

# Risk of Major Bleeding in Very Elderly Patients with Atrial Fibrillation-A Continuous Dilemma in the Real World Clinics with Evidence and Perspectives

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## EDITORIAL

The increasing prevalence of Atrial Fibrillation (AF) in elderly brings a high burden of its related complications, among which ischemic stroke is the most disabling and with high mortality and morbidity. Stroke prevention is necessary in the management of patients with AF. Really, appropriate Thromboembolic (TE) prophylaxis essentially requires Oral Anticoagulants (OACs) [1]. However, OACs used for TE event prevention in AF could confer an increased risk of major bleeding. The fear that OACs would induce major bleeding events in very elderly is a prominent reason that could explain why a significant group of physicians/cardiologists are still reluctant to prescribe OACs to this expanding group of very elderly patients with AF. Here, we like to focus on this dilemma in a manner that might facilitate the decision making and argues to the need of large prospective studies in this regard.

## CURRENT RECOMMENDATIONS

It is well known that AF increases ischemic stroke risk by fivefold, this risk might be doubled in the very elderly group of AF patients with multiple high risk comorbidities. The current European Society of Cardiology (ESC) guidelines recommend OACs to male patients with AF and CHA<sub>2</sub>DS<sub>2</sub>VASc score  $\geq 2$  and to female patients with CHA<sub>2</sub>DS<sub>2</sub>VASc  $\geq 3$  (class I), and to consider OACs (class IIa) for those patients with intermediate risk (i.e., males with CHA<sub>2</sub>DS<sub>2</sub>VASc  $\geq 1$  and females with CHA<sub>2</sub>DS<sub>2</sub>VASc  $\geq 2$ ) [2]. Age is a strong independent risk factor of having ischemic stroke event in AF patients. By the age variable alone, all very elderly patients with AF  $\geq 75$  year fall in the high risk category according to CHA<sub>2</sub>DS<sub>2</sub>VASc which in turn could strongly justify the use of OACs in these patients. The current ESC guidelines prefer the non-vitamin K oral anticoagulants (NOACs) over Vitamin K Antagonists (VKAs) for TE prevention in patients with AF (class I) [2]. In elderly/very elderly patients with AF, ischemic and bleeding risks might track each other.

## The net clinical benefit of OACs in very elderly patients with AF-Short literature review

The understanding of the risks and benefits of OACs is of great value in the real world clinical practice. OACs were superior to antiplatelet drugs at reducing stroke events in very elderly patients with AF. In BAFTA study conducted on elderly patients  $\geq 75$  year demonstrated that VKAs with the International Normalized Ratios (INRs) in the therapeutic range of 2-3 were superior to aspirin 75 mg daily in reducing the primary endpoint of stroke, Intracranial Haemorrhage (ICH), or significant arterial embolism by 52%, with no difference in the risk of major haemorrhage between VKAs and aspirin [3]. In WASPO trial, dose-adjusted warfarin was significantly better tolerated with fewer adverse events than aspirin 300 mg in the very elderly AF patients  $>80$  year old [4]. Moreover, the efficacy of NOACs in the subgroups of very elderly AF patients  $\geq 75$  year has been confirmed in different recent sub-analyses of phase III original trials of the NOACs (i.e., RELY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials) [5-8]. Apart from the trial populations, OACs recently have showed a clear net clinical benefit in a large real world cohort of very elderly patients  $>90$  year old with AF [9]. In very elderly patients ischemic and bleeding risks track each other and the decision making regarding anticoagulation might be complex due to the several comorbidities, poly-pharmacotherapy, cognitive and renal impairment, etc. Anticoagulation agents used for TE event prevention in AF could potentially increase the risk of minor, major and fatal bleeding events. Really, the incidence of ICH and fatal bleeding with OACs ranges from 0.3% to 1.8% and from 0.5% to 1.0%, respectively [10]. This risk might be more prevalent in very elderly patients and necessitates a delicate balance and proper decision making.

## Performance of bleeding risk scores in very elderly patients with NVAf

Several bleeding risk scores like HAS-BLED and ORBIT have been validated and shown strong predictability of major bleeding in the different studies conducted on general cohorts of AF patients

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[11,12]. However, recent studies have shown the poor predictability of these risk scores in the group of very elderly patients with AF [13,14]. This might be due the complex nature of such group of patients with multiple comorbidities, poly-pharmacotherapy, cognitive deficits, etc., that make the estimation of bleeding risk in patients relies more on an individualized approach rather than just a numerical sum of the different risk factors. This could strongly reflect the need for further refinement of the current risk assessment tools in regard to very elderly patients.

### **Individual risk factors that predispose major bleeding event in very elderly patients with AF**

Although the current bleeding risk scores might not show the strong predictability of major bleeding event in the very elderly patients with AF [13,14]. However, several individual factors were found to be independent predictors of major bleeding in very elderly patients with AF in several studies. Individual and easy detectable risk factors like: Anaemia, thrombocytopenia, renal impairment, history of prior bleeding event, non-steroidal anti-inflammatory drugs and antiplatelet drug have recently shown strong association with major bleeding events in elderly patients with AF [13-15]. The physicians/cardiologists should be alert of these risk factors with a motivation to modify them and to ensure proper management of associated comorbidities.

### **NOACs have widened the available options for very elderly patients with AF**

In the last decade, the emergence of NOACs drugs had revolutionized the landscape of anticoagulation treatment. Compared to VKAs, the NOACs drugs have a predictable dose response, lower rate of intracranial bleeding, no need for periodic INR blood test and fewer food and drug interactions. The findings continue to come from real world studies and confirm the main findings of the randomized controlled trials of dabigatran, rivaroxaban, and apixaban [16]. Age group sub-analyses of phase III original randomized controlled trials of the NOACs in very elderly patients with AF  $\geq 75$  year old have shown: 1) Significant lower rate of both ischemic stroke and intracranial bleeding with dabigatran 150 mg. However, dabigatran 150 mg was associated with significant higher rate of gastrointestinal bleeding in very elderly patients with AF [5]. 2) Rivaroxaban 20 mg showed similar rate of ischemic stroke and ICH compared to VKAs (i.e., non-inferior to VKAs) in the very elderly patients with AF  $\geq 75$  year old [6]. 3) Apixaban was associated with less ischemic stroke, less major bleeding, less total bleeding, and less intracranial haemorrhage compared to VKAs in very elderly patients with AF  $\geq 75$  year old [7]. 4) Low dose dabigatran 110 mg was associated with significant lower rate of intracranial bleeding, was non inferior to VKAs at preventing ischemic stroke event and showed similar rate of gastrointestinal bleeding compared to VKAs in the very elderly patients with AF  $\geq 75$  year old [5]. Studies with direct head to head comparison between individual NOACs in the real world setting of very elderly patients with AF are scarce. In a recent study on a large real-world cohort of elderly patients  $\geq 65$  year old, apixaban was associated with significantly lower risk of ischemic stroke and major bleeding than rivaroxaban and warfarin, and showed a trend towards better outcomes versus dabigatran [17]. A Danish real world study on a large contemporary cohort of AF patients with median age 73 year old, demonstrated that apixaban had a lower adjusted major bleeding risk compared with rivaroxaban, dabigatran, and warfarin [18]. These evidences might support the extended net

clinical benefit of NOACs to the elderly and very elderly patients with AF and might favour the use of apixaban, low dose dabigatran 110 mg and edoxaban 30 mg in very elderly patients with AF and a relatively high bleeding risk.

### **Very elderly patients with AF and high bleeding risk- a real world challenge**

High bleeding risk (i.e., HAS-BLED  $\geq 3$ ) does not constitute an absolute contraindication to OACs in AF patients. Bleeding and ischemic risks track each other and even AF patients with high bleeding risk are still derive clear benefits of OACs. In patients with high bleeding risk, efforts should be directed to high flag these patients for more and closer follow up visits, to control modifiable bleeding risk factors (i.e., uncontrolled high blood pressure, non-steroidal anti-inflammatory drugs, antiplatelets, excess alcohol, etc.) and for proper management of associated comorbidities (i.e., anemia, renal impairment, peptic ulcer, ulcerative bowel disease, etc.). Frequent falls if present should be assessed properly with attempts to treat its potential causes if possible (i.e., orthostatic hypotension, drug induced falls, etc.). Precautions and alerts should be maintained to reduce drug- drug interaction in very elderly patients who are on poly-pharmacotherapy regime. In the very elderly patients with AF, values of complete blood counts-platelets, renal and liver functions should be registered at base line before initiating OACs and at follow up (i.e., every 6-12 months). Patients preference and expected life better to be included in the decision making process.

Very elderly patients are underrepresented in the major clinical trials regarding the best anticoagulation strategy for AF despite the fact of increasing proportion of the group of the very elderly patients each year. There is intense need for more prospective studies on large cohorts of elderly/very elderly patients in this regard.

### **Important points to remember when starting OACs for newly diagnosed elderly/very elderly patients with AF**

- Current ESC guidelines preferred NOACs over VKAs for patients with non valvular AF [2].
- Choose the OACs drug that suits better with the patient renal and liver functions status.
- Anticoagulation card that describes the anticoagulation therapy to be kept with the patient.
- The frequency of follow up visits should be scheduled carefully according to the patient general condition, level of ischemic/bleeding risk and associated comorbidities. At least one month after initiation of OACs and every three month later on.
- Ensure the patient proper adherence to the drug during each follow up visit.
- Physician's alert and vigilance should be maintained of the possible drug-drug interaction during the follow up visits.
- Values of complete blood counts-platelets, renal and liver functions should be registered at base line and during follow up (i.e., at least every 6-12 months).
- Attempts should be continued for proper management of associated comorbidities (e.g., anemia, renal impairment, gastrointestinal disease, etc.) during the follow up visits.
- Good control of blood pressure is needed: preferred  $<140/90$  mmHg. Frequent falls if present should be assessed and to treat

its potential causes if possible (i.e., orthostatic hypotension, drug induced falls, etc.).

- Dementia when it is noted, it should be assessed carefully according to the general conditions of the patient and its potential effects on proper drug adherence and risk of OACs.
- Patient preference and expected life better to be included in the decision making process.

## CONFLICTS OF INTEREST

The author does not have conflict of interest to declare.

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