both thromboembolic and haemorrhagic complications in AF patients; thus, the comparative evaluation of those two risks and the assessment of the net clinical benefit with different antithrombotic strategies appear crucial in elderly patients with AF. A 2009 analysis of the Atrial Fibrillation Investigators database found that, as patients with AF age, the relative efficacy of antiplatelet agents to prevent ischaemic stroke appears to decrease, whereas it does not change for oral anticoagulants (OACs) [8]. Data from the ENGAGE AF-TIMI 48 trial have shown a 2-fold and 3-fold increase in the risk of thromboembolic and major bleeding events, respectively, in AF patients with age ≥ 75 years versus those aged <65 years [9]. Evidence from a recent subanalysis of the real-world PREFER in AF Registry indicated that, irrespective of the antithrombotic strategies, among very elderly (age ≥ 85 years) patients with AF the rates of thromboembolic events were higher than in any strata of younger age and here by far outweighed the major bleeding risk (4.8 vs 4 per 100 patients/year) [10]. This supports the use of OACs even in very elderly patients with AF for the prevention of thromboembolic complications.

However, the use of OACs in older populations with AF is associated with relevant concerns, related to comorbidities, which enhance the ischaemic and bleeding risks, and related to propensity to fall, cognitive impairment, low adherence, reduced body weight and impairment of renal function, all making the management of OACs more difficult. Aim of this work is to perform a detailed literature research on the

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topic and summarise the available evidence on the safety and efficacy of oral anticoagulation in older populations with AF, especially in light of some concerns related to anticoagulant therapy in this setting. A specific attention is here devoted to the evidence on the comparison between vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs). Although no specific prospective studies on the topic have been performed, therapeutic suggestions may be derived from subgroup analyses of phase III randomised trials or small-sized observational registries. From available data we provide indications on the type of oral anticoagulant therapy warranting the greatest net clinical benefit in elderly/very elderly patients with AF.

2. Vitamin K antagonists for the prevention of thromboembolic events in elderly patients with atrial fibrillation and barriers for their use

In the overall elderly population, the benefits of VKAs are considered to outweigh the risks. In particular, the randomised BAFTA trial was conducted on AF patients aged ≥75 years. This trial showed that, compared to aspirin 75 mg once a day, the use of warfarin (target INR 2–3) was associated with a significant 52% relative risk reduction of the composite outcome measure, including stroke, systemic embolism or intracranial bleeding [11]. Subsequent real-world data explored clinical outcome in an even older population (i.e., very elderly patients with age ≥ 85 years) demonstrating that OAC utilization (VKAs or NOACs) led to a 36% risk reduction of thromboembolic events versus antiplatelet or no OAC treatment [10]; notably, OACs did not increase the risk of major bleeding compared to antiplatelet therapy. As a result, a gradient in the net clinical benefit of OACs according to age strata was present, with the oldest patients deriving the greatest advantage (Fig. 1) [10]. This finding was confirmed in a study-level meta-analysis on 13,559 patients with AF [12]. Despite the abovementioned strong evidence supporting the dramatically favourable benefit/risk ratio of OACs also in elderly patients, VKA therapy is underutilised in these patients, due to the perception of healthcare professionals that these therapies are not safe [13–16].

Specific limitations of VKAs, generally over-represented in the older popualtions, lead to their under-utilization in the real-world setting: a low time in therapeutic range (TTR), impaired compliance and drug–drug interactions [17–19]. However, the fear of bleeding, mainly intracranial and gastrointestinal (GI), is the reason most commonly cited by physicians for not using anticoagulation in elderly patients [13]; in addition, many elderly patients are not considered good candidates for VKAs, because of disability and risk of fall [17]. An analysis of records of ground-level falls in elderly patients with AF or atrial flutter found that the risk of eventual death with head injury exceeded annualised stroke risk for patients with CHA_2DS_2-VASc scores of 0 to 2 [20]. Thus,

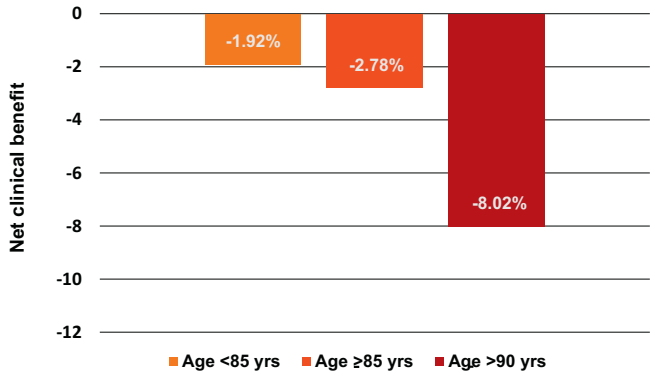

Fig. 1. Net clinical benefit, adjusted for the risk of subsequent death, of OACs vs no OACs according to different age groups [10]. The lower is the value, the higher the net benefit. OAC = Oral anticoagulant therapy.

the authors advised that patients with low CHA_2DS_2-VASc score at high risk for falls with identified risk factors should speak to their physicians regarding the risk/benefits of continued use of anticoagulation.

From the above, VKA utilization in the real world of elderly patients with AF remains suboptimal. In a recent cohort of individuals with ischaemic stroke surviving hospitalisation and AF ($n = 1405$, mean age 79), 44% of participants were not prescribed VKAs at discharge. By 1 year, 42.5% of those not receiving VKAs at discharge had died, compared with 19.1% of those receiving VKAs ($p < 0.001$) [21]; older age (odds ratio 8.96, 5.01–16.04) and disability (odds ratio 12.58, 5.82–27.21) were the strongest independent predictors of nonuse of OACs. Other concerns may exist around the use of OACs in older patient populations. These include a low body mass index (BMI) and the age-related decline in renal function [22]. The prevalence of chronic kidney disease (CKD) increases with age [23], and CKD is associated with increased risk of stroke and of bleeding [24].

Few studies have specifically and directly addressed the issue of anticoagulation in older populations. In a recent sub-analysis of the PREvention oF thromboembolic events-European Registry in Atrial Fibrillation (PREFER in AF) registry, factors significantly associated with OAC use were prior ischaemic stroke, heart failure and higher BMI, systolic blood pressure and diastolic blood pressure [25]. The majority of patients aged ≥80 years (approximately 83%) were receiving OAC therapy; this rate of OAC use is higher than previously reported, indicating a favourable trend in appropriate prescription patterns of doctors compared with previous surveys [21,26,27].

There is still, however, an urgent need for stroke prevention strategies alternative to VKAs to balance stroke prevention and bleeding risk in this the expanding patient elderly population. A wider use of NOACs promises to improve on these patterns in elderly patient populations.

3. Non-vitamin K antagonist oral anticoagulants in the elderly

3.1. Overall results with NOACs

Since 2010, the regulatory approval of NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) has provided an alternative to the use of warfarin for the prevention of stroke in AF deriving from phase III randomised trials [28–31]. Since there are no randomised studies directly comparing the NOACs, and each trial enrolled different baseline populations and used different methodologies, it is difficult to make comparisons between these four agents.

In a 2014 meta-analysis of randomised controlled trials comparing NOACs (rivaroxaban, apixaban, and dabigatran; insufficient data were available for edoxaban) with conventional therapy in patients aged ≥75 years with AF or venous thromboembolism, the authors found that NOACs did not cause excess bleeding and were associated with greater efficacy than conventional therapy. An analysis for individual NOACs showed that those agents were non-inferior or more effective than standard treatment [32]. These findings were confirmed in a subsequent meta-analysis of 11 randomised trials comparing NOACs and VKAs in elderly participants (aged ≥75 years) treated for acute venous thromboembolism or stroke prevention in AF [33], where the efficacy for each NOAC was similar or superior to VKAs. Regarding the safety, dabigatran 150 mg, but not the 110- mg dose, was associated with a non-significantly higher risk of major bleeding (odds ratio 1.18, 0.97–1.44), whereas dabigatran at both doses increased GI bleeding (150 mg: 1.78, 1.35–2.35; 110 mg: 1.40, 1.04–1.90) and decreased intracranial bleeding (150 mg: 0.43, 0.26–0.72; 110 mg: 0.36, 0.22–0.61). A significantly lower occurrence of major bleeding risk in comparison with VKAs was observed for apixaban (0.63, 0.51–0.77), edoxaban 60 mg (0.81, 0.67–0.98) and 30 mg (0.46, 0.38–0.57), whereas rivaroxaban showed similar risks.

A summary of studies investigating the efficacy and safety of individual NOACs in elderly populations is given below.