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Narrative Review

Oral anticoagulant therapy for older patients with atrial fibrillation: a review of current evidence

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ABSTRACT

Atrial fibrillation is more frequent in older patients, who have a higher risk of cardioembolic stroke and thromboembolism. Oral anticoagulant therapy is the standard of treatment for stroke prevention; however, under-prescription is still very common in older patients. The reasons underlying this phenomenon have not been systematically investigated, and true contraindications only partially account for it. An intimate skepticism on the real benefit-risk balance of oral anticoagulant therapy in the oldest patients seems to derive from the fact that most studies supporting it were conducted decades ago and included younger patients, with overall better functional and clinical status.

In this review we will focus on the main barriers to anticoagulant therapy prescription in older patients and summarize the available evidences on the efficacy and safety of vitamin K antagonists and direct oral anticoagulants in this population. The encouraging evidence of a higher net clinical benefit of direct oral anticoagulants compared with warfarin should hopefully widen the treatment options also for frail individuals, thereby allowing a greater number of patients to be treated according to current international guidelines.

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1. Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. Its incidence and prevalence increase with age, representing a significant burden for health services in western countries [1,2]. The most feared consequence of AF is cardio-embolic stroke, accounting for roughly one third of ischemic strokes in the elderly. Oral anticoagulant therapy (OAT), including Vitamin K Antagonists (VKAs) and Direct Oral Anticoagulants (DOACs), is currently recommended for patients with AF and high embolic risk [3]. However, OAT is widely underused, particularly in the oldest patients [4–7] who, in reason of their higher risk of stroke, might benefit more from it. Although the cut-off commonly adopted to define elderly patients is age > 65 years, this definition includes a large and heterogeneous group of patients and it is therefore of limited value in daily clinical practice. Indeed, a great proportion of AF patients in the real world is aged 75 years and over, and major uncertainties and concerns in OAT prescription have to do with this age group, which is underrepresented in randomized clinical trials (RCTs) and is characterized by varied health and functional status and high thromboembolic and bleeding risk.

In this paper we will review the prevalence and reasons of OAT under-prescription and the evidence supporting VKAs and DOACs use in older AF patients, which, to our knowledge, have not been systematically addressed yet. Scientific literature published in the last 20 years was retrieved by the authors (MB, YF and EB) from the MEDLINE database using the terms “atrial fibrillation” AND “antithrombotic therapy”, or “vitamin k antagonist”, or “direct oral anticoagulants”, or “aged” as keywords. Reviews, clinical trials and large observational studies in English published until February 2017 were thematically analyzed and included according to the relevance to the objective. Additional references were obtained from the reference list of the selected full-text manuscripts.

2. Underuse of oral anticoagulant therapy in older patients with atrial fibrillation

Despite international guidelines [3] strongly recommend OAT for patients with AF and high cardio-embolic risk according to the CHA₂DS₂-VASc (Congestive heart failure/left ventricular dysfunction, Hypertension, Aged ≥ 75 years, Diabetes Mellitus, Stroke/transient ischemic attack/systemic embolism, Vascular Disease, Aged 65–74 years, Sex Category) score, OAT under-prescription is still common in elderly patients in several clinical settings [4–11]. Although indication for OAT is irrespective of AF classification [3], several studies suggest

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that patients with paroxysmal AF are less commonly prescribed an OAT than patients with permanent AF [6,7,12,13], while it has not been clearly demonstrated that paroxysmal AF patients are at lower stroke risk [13].

Among the main reasons for anticoagulant underuse in older patients, advanced age itself, physician's perceived high risk of age-related and fall-related bleedings, and difficulties in monitoring VKAs-based therapies are the most frequently reported [4–7]. Furthermore, additional barriers to optimal use of anticoagulants include knowledge gaps about stroke risk extent and OAT benefit/harm balance, lack of recognition of expanded eligibility for OAT and DOACs in the elderly and in VKAs-unsuitable patients, and concerns about bleeding risk with novel DOACs [14].

2.1. Risk of bleeding

As stated previously, age-related high risk of bleeding is certainly a major reason for OAT under-prescription in older subjects. Ageing is associated with an increased bleeding risk in patients on OAT: the annual risk of major bleedings in VKAs-treated patients is estimated at 2–3%, while the rate of minor bleedings is reported to be around 10–15% [1, 4,15–17]. A threefold increase in major bleeding risk has been reported in patients on OAT aged ≥ 85 years as compared with subjects < 60 years [18,19]. However, there is evidence that well-conducted VKA therapy results in low bleeding rates also in older patients [16]. In a recent retrospective observational study in 798 VKA-naïve AF patients over 80 years of age, Granziera *et al.* observed an incidence of major bleedings of 3.4 per 100 patient-years, with a concomitant incidence of thromboembolic events of 1.3 per 100 patient-years [20].

Despite the age-associated increased bleeding risk, there is no recommendation that higher age-related bleeding risk should prompt physicians to avoid OAT, but a thorough evaluation and correction of bleeding predisposing factors are strongly advised in older AF patients. Unfortunately, currently recommended tools for bleeding risk evaluation, such as the HAS-BLED score, do not seem to be very accurate in elderly patients [20], and bleeding risk assessment tools focused on older patients should be implemented.

2.2. Falls

Predisposition to falls represents an important issue in starting OAT in older subjects with AF [21]. Gage *et al.* have shown that patients on VKAs at high risk of falls suffer intracranial hemorrhage more frequently [22], but this finding is controversial [23]. In a recent study, patients on OAT at high risk of falls did not have a significantly increased risk of major bleedings [24]. In a study on real-world patients with AF, prior history of falls was uncommon but independently associated with an increased risk of stroke/thromboembolism, bleeding and mortality, but not of hemorrhagic stroke during OAT [25]. A meta-analysis on OAT in elderly patients at high risk of falls concluded that, considering the median stroke risk, a patient on VKAs should fall nearly 300 times/year for the risk of bleeding to outweigh anticoagulation benefits [26]. According to these data, current guidelines do not require fall risk estimation in candidates to OAT [3].

2.3. Impact of contraindications

The weight of contraindications in OAT under-use among older patients has not received great attention. A recent study has demonstrated that contraindications are common but subjective, not only including prior bleeds, recent surgery and patient's refusal, but also high bleeding risk, frequent falls and frailty, which are not true contraindications to OAT [27]. In a prospective observational study on older medical in-patients with AF we observed a 16% prevalence of major contraindications to OAT [6], whereas in a sample of AF patients discharged from a geriatric ward, permanent or temporary contraindications to OAT were

observed in 24% of them [7]. Therefore, OAT under-use in older patients should not be routinely labeled as malpractice or therapeutic inertia, since in a relevant proportion of patients it might be accounted for by comorbidity-associated contraindications.

2.4. Dementia

A condition that commonly affects older people is dementia. Predictably, many older adults have both dementia and AF, but little is known about the best use of OAT for AF in these individuals along the natural history of dementia. In previous studies establishing the benefits of warfarin, patients with dementia were excluded or not specifically addressed in the analysis [28,29]. In a prospective study investigating the impact of dementia on the rate of antithrombotic (aspirin or warfarin) prescription in 297 individuals with previous stroke, even if 89% were prescribed an anticoagulant, those without dementia were more likely to be prescribed an anticoagulant (OR 2.57; 95% CI 1.04–6.30) [30]. In a frail nursing home population with AF, a high short-term mortality among patients with dementia and frequent falls has been observed, despite 85% of them was on warfarin [31]. Moreover, the natural history of individuals with AF taking warfarin who subsequently develop dementia is not well understood. A recent retrospective cohort study in 2572 Veterans ≥ 65 years (73% aged ≥ 75) investigated the effectiveness of warfarin in older patients with AF and dementia [32]. Patients who had been receiving warfarin for nonvalvular AF for at least 6 months and who were newly diagnosed with dementia were followed to assess the incidence of ischemic stroke, major bleedings and overall mortality. After diagnosis of dementia, only 16% of patients persisted on warfarin therapy. Using propensity score matching, the protective effect of continuing warfarin persisted in stroke prevention (HR 0.74; 95% CI 0.54–0.996, p 0.047) and mortality (HR 0.72; 95% CI 0.60–0.87, p < 0.001), with no statistically significant decrease in risk of major bleedings (HR 0.78; 95% CI 0.61–1.01, p 0.06), suggesting that warfarin discontinuation after a diagnosis of dementia is associated with a significant increase in stroke and mortality [32].

2.5. Geriatric syndromes and comprehensive geriatric assessment

Although each of the above-mentioned conditions may contribute to OAT under-use, other factors are relevant in the elderly. Guidelines recommend anticoagulation for AF merely on the basis of the individual's cardio-embolic risk, irrespective of global health status [3]. In real-world clinical practice, however, it is likely that several characteristics of geriatric patients (including physical and cognitive impairment, poor autonomy and reduced life-expectancy) may heavily influence the physician's decision. Noteworthy, geriatric syndromes such as frailty and functional dependence were not considered in most trials in AF patients both on VKAs and on DOACs. Frailty is a common syndrome in older subjects, and is associated with reduced survival, increased risk of hospitalization, and poor quality of life [33]. Frail older patients with AF are less likely to receive an appropriate anticoagulant prescription and, at the same time, are at greater risk of embolic stroke and death [18,34].

Few studies investigated OAT under-prescription through a comprehensive geriatric assessment. In a retrospective study on 1078 older patients with AF discharged from a geriatric ward, we observed that better functional status, home rather than long-term facility discharge, and higher hemoglobin levels were associated with OAT prescription [7]. In a prospective study on older patients with AF discharged from internal medicine and geriatric wards we observed that comorbidity was negatively associated with OAT prescription in patients without contraindications [6]. When physicians were specifically asked to explain the reasons for not prescribing OAT, advanced age, short life expectancy, difficult management of therapy, fear of bleeding and unfavorable benefit-risk balance were the most common reasons reported [6]. Pilotto *et al.* have recently reported significantly lower warfarin treatment rates

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