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Overview of oral antithrombotic treatment in elderly patients with atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is an age-related arrhythmia, particularly affecting elderly patients. The ultimate goals in the treatment of AF are to improve prognosis and quality of life. Anticoagulants are effective for stroke prevention in AF patients, however, managing anticoagulation in elderly patients is especially challenging; requiring a comprehensive assessment of the patient and deep understanding of available therapies and doses to maximize the net benefit. This review summarizes available evidence on the efficacy and safety of anticoagulation therapy, and provides contemporary updates on the management of elderly patients with AF.

1. Introduction

Atrial Fibrillation (AF) is often an age-related manifestation of underlying cardiac and non-cardiac conditions. A variety of pathophysiological changes common in the elderly, including structural remodeling of left atrium, autonomic neural dysregulation, ion channel dysfunction, and reduced LV diastolic filling contribute to the development of AF (Andrade et al., 2014). As such, the prevalence of AF is increasing worldwide, largely due to the aging of society (Chugh et al., 2014; Heeringa et al., 2006; Lloyd-Jones et al., 2004), and currently affects approximately 33.5 million people globally (Chugh et al., 2014).

Older individuals with AF are at a higher risk of stroke compared to younger individuals, in part related to other comorbidities. This is reflected in the CHA_2DS_2-VASc score, which assigns 2 points to patients aged ≥75 years. (Lip et al., 2010).

Despite the efficacy of Vitamin K Antagonists (VKAs) to prevent stroke in AF patients with at least one risk factor for stroke, previous studies have demonstrated that only approximately 50% of elderly AF patients receive oral anticoagulant therapy (OAC). When they do, they often receive a reduced dose (Akao et al., 2014). Predominantly this is due to the fear of bleeding complications by patients or their physicians even though under-treatment with lower target INR with VKA and reduced dose of non-vitamin K antagonsist oral anticoagulant (NOAC) are less effective to reduce stroke in elderly AF patients (Gage et al., 2000; Nieuwlaat et al., 2007).

One of the keys to managing elderly patients with AF is assessing the risk-benefit balance in each individual to simultaneously minimize the risk of stroke and serious bleeding. However, in an era of increasing life expectancy, clinical decision-making for AF patients at risk of stroke has become an even greater clinical challenge.

To tailor stroke prevention therapy, it is important to understand the effect of age on bleeding and ischemic risk in patients who are not treated with an anticoagulant. The limited available evidence demonstrates that as age increases, the risk of stroke increases more rapidly than the risk of bleeding (Fig. 1, left 2 panels) (Kodani et al., 2015; Patti et al., 2017), although little data exist in unanticoagulated younger patients. Since warfarin has been shown to reduce risk of stroke by approximately 64% compared to placebo (Hart et al., 2007), it would be unethical to randomize patients who are eligible for an anticoagulant to placebo, With VKA, the risk of bleeding increases more rapidly with aging, while ischemic stroke is reduced across the age ranges (Fig. 1, right panel) (Kato et al., 2016). As a result, the bleeding risk starts to outweigh ischemic stroke at around age of 55, and this trend increases steeply at around the age of 75. A similar pattern is observed with NOACs.

In this paper, we aim to review the available evidence and discuss some of the specific concerns relevant to anticoagulant treatment in elderly patients with AF.

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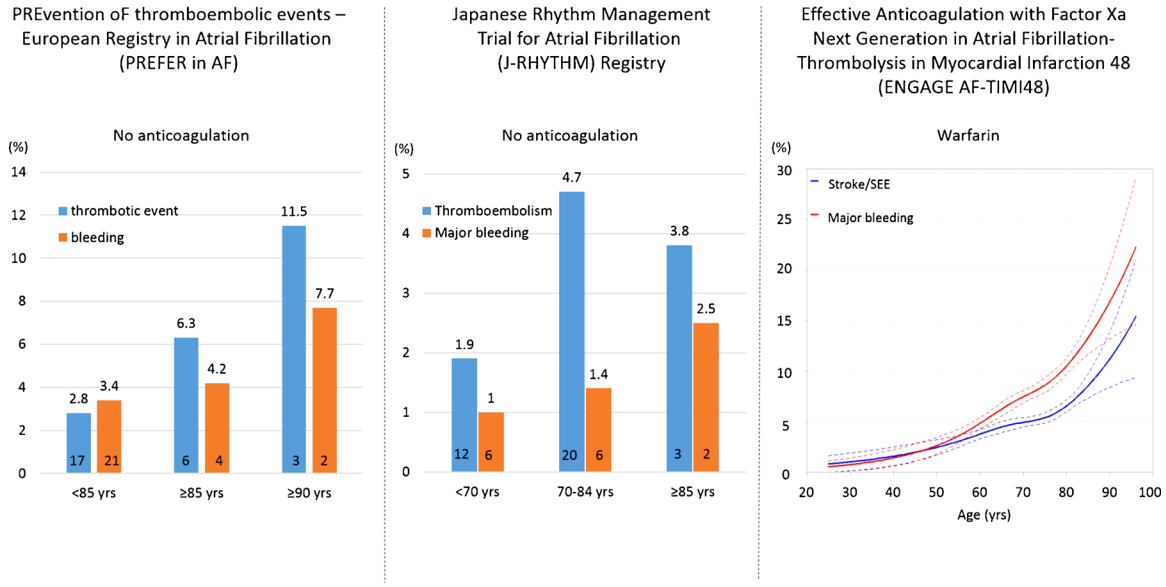

Fig. 1. The Effect of Age on Ischemic and Bleeding Risks (Kato et al., 2016; Kodani et al., 2015; Patti et al., 2017). The numbers in the bars indicate the number of patients with events.
The ischemic and bleeding risks both increase with increasing age regardless of anticoagulant use, however, without anticoagulants, the thrombotic risk is higher in the older age group. With VKA, the bleeding risk increases more rapidly with aging, while risk for ischemic stroke is reduced across the age ranges.

2. Use of anticoagulant therapy for prevention of stroke

2.1. Vitamin K antagonists (VKAs)

For over half a century, VKA therapy (e.g. warfarin) has been the gold standard in preventing AF related thromboembolism. Oral anticoagulant therapy with VKAs reduces the risk of stroke by ~64% compared to placebo and by ~39% compared to antiplatelet therapy (Hart et al., 2007). These benefits are preserved in elderly patients. The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study (Mant et al., 2007) demonstrated that warfarin was superior to aspirin in reducing thromboembolic events in elderly patients (age ≥75 years).

One of the difficulties with VKA therapy is its narrow therapeutic range. The risk of bleeding doubles with an INR > 3.0 and exponentially increases with INR > 4.5 compared to the recommended therapeutic range of 2.0–3.0 (Cannegieter et al., 1995; Fuster et al., 2011; Hylek et al., 2003). Moreover, the risk of stroke decreases significantly when the time in therapeutic range (TTR) is > 65% (Hellyer et al., 2017; Liu et al., 2017). A lower TTR is associated with a higher risk of stroke and bleeding, but more so for bleeding (Morgan et al., 2009). This represents a formidable challenge for clinicians since VKAs also have numerous drug-drug, and drug-food interactions, variable response to patient genotypes and variable intra- and inter-patient dose responses. Therefore, VKA-treated patients require frequent monitoring, dose adjustment, and close attention to changes in diet and concomitant therapies. Indeed, even in very well controlled studies, the reported TTR is only ~65%, with lower rates observed in community-based registries (Akao et al., 2014; Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011b; Hori et al., 2012; Patel et al., 2011).

Maintaining adequate INR levels in elderly patients is even more challenging as older patients generally have multiple comorbidities, are prescribed several medications, and are prone to frequent changes of concomitant therapies due to acute medical conditions (LaMori et al., 2012; Wang et al., 2016). In addition, declining physical function limits their ability to comply with clinic visits, they are more likely to undergo invasive procedures to manage their comorbidities (e.g., malignancy, orthopedic), and the slow onset and offset of VKA exposes elderly patients more frequently to potential adverse thromboembolic or haemorrhagic events.

Although VKA therapy is efficacious in preventing ischaemic events, the elderly are, by nature, already at increased risk of bleeding. Thus, maintaining a therapeutic INR to avoid additional haemorrhagic risk is essential in the elderly (Gurwitz et al., 1992). Consequently, a treatment with a more favorable benefit-risk ratio would be desirable, particularly in elderly patients.

2.2. Non-Vitamin K antagonist oral anticoagulants (NOACs)

Unlike VKAs, which inhibit the vitamin K dependent synthesis of clotting factors, the NOACs directly and specifically bind to the active site of either thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban) to inhibit coagulation. Due to fewer drug and food interactions and a rapid onset of action, the anticoagulant effects are more predictable with NOACs compared to VKAs, allowing them to be administered in fixed doses without routine anticoagulation monitoring (Ruff et al., 2014).

In the past decade four NOACs (apixaban, dabigatran, edoxaban and rivaroxaban), were evaluated in large Phase III trials as alternatives to VKAs in patients with AF at risk of stroke (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011b; Hori et al., 2012; Patel et al., 2011). In these trials, the NOACs proved to be non-inferior, if not superior, to warfarin for the prevention of stroke/systemic embolic events (SEE), and for reducing bleeding. However, the results in elderly patients varied according to the specific NOAC. Given the heterogeneity of the trials, and the lack of head-to-head trials between NOACs, it is not appropriate to directly compare results across the trials. However, some indirect observations vs. warfarin (which was the common comparator in the trials) related to age may be useful and raise interesting questions for future studies.

2.2.1. Efficacy outcomes in the elderly

The primary efficacy outcome for all four NOAC trials was stroke or SEE. Two fixed doses of dabigatran were evaluated in the Randomized Evaluation of Long-term Anticoagulation TherapY (RE-LY) trial. The mean $CHADS_2$ score among elderly patients was 3.7 (Halperin et al., 2014). The rate of stroke/SEE in the elderly (≥75 years) compared to warfarin was significantly reduced with dabigatran 150 mg BID (RR 0.67 [0.49, 0.90]) vs. warfarin and comparable with dabigatran 110 mg BID vs. warfarin (RR 0.76 [0.55, 1.04]). (Of note, the median TTR in the elderly population was not provided.) (Eikelboom et al., 2011).

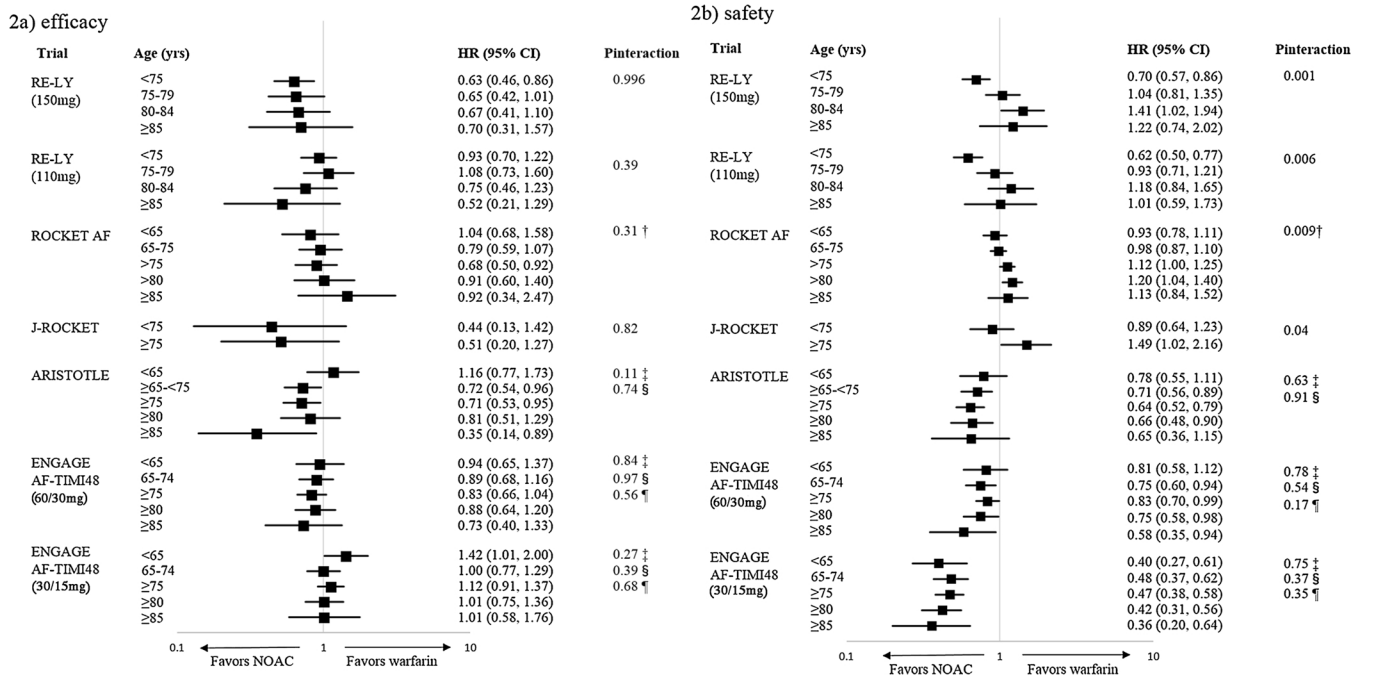

Fig. 2. Primary Efficacy and Safety Endpoints in Each AF NOAC Trials by Age Groups (Eikelboom et al., 2011; Halperin et al., 2014; Halvorsen et al., 2014; Hori et al., 2014; Kato et al., 2016; Lauw et al., 2017) (Product monograph, FDA and EMA product reviews).

a) Efficacy

b) Safety

There was a significant treatment effect modification due to age with dabigatran and rivaroxaban, in which an increased risk of bleeding with these two NOACS was observed in elderly patients, but not younger patients. (Halperin et al., 2014; Hori et al., 2014; Lauw et al., 2017). There was no interaction with age for apixaban and edoxaban on the risk of bleeding relative to warfarin. Bleeding was significantly decreased with apixaban and edoxaban regardless of age(Halvorsen et al., 2014; Kato et al., 2016). Data in very elderly patients were not available in J-ROCKET. $P_{interaction}$ represents interaction between age and treatment. †indicates $P_{interaction}$ between age (age cut point at 75 years) and treatment, ‡indicates $P_{interaction}$ between age (age cut point at < 65 years, 65–74 years, and ≥75 years) and treatment,§indicates $P_{interaction}$ between age (age cut point at 80 years), and ¶indicates $P_{interaction}$ between age (age cut point at 85 years). Otherwise, $P_{interaction}$ represents interaction between age and treatment at the shown age cut points.

Two large randomized trials were conducted with rivaroxaban compared to warfarin in patient with AF. The larger trial was 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), which tested 20 mg once daily of rivaroxaban vs. warfarin (Patel et al., 2011). The J-ROCKET AF trial, a separate phase III trial in Japan, was conducted as a consequence of pharmacokinetic modeling data that had demonstrated a 25–30% higher concentration of rivaroxaban in healthy Japanese patients compared with non-Japanese patients. As such, the dose of rivaroxaban was 15 mg daily in J-ROCKET AF. Additionally, a target INR for patients aged ≥70 years was set between 1.6–2.6 to abide by Japanese guideline recommendations (Hori et al., 2012). The mean $CHADS_2$ score among the elderly in ROCKET-AF was 3.7 (data not provided for the J-ROCKET trial). In the elderly, rivaroxaban was similar to warfarin (median TTR 56.9%) in preventing stroke/SEE in both ROCKET-AF (HR 0.95 [0.76, 1.19]), and J-ROCKET AF (HR 0.51 [0.20, 1.27]) (Halperin et al., 2014; Hori et al., 2014).

In the Apixaban for Reduction in STroke and Other ThromboemboLic Events in Atrial Fibrillation (ARISTOTLE) trial, the mean $CHADS_2$ score in the elderly population was 2.7. In this population, 5 mg apixaban BID significantly reduced stroke/SEE compared to warfarin (median TTR 67.2%) (HR 0.71 [0.53, 0.95]) (Halvorsen et al., 2014).

Edoxaban was studied in the ENGAGE AF- TIMI 48 trial. The mean $CHADS_2$ score in the elderly population was 3.2. Among patients ≥75 years of age, both the higher (60/30 mg once daily) and lower dose edoxaban regimens (30/15 mg once daily) had similar effects compared to well-managed warfarin (median TTR 69.6%) in the prevention of stroke or SEE (HR 0.83 [0.67, 1.04] for 60/30 mg regimen, and 1.12 [0.91, 1.37] for 30/15 mg regimen)(Giugliano et al., 2013; Kato et al., 2016).

2.2.2. *Safety outcomes in elderly patients*

In the elderly population of the RE-LY trial, the relative reduction (RR) in the primary safety endpoint (major bleeding) was comparable with dabigatran 150 mg BID (RR 1.18 [0.98, 1.42]) and with dabigatran 110 mg BID (RR 1.01 [0.83, 1.23]) vs. warfarin (Eikelboom et al., 2011).

The ROCKET AF and J-ROCKET trials were the only trials that used the composite of major bleeding and clinically relevant non-major (CRNM) bleeding as the primary safety endpoint. In elderly patients, the rivaroxaban groups had significantly increased rates of the primary safety endpoint as compared to warfarin in both ROCKET AF (HR 1.13 [1.02, 1.25]) and J-ROCKET AF (HR 1.49 [1.02, 2.16]) (Halperin et al., 2014; Hori et al., 2014). When limited to major bleeding alone, the increase was not statistically significant in either ROCKET AF (HR 1.11 [0.92–1.34]) or J-ROCKET AF (HR 1.51 [0.68–3.32]), although the HRs were nearly identical to the primary safety endpoint of major or CRNM bleeding.

Apixaban, in the ARISTOTLE trial, significantly reduced major bleeding compared to warfarin in the elderly population (HR 0.64 [0.52, 0.79]) (Halvorsen et al., 2014). Similarly, both edoxaban regimens in the ENGAGE AF-TIMI 48 trial significantly reduced major bleeding compared to warfarin (HR 0.83 [0.70, 0.99] for 60/30 mg regimen, and HR 0.47 [0.38, 0.58] for 30/15 mg regimen)(Giugliano et al., 2013; Kato et al., 2016).

In these trials, dabigatran, apixaban, and edoxaban significantly reduced the risk of intracranial haemorrhage (ICH) compared to warfarin in the elderly, while rivaroxaban had a similar rate of ICH

compared to warfarin (dabigatran 150 mg BID (RR 0.42 [0.29-0.62]), dabigatran 110 mg BID (RR 0.30 [0.19-0.45], apixaban (HR 0.34 [0.20, 0.57]), edoxaban 60/30 mg regimen (HR 0.40 [0.26, 0.62]), edoxaban 30/15 mg regimen (HR 0.30 [0.19, 0.49]), and rivaroxaban (HR 0.80 [0.50, 1.28]) in ROCKET AF)(Eikelboom et al., 2011; Halperin et al., 2014; Halvorsen et al., 2014; Kato et al., 2016; Lauw et al., 2017). Data on ICH in the elderly were not provided for J-ROCKET (44).

2.2.3. Interaction of age, treatment and outcomes

The absolute rates of bleeding and stroke increase with advancing age, a finding that was observed in each of the trials discussed in the previous section. In the individual subgroup analyses of elderly patients, there were no statistically significant interactions between age and treatment benefit for the primary efficacy endpoint (stroke/SEE) in any of the NOAC trials (Eikelboom et al., 2011; Halperin et al., 2014; Halvorsen et al., 2014; Hori et al., 2014; Kato et al., 2016; Lauw et al., 2017).

Similarly, there were no statistically significant interactions between age, treatment effect and major bleeding with edoxaban and apixaban in the ENGAGE AF-TIMI 48 and ARISTOTLE trial, respectively (Halvorsen et al., 2014; Kato et al., 2016). However, significant interactions were noted between age and treatment with respect to the primary safety endpoint with dabigatran in RE-LY and with rivaroxaban in both the ROCKET-AF and J ROCKET-AF trials (Fig. 2). In RE-LY, both doses of dabigatran showed significantly lower relative risks of major bleeding compared with warfarin in younger patients only. This reduction in major bleeding observed in younger patients was lost in patients aged ≥75 years ($P_{interaction} < 0.001$ and 0.006 for the 150 and 110 mg doses, respectively) (Eikelboom et al., 2011; Lauw et al., 2017). A subpopulation treatment effect pattern plot (STEPP) demonstrated a particularly steep increase in major bleeding rates with dabigatran in patients above the age of 72 years (Lauw et al., 2017). The increase in major bleeding was mainly driven by extracranial major bleeding (Eikelboom et al., 2011; Lauw et al., 2017). Likewise, in ROCKET AF and J-ROCKET AF, there were significant interactions between age and treatment with rivaroxaban for the end point of major or CRNM bleeding, with higher risks of bleeding observed with rivaroxaban (vs. warfarin) in the elderly population as compared to the relative risks in younger patients ($P_{interaction}$ between age and treatment 0.009 for ROCKET AF and 0.04 for J-ROCKET AF) (Fig. 2) (Halperin et al., 2014; Hori et al., 2014).

The varying pharmacologic properties of the four NOACs, differences in dose reduction strategies, and the diversity of trial characteristics are factors that contribute to the heterogeneous results. Summaries of pharmacological and patient characteristics for individual phase III randomized trials are shown in Tables 1 and 2 (Connolly et al., 2009; Eikelboom et al., 2011; Giugliano et al., 2013; Granger et al., 2011b; Halperin et al., 2014; Halvorsen et al., 2014; Hori et al., 2014, 2012; Kato et al., 2016; Lauw et al., 2017; Patel et al., 2011; Wallentin et al., 2010). The half-life is approximately 12 h for all NOACS; dabigatran has the lowest bioavailability and highest renal clearance. Note that the absorption of rivaroxaban is dependent upon feeding (higher if taken with a meal), while there are no significant food effects for the other NOACs. Rivaroxaban and apixaban are both metabolized by the cytochrome P-450 enzyme, and concomitant use of potent cytochrome P-450 inhibitors may result in supratherapeutic levels. Meanwhile, edoxaban and dabigatran have little to no interaction with the cytochrome P-450 system. Dabigatran and apixaban are taken twice daily whereas edoxaban and rivaroxaban are once daily agents.

The trial populations also differed substantially (Ruff et al., 2014). For example, patients in the ARISTOTLE trials on average were younger, with lower $CHADS_2$ score had shorter follow-up duration, and were more frequently lost to follow-up (Granger et al., 2011a). The ROCKET-AF trial population had a higher risk of stroke (higher $CHADS_2$ score and rate of prior TIA or stroke) but a lower TTR (median 58%) (Patel et al., 2011). The RE-LY and the J-ROCKET AF used an open-label trial design (Connolly et al., 2009; Hori et al., 2014). The ENGAGE AF-TIMI 48 trial had the largest number of elderly participants, the longest follow up period and the highest TTR (median 68.4%) (Connolly et al., 2009; Giugliano et al., 2013; Patel et al., 2011). Of note, trials usually include healthier elderly patients than are seen in clinical practice. Thus, careful interpretation is warranted when applying trial data to individual patients in clinical practice.

While there may be many explanations for the heterogeneity of these subgroup results, one major driver is likely to be the difference in dose reduction strategy for the NOACs. As shown in Table 3, dabigatran was the only NOAC without dose adjustment in a phase III randomized trial. In ROCKET AF, and J-ROCKET AF, renal impairment (creatinine clearance ≤50 ml/min) was the only criterion for dose reduction of rivaroxaban, however, the dose reduction was relatively modest (by 25–33% or 5 mg). In the ARISTOTLE and ENGAGE AF-TIMI 48 trials, three dose reduction criteria were used; renal dysfunction (serum creatinine ≥1.5 mg/dL), age ≥80 years, and bodyweight ≤60 kg for apixaban and renal dysfunction (creatinine clearance ≤50 ml/min), body weight ≤60 kg and the concomitant use of potent P-glycoprotein inhibitors for edoxaban. Patients needed to have ≥2 dose reduction criteria in ARISTOTLE to require dose-reduction of apixaban, whereas the edoxaban dose was reduced if a patient fulfilled any one of the dose reduction criteria in ENGAGE AF-TIMI 48. Both apixaban and edoxaban doses were halved when dose reduction criteria were met, which was a more aggressive approach than was used in the rivaroxaban trials.

In previous studies, age and renal dysfunction, two highly correlated factors, were found to be strongly associated with a higher plasma concentration of NOACs. These were the key clinical factors for bleeding in RE-LY and ENGAGE AF-TIMI 48 (Bohula et al., 2016; Eikelboom et al., 2011; Ruff et al., 2015). Aging is associated with decreased in renal mass, renal cortex, and the number of functioning glomeruli. Aging is also associated with an increase in glomerular sclerosis. Each of these factors leads to a deterioration in renal function. These changes are often a result of comorbidities including hypertension, diabetes and heart failure, which are more frequent in elderly patients (Hoang et al., 2003). Of note, 80–85% of total clearance of dabigatran is via the kidneys, however, no dose adjustment for renal function was implemented in RE-LY. Hence, fluctuations in creatinine clearance (CrCl) can increase dabigatran plasma drug concentration, thereby increasing the predisposition to bleeding, especially in elderly patients (Stangier et al., 2010). Since all of the NOACs are partially renally cleared, an evidence-based dose reduction plan may have played a decisive role in the heterogeneous bleeding results of the five NOAC trials.

Currently, guidelines on NOAC use in patients with chronic kidney disease differ by country (Table 2), and not all of the recommendations are based on clinical trial data. Results of ongoing studies are eagerly awaited to inform future recommendations.

2.3. Registry data

One of the limitations of clinical trial data relates to their generalizability. Registries and community based data include more diverse patients and treatment strategies, and are great resources to fill in knowledge gaps. However, a careful interpretation is warranted when comparing results from registries with those of randomized clinical trials. For example, in the Loire Valley AF Project, the risk of major bleeding did not increase with increasing age (Lip et al., 2015). However, this study included patients who were not treated with an anticoagulant. Similarly, in the PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation (PREFER in AF), the risk of stroke increased more than the risk of bleeding in the overall elderly population, however, when restricted to anticoagulated elderly patients, the risk of bleeding was higher(Patti et al., 2017). This latter finding is in line with the NOAC RCTs. Furthermore, there is a difference in dabigatran dosing used in trial vs. clinical practice. In all NOAC

Table 1
Comparison of Phase III Trials in AF Patients (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011b; Hori et al., 2012; Patel et al., 2011).

NOACs	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	direct thrombin inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor	direct factor Xa inhibitor
Oral bioavailability	6.5%	80%	50%	62%
Frequency	twice-daily	once-daily	twice-daily	once-daily
Half life, hours	12–17	5–9	9–14	10–14
Renal excretion	80%	33%	25%	~50%
Antidote/reversal agent	Idarucizumab	Adnexanet alpha or 4-factor PCC	Adnexanet alpha or 4-factor PCC	4-factor PCC
Trial	RE-LY	ROCKET-AF J-ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI48
Number of patients	18,113	14,264 1,278 (J)	18,201	21,105
Primary efficacy endpoint	Stroke or SEE	Stroke or SEE	Stroke or SEE	Stroke or SEE
Primary safety endpoint	ISTH major bleeding	ISTH major bleeding clinically relevant bleeding	ISTH major bleeding	ISTH major bleeding
Mean (median) age, yr	72	73 /71 (J)	70	72
Mean CHADS2	2.2	3.5/ 3.3 (J)	2.1	2.8
Median TTR	66	58/65 (J)	66	68
Median follow-up, yr	2	1.9 / NA	1.8	2.8
Lost to follow up, n (%)	20 (0.11)	32 (0.22)/NA (J)	50 (0.27)	1 (0.004)

NOACs: non-Vitamin K antagonist oral anticoagulants, TTR: time in therapeutic range, (J): J-ROCKET AF, SEE: systemic embolic events, ISTH: International Society on Thrombosis and Haemostasis.
NOAC trials included different populations with different $CHADS_2$ score criteria. In RE-LY and ARISTOTLE, patients with $CHADS_2$ score ≥ 1 were included whereas $CHADS_2$ score ≥ 2 was the enrollment criteria in ROCKET AF and ENGAGE AF- TIMI 48.

trials, due to ethical considerations, the comparison was not placebo but well-controlled warfarin. However, in many of the registries, TTR data are not provided, and change in medications are unknown. Moreover, patients in the registries are more often noncompliant or undertreated.

3. Other special considerations for elderly patients

3.1. Very elderly patients

The definition of "very elderly" varies in the literature, however, most studies in AF use either 80 or 85 years of age as the threshold (Mizuno et al., 2018; Patti et al., 2017; Poli et al., 2009). In trials, very elderly patients have been under-represented.

The BAFTA trial enrolled 386 patients aged 80–84 years, and 190 patients over 85 years of age. In BAFTA, warfarin reduced thromboembolic events in very elderly patients compared to aspirin (RR 0.30 [0.10-0.77] for 80–84 years and 0.50 [0.17–1.31] for over 85 years), with similar risks of major hemorrhage between warfarin and aspirin (RR 0.96 [0.39–2.33] for 80–84 years, and 0.77 [0.24–2.32] for over 85 years). In the AVERROES trial where 366 patients aged ≥ 85 years were included, apixaban had a significant 86% reduction of stroke or SEE compared with aspirin, and the benefit of apixaban was numerically greater with advancing age.

Subgroup analyses from the NOAC vs. warfarin trials, although under powered (Table 2), offer interesting insights. Dabigatran(150 mg) consistently had lower rates of stroke/SEE compared to warfarin across all age groups. On the contrary, dabigatran (150 mg and 110 mg) had significantly higher major bleeding rates in patients 80–84 or ≥ 85 years of age, but not in younger age groups ($P_{interaction}$ with age = 0.001)(Lauw et al., 2017). Rivaroxaban had comparable efficacy to warfarin patients > 80 years of age, but there was a significant increase in major bleeding (HR 1.44 [1.09–1.90]). Apixaban had numerically lower rates of stroke or SEE and major bleeding across age groups except for stroke or SEE rates in patients < 65years, which were similar between treatments (Canada, 2016; Halvorsen et al., 2014). The edoxaban 60/30 mg regimen demonstrated consistently lower rates of stroke/SEE and major bleeding compared to warfarin in all age group. Edoxaban 30/15 mg had an even better safety profile, however, at a cost of increased risk of stroke or SEE in younger patients (HR (1.42[1.01–2.00]) (Kato et al., 2016).

Registries are also important complementary sources of information in this population. A population-based study in Darlington, UK showed that the 64%of very elderly AF patients (≥ 85 years) did not receive OAC despite their higher risk; instead nearly 50% received antiplatelet monotherapy. Importantly, antiplatelet therapy is less effective in preventing stroke compared to warfarin (10.9% vs. 9.1%) in the very elderly, echoing the result from BAFTA (Wolff et al., 2015).

The Fushimi registry followed 479 Japanese patients with AF aged ≥ 85 years. Only 41.3% were on NOAC, while 39.8% was on antiplatelet monotherapy, and 3.2% on dual antiplatelet therapy. Interestingly, the ischemic stroke rate was much higher in

Table 2
Number of Patients in Each Age Group at Baseline (Canada, 2016; Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011b; Hori et al., 2012; Inc, B., 2017; Patel et al., 2011).

	< 65 yrs.	65-74 yrs.	≥75 yrs.	≥80 yrs.	≥85 yrs.
RE-LY	2971 (16.4)	7884 (43.5)	7258 (40.1)	3027 (16.7)	722 (4.0)
ROCKET-AF	3294 (23.1)	4741 (33.2)	6229 (43.7)	1305 (9.2)	663 (4.6)
J-ROCKET-AF	780 (61.0)		498 (39.0)		
ARISTOTLE	5471 (30.1)	7052 (38.7)	5678 (31.2)	2436 (13.4)	322 (1.8)
ENGAGE AF-TIMI 48	5497 (26.0)	7134 (33.8)	8474 (40.2)	3591 (17.1)	899 (4.3)

ENGAGE AF-TIMI 48 included highest number of elderly patients (defined as age > =75 years), whereas ARISTOTLE had more patients in relatively younger age groups. Data for patients ≥ 85 years was not available in the J-ROCKET-AF.

Table 3
Dose Reduction Criteria (Connolly et al., 2009; Giugliano et al., 2013; Granger et al., 2011b; Patel et al., 2011).

Trial		Dabigatran *RE-LY*	Rivaroxaban *ROCKET-AF/J-ROCKET AF*	Apixaban *ARISTOTLE*	Edoxaban *ENGAGE AF-TIMI 48*
Dose reduction criteria		None	CrCl 30–49 ml/min	Meets 2 of the below criteria: ①Age ≥ 80 years ②BW ≤ 60 kg ③Cr ≥ 1.5 mg/dl	Meets any one of the below: ①BW ≤ 60 kg ②CrCl ≤ 50 ml/min ③Strong P-gp inhibitor use
Dose reduction scheme		N/A	20mg→15 mg (ROCKET AF) 15 mg→10 mg (J-ROCKET AF)	5 mg→2.5 mg	60mg→30 mg
Drug information					
Europe	Dose reduction criteria	①Age ≥ 80 yrs. ②Verapamil use ③Age 75–80 yrs. ④moderate renal impairment ⑤with gastric disorder ⑥at increased risk of bleeding	CrCl 15–49 ml/min	Meets 2 of the below criteria: ①Age ≥ 80 years ②BW ≤ 60 kg ③Cr ≥ 1.5 mg/dl	Meets any one of the below: ①BW ≤ 60 kg ②CrCl ≤ 50 ml/min ③Strong P-gp inhibitor use
	Dose reduction scheme	① ②150 mg BID→110 mg BID, ③-⑥150 mg BID or 110 mg BID	20 mg→15 mg daily with evening meal	5 mg BID→2.5 mg BID	60 mg→30 mg daily
US	Dose reduction criteria	①CrCl 15–30 ml/min	CrCl < 50 ml/min	Meets 2 of the below criteria: ①Age ≥ 80 years ②BW ≤ 60 kg ③Cr ≥ 1.5 mg/dl	CrCl 15–50 ml/min
	Dose reduction scheme	① 150 mg BID→75 mg BID ② Avoid co-administration	20 mg→15 mg daily with evening meal	5 mg BID→2.5 mg BID	60 mg→30 mg daily
Japan	Dose reduction criteria	①CrCl 30–50 ml/min ②P-gp use ③Age ≥ 70 years ④history of intestinal bleeding	CrCl 15–49 ml/min	Meets 2 of the below criteria: ①Age ≥ 80 years ②BW ≤ 60 kg ③Cr ≥ 1.5 mg/dl	Meets any one of the below: ①BW ≤ 60 kg ②CrCl ≤ 50 ml/min ③Strong P-gp inhibitor use
	Dose reduction scheme	150 mg BID→110 mg BID	15 mg→10 mg daily with evening meal	5 mg BID→2.5 mg BID	60 mg→30 mg daily

The dose reduction strategy differed significantly across trials. ROCKET-AF had one dose reduction criterion for rivaroxaban, whereas ARISTOTLE and ENGAGE AF-TIMI 48 utilized three dose reduction criteria each apixaban and edoxaban, respectively. In addition, the dose reduction was more modest (25–33%) with rivaroxaban as compared to the 50% reduction with apixaban and edoxaban. There were no dose reduction criteria for dabigatran in the RE-LY trial. In the US only, edoxaban is not approved in AF patients with CrCl > 95 ml/min.
BW: body weight, Cr: creatinine, CrCl: creatinine clearance, P-gp: P-glycoprotein.

anticoagulated group compared to those without anticoagulation (7.3% vs. 2.2%) with comparable major bleeding rate (1.8% vs. 2.1%). This is likely due to differences in patient demographics and risk factors between the groups, with patients at higher thrombotic risk receiving OAC. Furthermore, the INRs were lower than those reported in most randomized trials. In the Fushimi Registry, 62.5% of INRs for elderly were within the range of 1.6–2.6 as recommended by Japanese guidelines. However, 31.3% of the INRs were < 1.6, which, may have contributed to a higher rate of ischemic stroke and lower rate of major bleeding (Yamashita et al., 2016).

A nationwide Cohort Study from Taiwan analyzed the risk of ischemic stroke and bleeding in patients with AF aged ≥90 years. Compared to warfarin, NOACs were associated with a lower adjusted risk of ICH (HR 0.29 [0.09-0.98]) with comparable reduction in ischemic stroke (adjusted HR 1.04 [0.45–1.97]); reassuringly showing a similar trend as was observed in the NOAC trials in very elderly patients.

Currently, there are several studies evaluating large populations of elderly, including the Global Anticoagulant Registry in the Field (GARFIELD) Registry and Gloria Registry on Long-Term Oral Antithrombotic Treatment in Patients with AF (GLORIA-AF). Also, there is one randomized placebo-controlled trial in the very elderly, the Edoxaban Low-Dose for Elder Care AF patients (ELDERCARE- AF, # NCT02801669) Study, which is assessing the efficacy and safety of edoxaban 15 mg in 800 patients age 80 or greater who cannot tolerate warfarin (Okumura et al., 2017).

3.2. Risk of falling and frailty

One of the major concerns voiced by physicians regarding anticoagulant use in the very elderly population is the risk of falls and related haemorrhagic events (Sinnaeve et al., 2012), particularly ICH, the most dreaded complication of anticoagulation (Gage et al., 2005; Man-Son-Hing et al., 1999). However, the Loire Valley Atrial Fibrillation Project demonstrated that a history of falls was independently associated with the increased risk of ischemic events, bleeding, and mortality, but not hemorrhagic stroke, in patients treated with oral anticoagulants (Banerjee et al., 2014). Importantly, results suggest that stroke prevention with anticoagulants outweigh the risk of ICH even in frail patients (Gage et al., 2005). Indeed, modeling performed in patients with AF treated with warfarin showed that a patient would need to fall nearly 300 times per year before the risk of bleeding complications exceeded that of embolic stroke (Man-Son-Hing et al., 1999). Since NOACs reduce ICH by 50% compared to warfarin at target INR2-3 (Ruff et al., 2014), this risk benefit ratio should be even more favorable with NOACs compared to warfarin in elderly patients at risk of falling.

Data on NOACs are limited in patients with an increased risk of falls. In ENGAGE AF- TIMI 48, outcomes in patients at increased risk of falling were assessed in a prespecified analysis. Any one of eight factors were used to identify a patient at increased risk of falling: 1) prior history of falls 2) lower extremity weakness 3) poor balance 4) cognitive impairment 5) orthostatic hypotension 6) use of psychotropic drugs 7) severe arthritis or 8) dizziness (Steffel et al., 2016). These criteria represent frailty, which is a syndrome characterized by reduced physiologic reserve and increased susceptibility to disability (Buchner and Wagner, 1992). The results from ENGAGE AF-TIMI 48 demonstrated that among the 900 patients at an increased fall risk, there was no increased risk of stroke/SEE relative to patients who were not at an increased risk of falling (HR 1.16 [0.89, 1.51]). However, a high risk for falls was an independent risk factor for major bleeding and mortality (HR 1.30 [1.04, 1.64] and HR 1.45 [1.23, 1.70], respectively) (Steffel et al., 2016). The efficacy and safety profile of edoxaban compared to warfarin was not altered by the risk of falling. Furthermore, since patients at higher risk of falling have more frequent events, the *absolute* benefits with edoxaban vs. warfarin were greater in this more vulnerable subgroup.

In the ARISTOTLE trial, patients who had a history of falls in the year before randomization had similar adjusted rates of stroke or SEE as those without a history of falls (HR 1.21 [0.80, 1.82]). However, a history of falls was associated with higher adjusted rates of major bleeding (HR 1.39 [1.05, 1.84]) and mortality (HR 1.70 [1.36, 2.14] (Rao et al., 2017). In patients with a history of falls, major bleeding rate was lower with apixaban compared to warfarin (4.35% vs. 5.38%). Thus, the benefits of apixaban compared with warfarin in preventing stroke or systemic embolism and major bleeding were preserved, irrespective of a prior history of falls.

Based on the available evidence, it seems that the risk of severe bleeding is counterbalanced by a reduction in the risk for stroke in these high-risk patients, provided the treatments and doses are carefully selected. Neither a high risk of falling or advanced age should represent reasons for withholding anticoagulant therapy. Instead, evaluation of gait and balance are recommended, followed by institution of measures to prevent falling. Indeed, under-treatment of very elderly individuals prompted a guideline to recommend that age alone should not be a factor in the decision to use appropriate pharmacological treatment in the secondary prevention of myocardial infarction (Williams et al., 2002). The same advice appears prudent for the prevention of stroke in elderly patients with AF.

3.3. Gastrointestinal bleeding in the elderly

An increase in gastrointestinal (GI) bleeding compared to warfarin has been a limitation of the NOACs, particularly in the elderly population (Eikelboom et al., 2011; Halperin et al., 2014; Kato et al., 2016). The relatively high proportion of lower GI bleeds with NOACs may be related to the incomplete absorption of the active NOACs, increasing bioavailability of NOAC in the lower GI tract, which can lead to bleeding, particularly in the presence of inflammation, erosions or malignancy(Blech et al., 2008). This is particularly relevant in the elderly, who are likely to have abnormal GI mucosa.

In addition, the role that intestinal and gut flora play in the development of GI bleeding may be relevant. The intestinal microbiota supplies nutrients and protects against pathogens, thus contributing significantly to homeostasis. Aging can affect the composition of the human gut microbiota, and it has been hypothesized that the changes in the composition of microbiota is a marker of progression of disease or frailty in the elderly (Jackson et al., 2016; Jeffery et al., 2016). The GI tract possesses a rich intra- and sub-mucosal blood supply, and microbiota along with digestive enzymes regulate the highly vascular lining of the GI tract (Sekirov et al., 2010).

The role of microbiota has been explored in the context of dabigatran therapy. The prodrug dabigatran etexilate has only 7% bioavailability; the remainder transverses the GI tract and is excreted in the faeces (Desai et al., 2013; Vanassche et al., 2014). During this passage, at least two-thirds of the prodrug is converted to active dabigatran, a process facilitated by esterases in the gut bacterial flora (Desai et al., 2013; Eikelboom et al., 2011; Vanassche et al., 2014). Non-absorbed dabigatran etexilate is cleaved in the intestinal lumen, yielding an active intra-luminal drug. It is hypothesized that a change in microbiota that reduces gut bacterial flora can increase the amount of incompletely absorbed dabigatran, thereby increasing the potential for topical drug activity (Biagi et al., 2010; Desai et al., 2013; Vanassche et al., 2014).

In contrast to dabigatran, over 95% of warfarin is absorbed in the intestines and non-absorbed warfarin within the gut lumen has no anticoagulant activity. The absorption of the other NOACs is intermediate between that of dabigatran and warfarin. The bioavailability of rivaroxaban (80%) (Mueck et al., 2014), apixaban (50%), (Frost et al., 2013) and edoxaban (62%) (Matsushima et al., 2013), however, even with these agents, non-absorbed active drug traverses the luminal GI tract and is excreted into the faeces. In theory, this could potentiate bleeding from vulnerable lesions.

Interestingly, a recent study suggests that NOAC initiation may unmask occult GI cancers. In RE-LY, 44 of 546 (8.1%) major GI bleeding originated from undiagnosed underlying luminal GI tract cancer, of which 34 patients were receiving dabigatran and 10 warfarin (Flack et al., 2017). In the HOKUSAI VTE Cancer trial that compared edoxaban with dalteparin for the treatment of cancer associated venous thromboembolism, the rate of major bleeding was higher with edoxaban. This result was mainly due to the higher rate of upper GI bleeding with edoxaban, which occurred most frequently in patients with GI cancer. While speculative, this may explain in part the higher GI bleeding rates in the elderly, a population that is more likely to have cancer. It also supports the need for a thorough investigation for GI bleeding in anticoagulated patients, particularly in the elderly.

3.4. Medication adherence

The efficacy and safety of any medical therapy depends on patients' adherence, which is typically higher during acute conditions, but substantial decreased after 6 months of therapy (Osterberg and Blaschke, 2005). Non-adherence to oral anticoagulant therapy is associated with worse outcomes including a higher risk of stroke and bleeding (Garkina et al., 2016).

The reasons for non-adherence are multifactorial. One of the factors for poor adherence is complexity of treatment (Rodriguez et al., 2013). Generally, NOACs have better adherence rates compared to VKAs due to greater ease of use, including lack of need for routine monitoring, fixed dosing, and fewer food and drug interactions (Garkina et al., 2016). Although NOACs are easier to manage, they are more expensive compared to VKAs, and cost may also play a part in non-adherence. The higher cost of NOACs particularly affects elderly patients who are more likely to have fixed incomes and concomitant conditions requiring multiple medications.

Another important consideration is frequency of drug intake. Patients taking twice-daily medications generally have lower rates of adherence than those taking once-daily medications (Alberts et al., 2016). Previous studies have demonstrated that AF patients treated with once daily dosing regimens have up to 61% higher likelihood of adherence compared with patients on twice-daily regimens (Laliberte et al., 2013).

In addition, the association between polypharmacy and poorer medication adherence is well described in the literature (Collerton et al., 2016; Proietti et al., 2016; Wang et al., 2015). Polypharmacy is associated with multiple comorbidities and frailty in various populations, and the risk of drug-drug interactions increases with the number of concomitant drug treatments. In this context, patients with polypharmacy are at higher risk for more complications with anticoagulation therapy.

An analysis from the ROCKET AF reported that half of the patients were prescribed 5–9 concomitant medications, and 13% were taking ≥10 concomitant medications (Piccini et al., 2016). Similarly, in ARISTOTLE, polypharmacy (≥5 drugs) was observed in 76.5% of participants. In both trials, more concomitant medications were used in older patients, and polypharmacy was independently associated with a higher risk of major bleeding, whereas the association was not as clear for ischaemic events (Jaspers Focks et al., 2016; Piccini et al., 2016).

Bleeding and side effects are common reasons for discontinuation of oral anticoagulants, accounting for approximately 20–30% of all discontinuations (O'Brien et al., 2014; Rodriguez et al., 2013; Umei et al., 2017). Since elderly patients are at a higher risk of bleeding, it is important for the prescribing physician to be aware of the various drug interactions that may increase drug plasma concentrations, which may further increase the risk of major bleeding.

4. Question for the future

The NOAC vs. warfarin trials provide a wealth of new information, adding data in > 10,000 elderly patients treated with an anticoagulant

for stroke prevention in AF. These data are complemented by reports from large registries. Nonetheless, a number of unanswered questions remain related to oral anticoagulation in elderly AF patients.

Since elderly patients are more likely to have comorbidities, more data in elderly patients with AF who also have advanced renal and hepatic failure are needed to help guide clinical care. While data in patients with valvular heart disease (excepting mechanical valves and mitral stenosis) treated with NOACs appear promising (Avezum et al., 2015; Breithardt et al., 2014; Carnicelli et al., 2017; Ezekowitz et al., 2016; Renda et al., 2017), additional studies in elderly patients with AF and severe aortic stenosis, transcutaneous aortic valvular replacement, and early (0–3 months) post-op valvular surgery are needed. Limited data in elderly AF patients with cancer are available (Fanola et al., 2018), and given the relationship between malignancy and age, this will become an increasingly relevant issue as populations age.

Finally, monitoring of anticoagulant activity and reversal of anticoagulant effect are two issues that are particularly relevant to elderly patients, who often are at risk for high drug levels and bleeding. Whether monitoring of drug levels or anticoagulant effect of NOACs is helpful, and how to effectively reverse a factor Xa inhibitor, remain important questions to be answered in the future.

5. Summary and expert recommendations

1 Elderly patients with AF are at an elevated risk of both stroke and bleeding.
2 In the elderly, all 4 NOACs demonstrated a similar-to-lower risk of stroke compared to the warfarin, while only apixaban and edoxaban significantly reduced major haemorrhagic events. Because a stronger association with age is observed with bleeding than with ischemic events, the net benefit of apixaban and edoxaban over warfarin is greater in elderly patients compared to younger patients.
3 All NOACs should be dose-reduced in patients who are anticipated to have excessively high drug levels, but age alone should not be the sole consideration.
4 Greater complexity of treatment adversely effects adherence and compliance, resulting in poorer outcomes. NOACs are considerably easier to use than VKAs.

Physicians increasingly acknowledge that treatment decisions should be based on biological age rather than chronological age. All currently available anticoagulant agents can be used in elderly patients, however, treatment decisions should focus on individual potential risks and benefits, and should incorporate shared decision-making with patients, to avoid under or over treatment.

6. Conclusions

Elderly patients with AF are both at high thromboembolic and bleeding risk. NOACs have fewer drug and food interactions, do not require routine monitoring, and, most importantly, have a lower risk intracranial bleeding than warfarin. Therefore, elderly patients may benefit even more from NOACs instead of warfarin compared to younger patients. Based on the totality of the evidence, it is our expert opinion that NOACs, particularly apixaban and edoxaban, should be preferred in elderly patients with AF due to their more favorable risk-benefit profiles. Furthermore, we strongly caution against under-dosing anticoagulants in elderly patients who do not meet dose reduction criteria as described in the prescribing labels and guidelines.

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