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Efficacy and safety of oral anticoagulant therapy in frail patients with atrial fibrillation

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Abstract

Antithrombotic treatment of frail patients with AF presents various challenges. The fear of bleeding often leds to a large underuse of anticoagulant agents in these patients, although more recent data indicate that oral anticoagulation (especially with the newer, direct anticoagulants) is increasingly used. While there is a need for more real world data, available evidence suggests that non-vitamin K antagonist oral anticoagulants (NOACs) are an effective alternative to warfarin in frail patients with AF for preventing thromboembolic events, with a better safety profile. Logical considerations and evidence-base data related to the reduced bleeding risk (also including major bleeding and intracranial bleeding) of NOACs make these drugs the anticoagulant agents of choice in frail patients; however, in this setting an individualised approach should be taken, taking into consideration the risk of thromboembolic and bleeding events, other comorbidities and patient-related factors, rather than a generalised "one drug fits all" approach.

Introduction

There are various definitions of frailty, which essentially identifies a *multidimensional syndrome of poor physiological reserve leading to increased vulnerability to stressors, resulting in dependency, poor health outcomes, and/or mortality* [1].

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Advancing age, usually represents a major determinant of frailty, although it is not necessarily associated with frailty and frail patients may not be older. In fact, a combination of other functional factors is equally important, including activities of daily living, physical function, medical comorbidities and cognitive function, which are crucial in the frailty assessment [1]. The concomitance of advancing age and comorbidities represents the usual presentation of frail patients; however, the treating physician must take into account different aspects for an accurate evaluation of frailty, *i.e.* exhaustion, loss of appetite, weakness, walking difficulties, cognitive deterioration, physical activity and concomitant morbidities [1].

In the setting of patients with AF, older age and frailty increase the risk of both thromboembolic (stroke or systemic embolism) and haemorrhagic complications; thus, the comparative assessment of these two risks and the evaluation of the net clinical benefit with various antithrombotic treatments are relevant in elderly, frail patients with AF. A previous observational registry indicated that as patients with AF become older, the protection of antiplatelet drugs from ischemic stroke decreases, whereas it does not change for oral anticoagulants (OACs)[2]. A sub-analysis from the ENGAGE AF-TIMI 48 trial have demonstrated a 2-fold and 3-fold elevation in the occurrence of thromboembolic and major bleeding complications, respectively, in AF patients aged ≥75 years *versus* those with age <65 years [3]. Data from the prospective, real-world PREFER in AF Registry recently showed that, regardless of the antithrombotic therapies, among very elderly (age ≥85 years) patients with AF, the incidence of stroke or systemic embolism was higher compared to any strata of younger age and here by far outweighed the risk of major bleeding (4.8 *versus* 4 per 100 patients/year); importantly, the propensity to bleeding was not increased in patients aged ≥85 years compared to those with age 75-84 years [4]. This clearly supports the use of OACs even in very elderly patients with AF for preventing arrhythmia-related thromboembolic events.

However, regarding the utilization of OACs in frail populations with AF, various concerns should be considered, in particular co-morbidities, which may raise the ischemic and bleeding risks, but also propensity to falling, cognitive impairment, reduced compliance, low body weight and decline of renal function, all making the management of OACs more difficult.

Vitamin K antagonists for the prevention of thromboembolic events in frail patients with atrial fibrillation

Among elderly and frail patients, the reduction of stroke and thromboembolic events by vitamin K antagonists (VKAs) is overall considered to outweigh the risk of bleeding complications. Of note, in the randomized BAFTA trial, performed on AF patients with age ≥75 years, the use of warfarin (target INR 2.3) compared to aspirin 75 mg daily (INR 2-3) led to a significant 52% relative risk reduction of the composite endpoint, including stroke, systemic embolism or intracranial bleeding.

5 Recent real-world, observational data evaluated the clinical outcome in an even older population (*i.e.*, very elderly patients aged ≥85 years), showing that OACs, essentially warfarin, were associated with a 36% relative decrease of thromboembolic complications *versus* antiplatelet or no antithrombotic therapy;4 importantly, OAC utilization did not increase the risk of major bleeding compared to antiplatelet treatment. These findings were confirmed also in the subgroup of extremely frail patients aged ≥90 years. As a result, a gradient in the net clinical benefit of OACs according to age strata was observed, with the oldest patients getting the greatest advantage [4].

Despite the abovementioned evidence strongly supporting the favourable benefit/risk ratio of OACs in frail patients, VKA therapy is underutilised in this setting, given the phisycians' perception that such treatment is not safe [6]. In fact, the fear of bleeding is the reason most widely advanced by healthcare professionals for not prescribing anticoagulation in frail patients [6]. In addition, many frail patients are not considered good candidates for VKA therapy, because of its limitations, leading to drug underutilization: low time in therapeutic range (TTR), reduced compliance, drug-drug interactions and haemorrhagic risk, mainly for intracranial and gastro-intestinal (GI) bleeding [6]. The risk of falling on VKAs is also crucial in frail and elderly patients, as it also represents a prevalent reason for not prescribing these agents [6].

From the above, the real-world use of VKA in frail patients with AF remains suboptimal. In a cohort of 1,405 survivors of ischemic stroke with AF (mean age 79), the prevalence of no VKAs prescription at discharge was 44% [7]. The most frequent conditions associated with lack of VKAs use were the risk of falling (26.7%), poor prognosis (19.3%), previous bleeding (17.1%), the individual's or family's refusal (14.9%), advanced age (11.0%) and dementia (9.4%).7 By one year, 42.5% of patients not receiving VKAs at discharge had died, *versus* 19.1% of those receiving VKAs (p<0.001); 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 non-OACs utilization [7]. Other concerns limit the prescription of OACs in the frail patient populations. These comprise a low body mass index (BMI) and the age-related deterioration of renal function. In particular, the prevalence of chronic kidney disease (CKD) increases with age; observational data from 200,000 adults with CKD indicated that incident AF was associated with a 67% relative increase of subsequent end-stage renal disease [8]. Moreover, the presence of CKD raises the risk of future stroke, and patients with AF and CKD more frequently experience bleeding complications when treated with VKAs compared to those with AF without CKD [8].

Thus, in frail patients with AF there is still an urgent need for strategies able to prevent thromboembolic events alternative to VKAs to balance ischemic protection and bleeding risk; a wider use of non-vitamin K antagonist oral anticoagulants (NOACs) promises to improve the clinical outcome in this setting.

Non-vitamin K antagonist oral anticoagulants in frail patients

Since 2010, the regulatory approval of NOACs has provided an alternative to the use of VKAs for preventing thromboembolic events in AF. Phase III studies of NOACs, including dabigatran, rivaroxaban, apixaban and edoxaban, in AF patients have demonstrated that all these agents have at least equal efficacy, but lower incidence of intracranial bleeding compared to warfarin; moreover, apixaban and edoxaban significantly decreased the rates of major bleeding in the overall trial population *versus* warfarin. Of note, in the real-world setting the incidence of intracranial bleeding in frail patients receiving warfarin may be higher than that observed in randomised studies (>2% *versus* <1% per year); thus, the absolute reduction of intracranial bleeding with NOACs *versus* warfarin may be even higher in clinical practice and may translate into a relevant survival benefit in frail patients. Since no randomised trial has been performed to directly compare different NOACS and each phase III randomised trial included populations at different baseline risk profile, it is not possible to perform head-to-head comparisons between these four drugs.

In a meta-analysis of controlled, randomised trials comparing NOACs (rivaroxaban, apixaban, and dabigatran; insufficient data were available for edoxaban) with conventional therapy in patients with AF or venous thromboembolism and age ≥75 years, the use of NOACs was associated with greater efficacy than conventional therapy, without bleeding excess [9]. Regarding the individual NOACs, in a large retrospective cohort study of propensity score-matched elderly patients with AF, dabigatran 150 mg twice daily reduced the occurrence of ischemic stroke, intracranial bleeding and death, but increased major GI haemorrhages, as compared with warfarin [10]. The analysis of the net clinical benefit, including the avoidance of ischemic stroke, life-threatening bleeding and all-cause mortality, from the ROCKET-AF trial showed a higher benefit of rivaroxaban *versus* warfarin in elderly than in younger patients, as well as in those with history of previous stroke (a condition frequently and robustly contributing to frailty) than in those without stroke [11]. In the ARISTOTLE study, the absolute decrease of major bleeding with apixaban *versus* warfarin was more pronounced in elderly patients with HAS-BLED score ≥3 compared to those with HAS-BLED 0-1 (1.24% *versus* 0.80%), whereas the relative reduction of intracranial bleeding on apixaban was >2-fold higher in patients at high bleeding risk compared to those with low bleeding risk (78% *versus* 34%) [12]. A pre-specified analysis from the ENGAGE AF-TIMI 48 trial was focused on frail patients at risk of falling (n=900), *i.e.* those with prior history of falls, lower extremity weekness, poor balance, cognitive impairment, orthostatic hypotension, use of pshycotropic drugs, severe arthritis or dizziness [13]; this analysis demonstrated that patients at risk of falling had a 1.2% absolute increase of stroke rates compared to those not at risk, but in the former the elevation in the risk of major bleeding was even higher (2.4% increase) (Figure 1). Importantly, the benefit of edoxaban over warfarin in terms of absolute decrease of adverse events was greater in patients at increased risk of falling (Table 1), in whom edoxaban was also associated with a higher relative reduction in intracranial hemorrhage (hazard ratio 0.16, 0.04-0.71) and a 6-fold decrease in the risk of fatal bleeding.

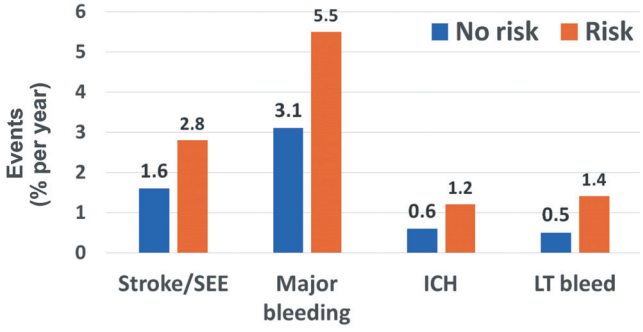

Figure 1. Incidence of thromboembolic and bleeding events in patients with or without risk of falling enrolled in the ENGAGE trial [13]. ICH, intracranial hemorrhage; LT, life-threatening; SEE, systemic embolic event.

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A major limitation of investigations evaluating individual NOACs among older and frailer patients is that they are subgroup analyses from randomized studies, although often pre-specified, including a low number of patients; in addition, frail patients in clinical trial populations generally have a higher compliance to therapy than frail patients in clinical practice. In fact, withdrawal of and non-adherence to NOACs in the real-world setting of elderly and frail patients is commonly reported, although in lower proportions than for VKA use [6]. An interesting finding of the prospective PREFER in AF registry was that difficulties with self-care were associated with non-use of OACs;4 this might reflect physicians' fear that patients would not be able to take medication adequately.

To date, few real-world data are availbale on clinical outcome in elderly and frail patients receiving NOACs. A recent retrospective study (n=142) assessed the safety of NOACs in elderly patients (age ≥75) [14]. Over a mean of 2.6 years, the incidence of major bleeding was low (1.37 per 100 person years) and this complication was associated with a decline in estimated creatinine clearance (eCrCl) compared to baseline. The authors conclude that NOACs appear to be effective and safe in elderly patients with AF, but emphasise the need for regular monitoring of renal function.

Special considerations regarding the use of non-vitamin K antagonist oral anticoagulants in frail patients with atrial fibrillation

In frail patients, various factors may affect their adherence to therapy. These comprise understanding of their condition, cognitive function, depression, social isolation and drug-related factors, such as adverse effects and regimen complexity [6]. Given their rapid onset and offset of action, the issue of adherence is particularly relevant with NOACs; while once-daily dosing might help with compliance, also individual patient factors should be taken into account. Furthermore, malnutrition and hypoalbuminemia may affect a relevant proportion of frail populations with AF. Rivaroxaban and apixaban have high binding to proteins (93% and 87%, respectively), whereas edoxaban and dabigatran a lower binding to proteins (50% and 35%, respectively). However, the impact of malnutrition on the bleeding risk in geriatric populations with NOACs needs to be specifically clarified. Malnutrition must be globally diagnosed and treated in this poluation, and the use of NOACs in frail patients should require a comprehensive geriatric evaluation to specifically assess co-morbidities, cognitive function, risk of falling, nutritional status, depression, polypharmacy and social environment.

Finally, a contemporary, relevant concern is the great proportion of patients who in the real world inappropriately are given a reduced dose of NOAC, beyond the specific reduction criteria fixed in phase III trials; the fear of bleeding is mainly responsible of such dose reduction, being therefore prevalent among frailer patients. Of note, recent data, adjusted for the paients' risk profile, have clearly indicated that an inappropriate dose reduction of NOACs is associated with lower protection from thromboembolic events [15].

Table 1. NNT to avoid one bleeding event using edoxaban instead of warfarin in patients with or without risk of falling enrolled in the ENGAGE trial [13].

	Patients at risk of falling	Patients not at risk of falling
Intracranial bleeding	55	250
Fatal bleeding	166	500
Life-threatening bleeding	71	250

Conclusions

Antithrombotic treatment of frail patients with AF presents various challenges. The fear of bleeding often leds to a large underuse of anticoagulant agents in these patients, although more recent data indicate that oral anticoagulation (especially with NOACs) is increasingly used. While there is a need for more real world data, available evidence suggests that NOACs are an effective alternative to warfarin in frail patients with AF for preventing thromboembolic events, with a better safety profile. Logical considerations and evidence-base data related to the reduced bleeding risk (also including major bleeding and intracranial bleeding) of NOACs make these drugs the anticoagulant agents of choice in frail patients; however, in this setting an individualised approach should be taken, taking into consideration the risk of thromboembolic and bleeding events, other comorbidities and patient-related factors, rather than a generalised "one drug fits all" approach.

References

1. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14:392-7.
2. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke 2009;40:1410-6.
3. Kato ET, Guigliano RP, Ruff CT, et al. Efficacy and safety of edoxaban for the management of elderly patients with atrial fibrillation: Engage AF-TIMI 48. J Am Heart Assoc 2016;5pii:e003432.
4. Patti G, Lucerna M, Pecen L, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: A sub-analysis from the PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation). J Am Heart Assoc 2017;6pii:e005657.
5. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493-503.
6. Perera V, Bajorek BV, Matthews S, Hilmer SN. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. Age Ageing 2009;38:156-62.
7. McGrath ER, Go AS, Chang Y, et al. Use of oral anticoagulant therapy in older adults with atrial fibrillation after acute ischemic stroke. J Am Geriatr Soc 2017;65:241-8.
8. Bansal N, Fan D, Hsu CY, et al. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation 2013;127:569-74.
9. Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. J Am Geriatr Soc 2014;62:857-64.
10. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 2015;131:157-64.
11. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K Antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). Circulation 2014;130:138-46.

12. Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J 2014;35:1864-72.
13. Steffel J, Giugliano RP, Braunwald E, et al. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF-TIMI 48 Analysis. J Am Coll Cardiol 2016;68:1169-78.
14. Khan F, Huang H, Datta YH. Direct oral anticoagulant use and the incidence of bleeding in the very elderly with atrial fibrillation. J Thromb Thrombolysis 2016;42:573-8.
15. Nielsen PB, Skjøth F, Søgaard M, et al. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ 2017;10;356:j510.