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REVIEW

Unmet Clinical Needs in Elderly Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation

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ABSTRACT

Vitamin K antagonists have been used for many years as the treatment of choice for long-term oral anticoagulation in patients with non-valvular atrial fibrillation. Unfortunately, the use of those drugs in the real-world setting, particularly among elderly patients, is suboptimal because of their limitations in management. Therefore, many patients were not adequately anticoagulated. Direct oral anticoagulants have been demonstrated to overcome almost all the limitations derived from the use of vitamin K antagonists. Direct oral anticoagulants are at least as effective as vitamin K antagonists in preventing thromboembolic events in patients with non-valvular atrial fibrillation and safer in reducing the risk of intracranial haemorrhage and all-cause mortality. However, as a result of the strict inclusion and exclusion criteria applied to patients, data coming from randomized controlled trials might not apply to the general population. Furthermore, elderly patients were scarcely represented in randomized controlled trials with direct oral anticoagulants. Therefore in elderly patients with non-valvular atrial fibrillation, unmet clinical needs still exist. This

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review article highlights some of them and provides potential answers based on the results coming from randomized clinical trials, real-world data, and the authors' clinical experience.

Keywords: Direct oral anticoagulants; Atrial fibrillation; Elderly; Unmet clinical needs

Key Summary Points
Why carry out this study?
Direct oral anticoagulants overcome almost all the limitations derived from the use of vitamin K antagonists, demonstrating better efficacy and safety in patients with non-valvular atrial fibrillation
Elderly patients were scarcely represented in pivotal randomized controlled trials with direct oral anticoagulants and therefore unmet clinical needs still exist
What was learned from the study?
This review article highlights eight main clinical areas of unmet needs in elderly patients. It also provides potential answers based on the results coming from randomized clinical trials, real-world data, and the authors' clinical experience
A table summarizes unmet clinical needs and potential answers for the eight areas considered in the text

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14511633.

INTRODUCTION

Vitamin K antagonists (VKAs) have been used for many years as the treatment of choice for long-term therapy in patients with non-valvular atrial fibrillation (NVAF). The issue of the definition of NVAF is of relevance because several patients with "valvular AF" were excluded from recent trials testing direct oral anticoagulants (DOACs) in patients with NVAF. Reasons to exclude them were major uncertainties on whether thrombogenesis in such patients is similar to that occurring in the more common forms of NVAF. Although criteria for excluding such patients varied in pivotal trials with the DOACs, there is reason to believe that stringent exclusion of most patients with valvular disease implemented in some studies was not justified by the comparative outcomes of VKAs vs DOACs in trials where exclusion criteria were more lenient, in admitting patients with non-rheumatic valvular disease, valve repair, or bioprostheses to the studies [1]. However, difficulties in keeping an optimal time in therapeutic range (TTR), increased risk of bleeding events, several drug–drug and food–drug interactions are the main reasons for suboptimal use of VKAs in the real-world setting, particularly among elderly patients [2]. As a result, many patients were not adequately anticoagulated. In contrast to VKAs, new DOACs have a rapid onset of action, a predictable effect, and do not require periodic monitoring or continuous dose adjustments (Table 1). DOACs specifically inhibit factor Xa (rivaroxaban, apixaban, edoxaban) or factor IIa (dabigatran), are given in fixed doses once or twice daily, have scarce drug–drug interactions, and do not interfere with food. Overall, compared to VKAs, DOACs are at least as effective for the prevention of thromboembolic events in patients with NVAF [3–6] and safer in reducing the risk of intracranial haemorrhage and all-cause mortality [7]. However, as a result of the strict inclusion and exclusion criteria applied to the included patients, data coming from randomized clinical trials (RCTs) might not apply to the general population. It becomes necessary to collect information from the real-world setting of patients, which can

complement evidence acquired in RCTs and assess a wide range of outcomes representative of the everyday clinical field. These data mainly relate to patients' specific subgroups, generally scarcely represented in the RCTs, such as elderly patients. Real-world evidence focused on the clinical performance of DOACs in the elderly is relevant to address currently unmet medical needs and define better treatments for this subset of patients. Data coming from the RCTs showed that DOACs offer benefits and increased convenience in elderly patients. Particularly, a meta-analysis of RCTs of DOACs in patients with NVAF aged at least 75 years found lower rates of stroke and systemic embolic events than conventional treatment and no statistically significant interactions between age, treatment effect, and major bleeding with edoxaban and apixaban [8]. In elderly patients with NVAF, unmet clinical needs still exist and need to be solved. This paper aims to highlight some of them and provide each a potential answer based on results of RCTs, real-world data, and the authors' clinical experience. It is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The list of unmet clinical needs and potential answers for any subset considered in the paper are in Table 2.

COMORBIDITY AND FRAILTY IN THE ELDERLY

Most patients with NVAF show at least one concomitant disease, and this association becomes stronger with age [9]. Many patients with comorbidities can often be defined as "frail", even though a distinction between these two clinical entities must be made. There is no single definition of frailty that can be identified as a dynamic condition of increased vulnerability, with multisystemic, partly age-related, pathophysiological changes associated with worse outcomes [10]. Moreover, frailty is partly reversible when at an initial stage, making its early identification clinically useful. Numerous scales designed for this purpose exist, and the most used is undoubtedly the Clinical Frailty Scale [11]. Unfortunately, many of these scores are not specific and lack validation.

Age is not per se a sufficient criterion in deciding whether to introduce antithrombotic therapy in patients with NVAF. The PREFER-AF study shows how, with age, cardioembolic risk exceeds haemorrhagic risk and how the introduction of oral anticoagulant therapy is associated with a favourable net clinical benefit [12]. Historically, VKAs were suggested as the first-line therapy to prevent cardioembolic complications in comorbid or frail patients with NVAF [13].

Although several data comparing VKAs to DOACs show that the efficacy and safety ratio favouring DOACs are maintained and improve with age and in more frail/comorbid patients even very recently, the probability of receiving DOAC compared to VKA was lower in the presence of high bleeding and thromboembolic risk [14]. In the subanalysis of the ENGAGE-AF study in elderly patients (aged over 75 years), edoxaban was equally effective in reducing cardioembolic events and showed significantly lower major bleeding complications compared to warfarin. Furthermore, considering a greater absolute risk of events in older patients, the net clinical benefit of edoxaban compared to warfarin is maintained [15]. In a more recent subanalysis of the ENGAGE-AF study, patients were stratified according to concomitant burden disease using the updated Charlson Comorbidity Index. The efficacy, safety, and net clinical benefit outcomes of edoxaban compared to warfarin were independent of the degree of comorbidity [16].

In a post hoc subgroup analysis of the ARISTOTLE trial, patients were categorized by the number of comorbid conditions at baseline as patients without multimorbidity (0–2 comorbid conditions), patients with moderate multimorbidity (3–5 comorbid conditions), and patients with high multimorbidity (6 or more comorbid conditions). Multimorbidity was highly prevalent in these patients (64% of the whole population). Adjusted rates of stroke/systemic embolism, death, and major bleeding increased with multimorbidity (Reference no multimorbidity; moderate multimorbidity 1.42 [1.24–1.64] and high multimorbidity 1.92

Table 1 Pharmacokinetic characteristics of direct oral anticoagulants

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	FXa	FXa	FXa
Bioavailability (%)	6.5	80	50	60
Prodrug	Yes	No	No	No
Active metabolites	No	No	No	Yes
Vd (L)	60–70	50	21	> 300
Plasma protein binding (%)	35	> 90	87	40–59
Cmax (h)	1–3	2–4	3–4	2
Elimination half-life (h)	12–17	5–9	8–15	8–11
Metabolism (CYP)	No	3A4, 2J2	3A4 (25% elimination)	3A4 (< 4% elimination)
P-gp substrate	Yes	Yes	Yes	Yes
Other transporters	Not known	BCRP/ ABCG2	BCRP/ABCG2	No
Renal elimination (%)	80	65	27	35
Renal clearance (mL/min)	80	58	15	183
Posology	BID	OD	BID	OD
Expected range of plasma levels at peak for std. dose (ng/mL)	64–443	184–343	69–321	91–321
Expected range of plasma levels at trough for std. dose (ng/mL)	31–225	12–137	34–230	31–230

[1.59–2.31]), with no interaction concerning efficacy or safety of apixaban [17]. Finally, in another subanalysis of the ENGAGE-AF study, researchers considered a subgroup of patients judged as being at higher risk of falling (a valid proxy of frailty) if they had at least one of the following: prior history of falls, lower extremity weakness, poor balance, cognitive impairment, orthostatic hypotension, use of psychotropic drugs, severe arthritis, or dizziness. Again no treatment interaction was observed between edoxaban and warfarin for the efficacy and the safety outcomes. Moreover, in absolute terms, the reduction of mortality and severe bleedings appears to be more evident in these frail patients [18].

ETNA-AF Europe is a prospective, multicentre, post-authorization, observational study that enrolled 13,092 patients treated with edoxaban, where 10.6% were defined as frail. The study had no specific definition for frailty as it was left to the physician's discretion. At 1-year follow-up, patients who were elderly (over 75 years) and frail were at higher risk of events. The data accumulated so far, including ETNA-AF-Europe, reinforce the ability of DOACs to improve outcomes and quality of life in elderly and frail patients [19]. The Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF) is a prospective, multinational, observational study of adults with recently diagnosed NVAF and at least one risk factor for stroke. After patients at low risk of complications (patients

Table 2 Unmet clinical need and potential answer for any subset considered in the text

Subset	Unmet clinical need	Potential answer
Comorbidity and frailty in the elderly	There is no single definition of frailty, and there are no universal scales to assess it	Comorbid and frail patients could benefit from DOACs, and the decline in cardioembolic complications has a more substantial impact than the small increase of bleeding complications related to their use. DOACs have a better risk–benefit profile than VKAs in this population
Elderly patients with chronic kidney disease	Calculated CrCl and eGFR are discordant in elderly patients with very low renal function making a relevant clinical impact when choosing the appropriate dose of DOAC	Anti-Xa inhibitors are the preferable DOACs for elderly patients when the eGFR is 15–30 mL/min/1.73 m^2. No substantial evidence supports treatment with DOACs when the eGFR rate is < 15 mL/min/1.73 m^2, although their use may be reasonable in selected patients
Elderly patients with non-valvular AF and ischemic stroke	The early introduction of DOACs after acute ischemic stroke remains challenging as patients were excluded from RCTs if they had an ischemic stroke 7–30 days before enrolment	The benefit of early anticoagulation should be balanced with the risk of ICH, especially in elderly patients and in severe strokes. Early introduction of DOACs might be reasonable in elderly patients because their risk of recurrent ischemic stroke is higher than that of ICH
Cardioversion of non-valvular AF in the elderly	There is a paucity of data on cardioversion of NVAF in the elderly. VKAs require ongoing dosing management to maintain a therapeutic effect, and cardioversion may be delayed when INR levels are sub-therapeutic	When cardioversion is necessary to improve symptoms, the treatment approach for older patients is the same as for younger patients. DOACs have a more rapid onset and consistent anticoagulation level, allowing a more rapid and precise cardioversion strategy than VKAs also in the elderly
Antithrombotic therapy after PCI in the elderly	Data regarding the optimal antithrombotic combination therapy in patients undergoing stenting and suffering from NVAF can be challenging to apply in the real world. The competing ischemic and bleeding risks are even more difficult to disentangle in elderly patients, at best, underrepresented in RCTs	Choices must be personalized and involve an in-depth discussion between clinical and interventional cardiologists, including other specialists (geriatricians, endoscopists, rehabilitation specialists) in many cases

Table 2 continued

Subset	Unmet clinical need	Potential answer
Elderly patients with non-valvular AF and cancer	In patients with NVAF and cancer, no clinical scores for predicting thromboembolic events were validated. However, they are currently used along with an evaluation of the type of cancer and concomitant therapies. The risk of stroke is likely to be underestimated in NVAF and cancer, while the bleeding risk depends on cancer and comorbidities	DOACs seem to offer higher protection from stroke or systemic embolism than warfarin in patients with NVAF and cancer. A multidisciplinary approach is necessary to evaluate thromboembolic and bleeding risks, drug–drug interactions, and patient preferences
Management of DOACs in elderly patients undergoing an invasive procedure or surgery	Conversely to VKAs discontinuation, thrombotic risk assessment is far less relevant than the bleeding risk assessment that should be used as the main determinant of DOAC discontinuation strategy for invasive procedure or surgery	In patients at risk for relevant residual drug concentrations and elderly with renal impairment, it might be helpful to run routine lab testing before high-risk surgery or invasive procedures. When stopping DOACs, it is suggested to use a prophylactic dose of heparins for VTE only, as in patients with NVAF undergoing the same type of surgery. Restarting full-dose DOAC at least 48–72 h after surgery is probably safer
Pharmacokinetic characteristics of DOAC and drug interactions	Most of the recommendations for using DOACs in polytreated patients are based on in vitro experimental data, and only a few pharmacokinetic studies have been performed to verify the extent of the variation of DOAC plasma concentrations	The use of DOACs with lower inter-patient and intra-patient variability of plasma concentrations and less susceptible to CYP3A4 enzymatic activity would be safer

AF atrial fibrillation, *CrCl* creatinine clearance, *DOAC* direct oral anticoagulant, *eGFR* estimated glomerular filtration rate, *ICH* intracranial haemorrhage, *INR* international normalized ratio, *NVAF* non-valvular atrial fibrillation, *PCI* percutaneous coronary intervention, *RCT* randomized clinical trial, *VKA* vitamin K antagonist, *VTE* venous thromboembolism

with CHA_2DS_2-VASc score less than 2 excluding gender) were excluded, DOAC use compared with VKA use was associated with a lower risk of all-cause mortality and major bleeding with a similar risk of non-haemorrhagic stroke/systemic embolism [20].

ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

Older patients with NVAF have a higher risk of stroke, systemic embolic events, and bleeding than younger patients. They often have chronic kidney disease, which predisposes to NVAF-related thromboembolic events and bleeding [15, 21]. Among 24,962 patients enrolled in the

ETNA-AF Global observational study, 39% and 11% of them were aged 75–85 and at least 85 years, respectively. Compared with patients aged 65 years or younger, they had 50% lower mean creatinine clearance values and higher CHA_2DS_2VASc and HAS-BLED scores. Elderly patients faced more ischemic and haemorrhagic events, with the notable exception of intracranial haemorrhage, at 1-year follow-up [22].

Overall, analyses of phase III RCTs and real-world data indicate that DOACs retain their favourable safety and efficacy profile over VKAs in elderly individuals with NVAF and creatinine clearance values of 30–50 mL/min [23]. Caution should be paid in choosing dabigatran if creatinine clearance values are slightly above 30 mL/min since renal function progressively declines in most patients with NVAF, and dabigatran is not approved for use if the creatinine clearance is below 30 mL/min [24]. Moreover, in the RE-LY trial, both dabigatran dosages were associated with higher bleeding rates than warfarin in participants who were at least 80 years old [25].

The clinician should also consider that creatinine clearance is obtained with the Cockroft–Gault equation. However, most laboratory reports provide an estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations. In underweight and elderly patients and when moderate or severe chronic kidney disease is present, the Cockroft–Gault equation underestimates renal function compared to the MDRD and CKD-EPI equations [26, 27].

Finding the balance between protection against ischemic and haemorrhagic events is notably complex in stage 4 chronic kidney disease, i.e. creatinine clearance 15–30 mL/min. On the one hand, the risk of stroke and systemic embolism is higher; on the other hand, factors such as uremia-induced platelet dysfunction, uncontrolled blood pressure, and haemodialysis predispose to bleeding [28]. The INR control is also challenging: among over 7700 patients with newly diagnosed NVAF initiating warfarin in Sweden between 2006 and 2011, the TTR significantly decreased across eGFR categories and was lowest for eGFR below 30 mL/min/1.73 m^2 (while median age significantly increased from 70 to 80 years) [28]. Furthermore, VKAs can give rise to additional side effects, including vascular calcification, anticoagulant nephropathy, and calcific arteriopathy [29]. On the basis of these considerations, DOACs may be favoured over VKAs in elderly subjects with stage 4 chronic kidney disease. Apixaban and rivaroxaban have also been used in stage 5 chronic kidney disease, when the creatinine clearance is below 15 mL/min, although off-label. Retrospective investigations showed a lower bleeding risk with DOACs than with VKAs in NVAF with concomitant advanced chronic kidney disease with or without dialysis [30, 31]. However, the only RCT that, so far, has compared a DOAC with warfarin in stage 5 chronic kidney disease did not demonstrate any significant difference in the rates of stroke and of major or clinically relevant non-major bleeding [32]. Remarkably, about 25% of the patients enrolled in this study were at least 75 years old.

ELDERLY PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION AND ISCHEMIC STROKE

A recent meta-analysis showed that DOACs had superior efficacy in reducing stroke or systemic embolism and superior safety in reducing intracranial haemorrhage compared with warfarin in patients with NVAF who were over 75 years old [33]. Compared with VKAs, DOACs were associated with a lower intracranial haemorrhage risk in the very elderly (age at least 90 years) with NVAF [34].

The decision about the early introduction of DOACs after acute ischemic stroke remains challenging as patients were excluded from RCTs if they had an ischemic stroke 7 days before enrolment in ARISTOTLE, 14 days before in RE-LY and ROCKET-AF, and 30 days in ENGAGE-AF. Patients with severe disabling stroke in the previous 3–6 months were excluded in ROCKET-AF and RE-LY.

In clinical practice, the main reason to start an anticoagulant treatment early after an index ischemic stroke is to prevent a recurrent event.

However, the benefit of early anticoagulation should be balanced with the risk of intracranial haemorrhage, especially in elderly patients and in severe strokes. Elderly age is a predictor of recurrent cerebral ischemic events in patients with NVAF, while small lesions (at most 1.5 cm) inversely correlate with major bleeding and recurrent cerebral ischemic events [35]. Also, cerebral microbleeds, i.e. radiological biomarkers of the cerebral small vessel diseases that are prone to bleed and the leading cause of spontaneous intracranial haemorrhage in the elderly, are associated with a greater risk for subsequent intracranial haemorrhage than for recurrent ischemic stroke in patients treated with oral anticoagulant therapy for recent ischemic stroke. However, the absolute risk of recurrent ischemic stroke is higher than that of intracranial haemorrhage [36].

Given the lack of a current stratification system that simultaneously predicts the risk of recurrent ischemic stroke and intracranial haemorrhage in patients with recent ischemic stroke and NVAF, the profile of DOACs seems the most appropriate to satisfy the therapeutic rationale. Therefore, four RCTs (ELAN, NCT03148457; TIMING, NCT02961348; OPTIMAS, EudraCT, 2018-003859-38; START, NCT03021928) are currently investigating the safety and efficacy of early versus late introduction of DOACs after stroke in patients with NVAF, without an upper limit of age and stroke severity. Several prospective observational studies have explored the potential risks and benefits of early DOAC introduction. A pooled individual patient data analysis showed that early DOACs introduction (5 days median time from index event) was associated with reduced risk of poor clinical outcomes than with VKAs, mainly attributed to lower intracranial haemorrhage risk. Also, no significant interactions were observed between overall treatment effects in the subgroups identified by age, stroke severity, and early anticoagulant introduction [37]. In patients aged 65 years or older who had an ischemic stroke and NVAF, the use of DOACs at discharge was associated with a better long-term outcome than warfarin. Also, no significant interactions were observed between overall treatment effects in the subgroups identified by age and stroke severity [38].

CARDIOVERSION OF NON-VALVULAR AF IN THE ELDERLY

The debate continues on rate control versus rhythm control strategies for NVAF. Given that NVAF is an abnormality of cardiac rhythm, it is reasonable to assume that rhythm control is favourable over rate control. However, all-cause mortality and all-cause hospitalization were significantly lower in the AFFIRM study in the rate control group, in patients aged 70–80, compared to the respective rhythm control group [39]; however, when an early rhythm control strategy (antiarrhythmic drugs and/or ablation) was applied, the risk of adverse cardiovascular outcomes (mainly death or stroke) was lower compared to usual management of only NVAF-related symptoms [40]. Despite such evidence, there is a paucity of data regarding older age groups since cardioversion is more seldom performed in octogenarians and nonagenarians. While some studies suggest that rate control strategies are superior in cost-effectiveness, others have noted better outcomes with rhythm control interventions [41, 42]. In certain situations, cardioversion attempts may be reasonable even in elderly adults (e.g. those who remain symptomatic despite adequate rate control therapy). When cardioversion is necessary to improve symptoms, the treatment approach for elderly patients is the same as for younger subjects [43]. A substantial risk associated with the re-establishment of sinus rhythm through cardioversion is thromboembolism. Early observational studies reported a 1.76% rate of thromboembolic events after NVAF cardioversion in patients not receiving oral anticoagulant therapy [44]. In contrast, the thromboembolic event rate was reduced by oral anticoagulant therapy used before cardioversion, with only 0.45% of thromboembolic events within 30 days after the procedure [45]. These observational results led to early recommendations regarding the use of oral anticoagulant therapy surrounding the cardioversion of NVAF. VKAs have been extensively studied for

stroke prophylaxis. Furthermore, large RCTs demonstrated the non-inferiority of DOACs compared to VKAs in patients with NVAF [7]. VKAs require continuing dosing management to maintain a therapeutic effect, and cardioversion may be delayed when INR levels are sub-therapeutic. By contrast, DOACs have a more rapid onset and consistent level of anticoagulation. The safety and efficacy of DOACs in patients with NVAF undergoing cardioversion have been analysed in several systematic reviews and meta-analyses of RCTs, thus supporting their use as a standard of care in pericardioversion [46, 47]. DOACs administered de novo or as ongoing therapy had comparable efficacy and safety to VKAs treatment. This observation applied to both the early (using transoesophageal echocardiography) and the delayed cardioversion strategy [48–50]. In the X-VeRT study delayed strategy, rivaroxaban treatment allowed faster cardioversion than VKAs (after a mean of 25 vs 34 days). In the VKAs group, patients could not achieve adequate anticoagulation before cardioversion (95 patients vs one patient in the rivaroxaban group) [48]. The rapid onset of action (2–4 h), short half-life, and predictable pharmacokinetics and pharmacodynamics allow DOACs to be particularly useful in the setting of elective cardioversion.

ANTITHROMBOTIC THERAPY AFTER PERCUTANEOUS CORONARY INTERVENTION IN THE ELDERLY

In patients with NVAF and concomitant acute coronary syndrome or percutaneous coronary intervention, generally with stent implantation, the optimal antithrombotic regimen and its duration remain undefined. Six RCTs have evaluated several antithrombotic strategies. The drug combinations tested included one oral anticoagulant drug to reduce stroke risk and at least one antiplatelet drug to secure the coronary ischemic risk, both stent-related and unrelated. The studies addressed whether dual antithrombotic therapy (a regimen in which one antiplatelet drug, generally aspirin, is omitted after percutaneous coronary intervention, either immediately or at the end of the index hospitalization) as compared to triple antithrombotic therapy, was safer in terms of bleeding risk, and potentially as effective regarding the risk of systemic embolization and of coronary events [51–56].

International societies propose differing recommendations, with North Americans suggesting that oral anticoagulant therapy plus a $P2Y_{12}$ inhibitor should be considered for most patients at discharge, and Europeans affirming that an initial triple antithrombotic therapy should be used in most patients with NVAF undergoing percutaneous coronary interventions, whereas the latest European Society of Cardiology guideline on non-ST elevation myocardial infarction also inclines toward dual antithrombotic therapy at discharge as the "default" strategy [57–60]. Of note, several recently published meta-analyses report inconsistent efficacy results for dual antithrombotic therapy, raising some "red flags" against early aspirin discontinuation [61–65]. In the elderly, this uncertainty is further compounded by the patients at low-to-medium bleeding and ischemic risk included in the six RCTs, scarcely reflecting real-life complexity. A few examples: average CHA_2DS_2-VASc was 3.5 ± 1.5 in the RE-DUAL PCI trial and 3.9 ± 1.6 in the AUGUSTUS study (the only dual vs triple antithrombotic therapy RCT including an arm of DOAC-based triple antithrombotic therapy), whereas age was 71.6 ± 8.9 years in the dabigatran 110 mg comparison and 68.7 ± 7.7 years in the dabigatran 150 mg comparison of the RE-DUAL PCI, and 70.7 years (range 64.2–77.2) in the AUGUSTUS trial [51, 55].

It might seem instinctive that dual antithrombotic therapy should be standard in the elderly, also because it has emerged as somewhat safe in the trials and some (but not all) meta-analyses. Several doubts, however, remain unanswered. Firstly, what is the role of percutaneous coronary intervention complexity in the elderly? The dual vs triple antithrombotic therapy trials do not report any data regarding the percutaneous coronary intervention complexity (e.g. number and techniques of implanted stents, location of stented lesions). In many elderly patients, complex percutaneous

coronary interventions are performed involving high-risk lesions such as the left main bifurcation, or extensive three-vessel reconstructions, as an alternative to surgical revascularization, often deemed at prohibitive risk [66]. In these patients, immediate dual antithrombotic therapy cannot be safely managed, as the feared and often lethal risk of stent thrombosis is very high in the first 1–3 months [67].

Secondly, even with a short triple antithrombotic therapy strategy, the timing of antiplatelet drug reduction (often involving withholding aspirin because of its higher upper gastrointestinal toxicity) is uncertain. Many bleedings occur in the first month of triple antithrombotic therapy. Unfortunately, this is the same timing of stent thrombosis occurrence. However, the bleedings are mainly minor, as it is likely that many patients have been "primed" by the variable period of in-hospital triple antithrombotic therapy (generally involving heparins instead of DOACs or VKAs) that occurs before or just after percutaneous coronary interventions.

ELDERLY PATIENTS WITH NON-VALVULAR AF AND CANCER

The REGARDS study reported a 20% higher risk of NVAF in patients with cancer than those without cancer [68]. NVAF predisposes patients with cancer to a fivefold increased risk of stroke, a threefold increased risk of heart failure, and a nearly doubled risk of death [69]. The treatment of NVAF in patients with cancer may be a dilemma because specific recommendations are lacking. Current clinical scores for predicting thrombotic ($CHADS_2$ and CHA_2DS_2-VASc) or bleeding events (HAS-BLED) used to guide antithrombotic therapy in the general population have not yet been validated for patients with cancer [70]. Patients with NVAF and active malignancy constitute a higher-risk population for major bleeding that warrants careful risk–benefit assessment in stroke prevention therapies. Encouraging data for DOAC prescription in patients with NVAF and cancer are emerging. In a sub-analysis of the ENGAGE-AF trial, 1153 patients with a mean age of 75 years developed a new diagnosis or a recurrent malignancy during a mean follow-up of 2.8 years. The benefit of edoxaban versus warfarin was higher in protecting from stroke/systemic embolic events, and relative outcomes were consistent regardless of malignancy status for major bleeding [71]. In a sub-analysis of the ARISTOTLE trial, apixaban was effective and safe compared with warfarin for the composite endpoint of stroke or systemic embolism, myocardial infarction, and death in patients with active cancer when compared with patients without cancer, but not in those with a history of cancer [72]. A small study including 163 patients with active cancer using rivaroxaban showed results comparable to the ROCKET-AF trial but with a cumulative incidence of mortality of 22.6% at 1 year, reflecting an active cancer population [73]. A large Danish nationwide population-based cohort of patients with NVAF compared DOACs with warfarin in patients with or without cancer. The thromboembolic and bleeding events were similar in patients with and without cancer, irrespective of the treatment [74]. A meta-analysis comparing DOACs to warfarin in patients with cancer and NVAF reported a lower bleeding rate with apixaban and the same with dabigatran and rivaroxaban. Edoxaban was not yet approved at the time of the study [75]. The incidence of NVAF and stroke increases with age, and there are shared risk factors for NVAF and cancer in ageing populations [68, 76]. The ENGAGE-AF trial included the highest number of elderly patients, approximately 40.2% aged at least 75 years old, and 17.1% aged at least 80. The management with DOACs in patients with NVAF and cancer seems safe and effective and may represent a more practical alternative to VKAs or heparin.

Data from a Swedish registry enrolling patients with NVAF and cancer diagnosed in the previous year and patients without cancer showed a clear benefit of DOACs compared with warfarin, assessed by the composite outcome of ischemic stroke, all major bleedings and death in patients with high–intermediate estimated stroke risk. Moreover, there was a net cerebrovascular benefit with DOACs over warfarin in patients with active cancer and NVAF [77].

In conclusion, the International Society on Thrombosis and Haemostasis Guidelines recommend sharing with the patient the risks and benefits of anticoagulant therapy. In patients with cancer who are already on anticoagulant regimens for NVAF before starting chemotherapy, it is recommended to continue with the same therapy without drug–drug interactions. In patients with VKA interactions with chemotherapy, a DOAC may be considered in the absence of additional drug–drug interactions or close monitoring of VKA. In case of vomiting or diarrhoea, parenteral anticoagulant therapy is preferable, with the resumption of previous therapy as soon as possible. In patients on chemotherapy and with a new diagnosis of NVAF, in the absence of gastrointestinal cancer or active gastrointestinal mucosal abnormalities, it is preferable to prescribe a DOAC with respect to VKAs or low molecular weight heparin [78].

MANAGEMENT OF DOACS IN ELDERLY PATIENTS UNDERGOING AN INVASIVE PROCEDURE OR SURGERY

In patients undergoing an invasive procedure or surgery, clinical (including age, history of bleeding complications, concomitant medication, and kidney function) as well as surgical factors need to be taken into account when discontinuing and restarting a DOAC [79, 80]. In contrast to VKAs discontinuation, thrombotic risk assessment is far less relevant than the bleeding risk assessment that should be used as the primary determinant of DOACs discontinuation strategy for invasive procedure or surgery. Perioperative full-dose heparin bridging has been used in DOAC-treated patients. However, this practice does not have a pharmacologic rationale given the short (8–14 h) DOAC elimination half-lives, its association with increased bleeding risk, and its questionable efficacy, as suggested by the BRIDGE trial. In 1884 patients with NVAF who had warfarin discontinuation for elective surgery—mainly at low bleeding risk—or other elective invasive procedure, the incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group (RR 0.41; 95% CI 0.20–0.78) with similar thrombotic risk (0.4% and 0.3%, respectively) [81]. In the PAUSE study, a simple, standardized perioperative DOAC therapy interruption and resumption strategy based on DOACs' pharmacokinetic properties, procedure-associated bleeding risk, and creatinine clearance levels, without full-dose heparin bridging or measurement of coagulation function, was investigated in 3007 patients with NVAF undergoing invasive procedure or surgery, mainly at low bleeding risk. The DOAC regimens (apixaban, rivaroxaban, and dabigatran with a creatinine clearance of 50 mL/min or above) were omitted for 1 day before a low-bleeding-risk procedure and 2 days before a high-bleeding-risk procedure (2 and 4 days before, respectively, for dabigatran with a creatinine clearance below 50 mL/min). The DOAC regimens were resumed 1 day after a low-bleeding-risk procedure and 2–3 days after a high-bleeding-risk procedure [82]. In summary, the 30-day postoperative rate of major bleeding was 1.35% (95% CI 0–2.0) in the apixaban cohort, 0.90% (95% CI 0–1.73) in the dabigatran cohort, and 1.85% (95% CI 0–2.65) in the rivaroxaban cohort. All 43 major bleeding events and 9 of 10 arterial thromboembolic events occurred postoperatively at a median of 2 (IQR 0–6) days [82].

The EMIT-AF/VTE study documents the risks of bleeding and thromboembolic events in patients on edoxaban undergoing diagnostic and therapeutic procedures—mainly at low bleeding risk—in clinical practice. In 1155 procedures, there were 4.2% (95% CI 3.2–5.6) episodes of bleeding, of which 0.4% (95% CI 0.1–1.0) were classified as major. There were 0.5% (95% CI 0.2–1.1) acute thromboembolic events [83].

PHARMACOKINETIC CHARACTERISTICS OF DOACS AND DRUG INTERACTIONS

The knowledge of pharmacokinetics may be informative for avoiding potential drug–drug

interactions (Table 1). The absorption of DOACs is dependent on the intestinal P-gp system that limits their systemic exposure [84]. The extent of the interindividual variability of a plasmatic drug concentration may significantly impact P-gp inhibitor or inducer interaction. Dabigatran, as a result of the low bioavailability, and rivaroxaban, as a result of the once-daily posology, are expected to have a higher variability of peak and trough concentrations and may more easily undergo clinically relevant drug–drug interactions [85, 86]. On the contrary, edoxaban, also administered once-daily owing to its longer elimination half-life time, shows a lower variability than rivaroxaban and a low intersubject variability and dose linearity with a predictable and consistent pharmacokinetic profile [87].

Importantly, post hoc analysis of the Hokusai-VTE trial demonstrated that edoxaban plasma concentrations were independent of comorbidity and polypharmacy [88]. The ARISTOTLE trial also confirmed a risk reduction of apixaban versus warfarin for primary and secondary efficacy endpoints and major bleeding rates independently from an increasing number of concomitant drug treatments [89]. In the ROCKET-AF trial, rivaroxaban showed a lower risk of major bleeding than warfarin only in patients taking 0–4 medications, suggesting a possible negative interaction in patients treated with more than four drugs [90]. This result fits well because metabolism of edoxaban and apixaban is only marginally involved in their clearance. Thus inhibitors or inducers of these enzymes are unlikely to be involved in clinically relevant interactions [91, 92]. Conversely, a more relevant CYP3A4-dependent elimination is observed for rivaroxaban [93, 94].

Among DOACs, edoxaban is the only one to have active metabolites [95]. This property is useful when edoxaban is administered with potent inducers of CYP3A4/5 and P-gp, such as rifampin and antiepileptic drugs. These inducers determine a decrease in the total exposure of the parental drug, which is partially compensated by a significant increase of active metabolites [96, 97]. Finally, all DOACs undergo some degree of renal clearance, with 80%, 50%, 33%, and 27% of the absorbed doses of dabigatran, edoxaban, rivaroxaban, and apixaban, and with a renal clearance of 80 mL/min, 183 mL/min, 58 mL/min, and 15 mL/min, respectively [96]. The pharmacokinetics of dabigatran is strongly influenced by renal function. Edoxaban has the highest renal clearance, which exceeds the glomerular filtration rate, suggesting active secretion involvement [97]. In patients with creatinine clearance of 80 mL/min or above, rates of systemic embolic events for edoxaban were slightly higher than with warfarin.

In conclusion, the pharmacokinetic profile of DOACs may determine a significant difference in terms of potential drug–drug interactions. In response to anticipated drug–drug interactions, possible strategies, including dosage reduction or a different administration time, are recommended.

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REFERENCES

1. De Caterina R, Camm AJ. What is 'valvular' atrial fibrillation? A reappraisal. Eur Heart J. 2014;35:3328–35.
2. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. Stroke. 2009;40:235–40.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
4. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
5. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
6. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.
7. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. Lancet. 2014;383:955–62.
8. Kato ET, Gotob S, Giugliano RP. Overview of oral antithrombotic treatment in elderly patients with atrial fibrillation. Ageing Res Rev. 2019;49:115–24.
9. Dunlay SM, Chamberlain AM. Multimorbidity in older patients with cardiovascular disease. Curr Cardiovasc Risk Rep. 2016;10:3.
10. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365–75.
11. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95.
12. 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;6(7):e005657.
13. Ho P, Brooy BL, Hayes L, Lim WK. Direct oral anticoagulants in frail older adults: a geriatric

perspective. Semin Thromb Hemost. 2015;41(4):389–94.

14. Ehrlinder H, Orsini N, Modig K, Hofman-Bang C, Wallén H. Gigante B (2020) Clinical characteristics and antithrombotic prescription in elderly hospitalized atrial fibrillation patients: a cross-sectional analysis of a Swedish single-center clinical cohort. Int J Cardiol Heart Vasc. 2020;27:100505. https://doi.org/10.1016/j.ijcha.2020.100505.

15. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc. 2016;5(5):e003432.

16. Nicolau AM, Corbalan R, Nicolau JC, et al. Efficacy and safety of edoxaban compared with warfarin according to the burden of diseases in patients with atrial fibrillation: insights from the ENGAGE AF-TIMI 48 trial. Eur Heart J Cardiovasc Pharmacother. 2020;6(3):167–75.

17. Alexander KP, Brouwer MA, Mulder H, et al. Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: insights from the ARISTOTLE trial. Am Heart J. 2019;208:123–31.

18. 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(11):1169–78.

19. de Groot JR, Weiss TW, Kelly P, et al. Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: 1-year follow-up of the prospective observational ETNA-AF-Europe study. Eur Heart J Cardiovasc Pharmacother. 2021;7:f30–f39. https://doi.org/10.1093/ehjcvp/pvaa079.

20. Camm AJ, Fox KAA, Virdone S, et al. Comparative effectiveness of oral anticoagulants in everyday practice. Heart. 2021. https://doi.org/10.1136/heartjnl-2020-318420.

21. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 Trial. Circulation. 2016;134(1):24–36.

22. Wang CC, Kim YH, Brüggenjürgen B, et al. One-year follow-up of elderly patients with atrial fibrillation: data from the global noninterventional programme on edoxaban treatment in routine clinical practice in atrial fibrillation. Presented at the European Society of Cardiology Congress 2019, August 31–September 4, 2019, Paris, France.

23. Zathar Z, Karunatilleke A, Fawzy AM, Lip GYH. Atrial fibrillation in older people: concepts and controversies. Front Med. 2019;6:175.

24. Yao X, Tangri N, Gersh BJ, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol. 2017;70(21):2621–32.

25. Lauw MN, Eikelboom JW, Coppens M, et al. Effects of dabigatran according to age in atrial fibrillation. Heart. 2017;103(13):1015–23.

26. Lee KN, Choi JI, Kim YG, et al. Comparison of renal function estimation formulae for dosing direct oral anticoagulants in patients with atrial fibrillation. J Clin Med. 2019;8(12):2034.

27. Hawkins NM, Jhund PS, Pozzi A, et al. Severity of renal impairment in patients with heart failure and atrial fibrillation: implications for non-vitamin K antagonist oral anticoagulant dose adjustment. Eur J Heart Fail. 2016;18(9):1162–71.

28. Szummer K, Gasparini A, Eliasson S, et al. Time in therapeutic range and outcomes after warfarin initiation in newly diagnosed atrial fibrillation patients with renal dysfunction. J Am Heart Assoc. 2017;6(3):e004925.

29. Kumar S, Lim E, Covic A, et al. Anticoagulation in concomitant chronic kidney disease and atrial fibrillation: JACC review topic of the week. J Am Coll Cardiol. 2019;74(17):2204–15.

30. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation. 2018;138(15):1519–29.

31. Coleman CI, Kreutz R, Sood NA, et al. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. Am J Med. 2019;132(9):1078–83.

32. Pokorney SD. RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation - RENAL-AF. Presented at the American Heart Association Annual Scientific Sessions 2019.

33. Malik AH, Yandrapalli S, Aronow WS, Panza JA, Cooper HA. Meta-analysis of direct-acting oral anticoagulants compared with warfarin in patients >75 years of age. Am J Cardiol. 2019;123:2051–7.

34. Chao TZ, Liu CJ, Lin YJ, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. Circulation. 2018;138:37–47.

35. Paciaroni M, Agnelli G, Caso V, et al. Prediction of early recurrent thromboembolic event and major bleeding in patients with acute stroke and atrial fibrillation by a risk stratification schema: the ALESSA score study. Stroke. 2017;48:726–32.

36. Wilson D, Ambler G, Lee KJ, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. Lancet Neurol. 2019;18:653–65.

37. Seffige DJ, Paciaroni M, Wilson D, et al. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. Ann Neurol. 2019;85:823–34.

38. Xian Y, Xu H, O'Brien EC, et al. Clinical effectiveness of direct oral anticoagulants vs warfarin in older patients with atrial fibrillation and ischemic stroke findings from the patient-centered research into outcomes stroke patients refer and effectiveness research (PROSPER) study. JAMA Neurol. 2019;76:1192–202.

39. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347(23): 1825–33.

40. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med. 2020;383(14):1305–16.

41. Perez A, Touchette DR, DiDomenico RJ, Stamos TD, Walton SM. Comparison of rate control versus rhythm control for management of atrial fibrillation in patients with coexisting heart failure: a cost-effectiveness analysis. Pharmacotherapy. 2011;31: 552–65.

42. Tsadok MA, Jackevicius CA, Essebag V, et al. Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. Circulation. 2012;126:2680–7.

43. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.

44. Moreyra E, Finkelhor RS, Cebul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. Am Heart J. 1995;129:71–5.

45. Gibson CM, Basto AN, Howard ML. Direct oral anticoagulants in cardioversion: a review of current evidence. Ann Pharmacother. 2018;52:277–84.

46. Um KJ, Pandey A, et al. Direct oral anticoagulants versus vitamin K antagonists in patients undergoing cardioversion for atrial fibrillation: a systematic review and meta-analysis. Cardiovasc Drugs Ther. 2019;33:339–52.

47. Telles-Garcia N, Dahal K. Non-vitamin K antagonists oral anticoagulants are as safe and effective as warfarin for cardioversion of atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol. 2018;268:143–8.

48. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur J Cardiol. 2014;35:3346–55.

49. Goette A, Merino JL, Ezekowitz MD, et al. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomized, open-label, phase 3b trial. Lancet. 2016;388(10055):1995–2003.

50. Ezekowitz MD, Pollack CV Jr, Halperin JL, et al. Apixaban compared to heparin/vitamin K antagonist in patients with atrial fibrillation scheduled for cardioversion: the EMANATE trial. Eur Heart J. 2018;39:2959–71.

51. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. New Engl J Med. 2017;377(16): 1513–24.

52. Dewilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomized, controlled trial. Lancet. 2013;381(9872):1107–15.

53. Fiedler KA, Maeng M, Mehilli J, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. J Am Coll Cardiol. 2015;65(16): 1619–29.

54. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med. 2016;375(25):2423–34.

55. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med. 2019;380(16): 1509–24.

56. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomized, open-label, phase 3b trial. Lancet. 2019;394(10206):1335–43.

57. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):

1289–1367. https://doi.org/10.1093/eurheartj/ehaa575.

58. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective–2018 update. Circulation. 2018;138(5):527–36.

59. Lip GYH, Collet J-P, Haude M, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace. 2019;21(2):192–193.

60. Capodanno D, Huber K, Mehran R, et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI. J Am Coll Cardiol. 2019;74(1):83–99.

61. Potpara TS, Mujovic N, Proietti M, et al. Revisiting the effects of omitting aspirin in combined antithrombotic therapies for atrial fibrillation and acute coronary syndromes or percutaneous coronary interventions: meta-analysis of pooled data from the PIONEER AF-PCI, RE-DUAL PCI, and AUGUSTUS trials. Europace. 2020;22(1):33–46.

62. Galli M, Andreotti F, D'Amario D, et al. Dual therapy with direct oral anticoagulants significantly increases the risk of stent thrombosis compared to triple therapy. Eur Heart J Cardiovasc Pharmacother. 2020;6(2):128–9.

63. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J. 2019;40(46):3757–67.

64. Haller PM, Sulzgruber P, Kaufmann C, et al. Bleeding and ischaemic outcomes in patients treated with dual or triple antithrombotic therapy: systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother. 2019;5(4):226–36.

65. Galli M, Andreotti F, Porto I, Crea F. Intracranial haemorrhages vs. stent thromboses with direct oral anticoagulant plus single antiplatelet agent or triple antithrombotic therapy: a meta-analysis of randomized trials in atrial fibrillation and percutaneous coronary intervention/acute coronary syndrome patients. Europace. 2020;22(4):538–46.

66. Damluji AA, Resar JR, Gerstenblith G, Gross AL, Forman DE, Moscucci M. Temporal trends of percutaneous coronary interventions in older adults with acute myocardial infarction. Circ Cardiovasc Interv. 2019;12(5):e007812.

67. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. Eur Heart J. 2015;36(47):3320–31.

68. O'Neal WT, Lakoski SG, Qureshi W, et al. Relation between cancer and atrial fibrillation (from the reasons for geographic and racial differences in stroke study). Am J Cardiol. 2015;115(8):1090–4.

69. Raschi E, Diemberger I, Cosmi B, De Ponti F. ESC position paper on cardiovascular toxicity of cancer treatments: challenges and expectations. Intern Emerg Med. 2018;13(1):1–9.

70. D'Souza M, Carlson N, Fosbol E, et al. CHA2DS2-VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. Eur J Prev Cardiol. 2018;25:651–8.

71. Fanola CL, Ruff CT, Murphy SA, et al. Efficacy and safety of edoxaban in patients with active malignancy and atrial fibrillation: analysis of the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc. 2018;7(16):e008987.

72. Melloni C, Dunning A, Granger CB, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE trial. Am J Med. 2017;130(12):1440–8.

73. Laube ES, Yu A, Gupta D, et al. Rivaroxaban for stroke prevention in patients with non-valvular atrial fibrillation and active cancer. Am J Cardiol. 2017;2:213–7.

74. Ording AG, Horváth-Puhó E, Adelborg K, Pedersen L, Prandoni P, Sørensen HT. Thromboembolic and bleeding complications during oral anticoagulation therapy in cancer patients with atrial fibrillation: a Danish nationwide population-based cohort study. Cancer Med. 2017;6(6):1165–72.

75. Shah S, Norby FL, Datta YH, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Adv. 2018;2:200–9.

76. Wolff A, Shantsila E, Lip GY, Lane DA. Impact of advanced age on management and prognosis in atrial fibrillation: insights from a population-based study in general practice. Age Ageing. 2015;44:874–8.

77. Atterman A, Friberg F, Asplund K, Engdahl J. Net benefit of oral anticoagulants in patients with atrial fibrillation and active cancer: a nationwide cohort study. Europace. 2020;22(1):58–65.

78. Delluc A, Wang T-F, Yap E-O, et al. Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH Practice Guideline. J Thromb Haemost. 2019;17(8):1247–52.

79. Spyropoulos AC, Brohi K, Caprini J, et al. Scientific and Standardization Committee Communication: guidance document on the periprocedural management of patients on chronic oral anticoagulant therapy: recommendations for standardized reporting of procedural/ surgical bleed risk and patient-specific thromboembolic risk. J Thromb Haemost. 2019;17:1966–72.

80. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330–93.

81. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373:823–33.

82. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative management of patients with atrial fibrillation receiving a direct oral anticoagulant. JAMA Intern Med. 2019;179(11):1469–78.

83. Colonna P, von Heymann C, Santamaria A, et al. Routine clinical practice in the periprocedural management of edoxaban therapy is associated with low risk of bleeding and thromboembolic complications: the prospective, observational, and multinational EMIT-AF/VTE study. Clin Cardiol. 2020;43(7):769–80.

84. Chang CJ, Hsu LA, Ko YH, et al. Thrombin regulates matrix metalloproteinase-9 expression in human monocytes. Biochem Biophys Res Commun. 2009;385:241–6.

85. Gosselin RC, Adcock DM, Bates SM, et al. International council for standardization in haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost. 2018;118:437–50.

86. Testa S, Tripodi A, Legnani C, et al. Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: results observed in four anticoagulation clinics. Thromb Res. 2016;137:178–83.

87. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol. 2010;50(7):743–53.

88. Vanassche T, Verhamme P, Wells PS, et al. Impact of age, comorbidity, and polypharmacy on the efficacy and safety of edoxaban for the treatment of venous thromboembolism: An analysis of the randomized, double-blind Hokusai-VTE trial. Thromb Res. 2018;162:7–14.

89. Jaspers Focks J, Brouwer MA, Wojdyla DM, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. BMJ. 2016;353:i2868.

90. Piccini JP, Hellkamp AS, Washam JB, et al. Polypharmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation. Circulation. 2016;133:352–60.

91. Parasrampuria DA, Truitt KE. Pharmacokinetics and pharmacodynamics of edoxaban, a non-vitamin K antagonist oral anticoagulant that inhibits clotting factor Xa. Clin Pharmacokinet. 2016;55:641–55.

92. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015;17(10):1467–507.

93. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. Br J Clin Pharmacol. 2013;76:455–66.

94. Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology. 2002;36:164–72.

95. LIXIANA. http://www.emaeuropaeu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf. 2018. Accessed 3 July 2015.

96. Padrini R. Clinical pharmacokinetics and pharmacodynamics of direct oral anticoagulants in patients with renal failure. Eur J Drug Metab Pharmacokinet. 2019;44(1):1–12.

97. Camm AJ, Bounameaux H. Edoxaban: a new oral direct factor Xa inhibitor. Drugs. 2011;71:1503–26.