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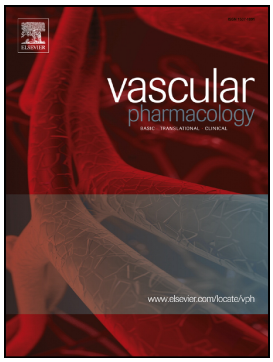

State of play and future direction with NOACs: An expert consensus

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Abstract

Atrial fibrillation (AF) and venous thromboembolism (VTE) are cardiovascular conditions significant in contemporary practice. In both, the use of anticoagulation with vitamin K antagonists (VKAs) has been traditionally used to prevent adverse events. However, VKA therapy is associated with challenges relating to dose maintenance, the need to monitor anticoagulation, and bleeding risks. The non-vitamin K oral anticoagulants (NOACs) are becoming accepted as a clear alternative to VKA therapy for both AF and VTE management. The aim of this paper was to review contemporary evidence on the safety of NOACs in both conditions. A comprehensive literature review was conducted to explore key safety issues and expert consensus was achieved from eight professionals specialised in AF and VTE care. Consensus-based statements were formulated where available evidence was weak or contradictory. The expert statements in this paper form a key overview of the safety of NOACs compared with VKA therapy, and the comparative safety of different NOACs. It is apparent that a detailed patient work-up is required in order to identify and manage individual risk factors for bleeding and thrombosis prior to NOAC therapy. Additional measures, such as dose reductions, may also be used to maintain the safety of NOACs in practice.

Keywords: oral anticoagulants, pulmonary embolism, deep vein thrombosis, atrial fibrillation, expert consensus

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an incidence of 0.85–4.1 per 1000 person-years, depending on the cohort studied (1–3). Morbidity and mortality are associated with AF, which particularly increases stroke risk five-fold. Approximately 20% of ischaemic strokes are directly attributable to AF (4).

Venous thromboembolism (VTE) is a term used to describe pulmonary embolism (PE) and deep vein thrombosis (DVT) or both. It is estimated that VTE affects over 1 million people in Europe annually (5), with a 21.6% all-cause mortality after one year of diagnosis (6). Without anticoagulation therapy, recurrence of VTE occurs at a rate of 12.9% within the first year of diagnosis (7). The rate of recurrence with anticoagulation therapy peaks at 11.1 per 100 person-years within 180 days following the first event, falling to 8.1 per 100 person years between 181–365 days post-event (6).

For both AF and VTE, the use of long-term anticoagulation strategies is recommended to prevent stroke in AF patients and/or thromboembolic events in both. The use of vitamin K antagonists (VKAs), including warfarin, is a common approach to anticoagulation, but is associated with a number of practical challenges, including the unpredictable nature of anticoagulation achieved with the drug on a patient-by-patient basis, numerous food and dietary interactions, and the need for constant anticoagulation monitoring (8,9). Optimal anticoagulation with VKA therapy in AF and VTE is defined as an international normalised ratio (INR) of 2–3 (10). Deviation from this range, with poor anticoagulation control, has the potential to decrease the efficacy or increase the bleeding risk of the drug (11–14).

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The non-vitamin K antagonist oral anticoagulants (NOACs) have emerged as viable alternatives to VKA therapy in patients with AF or VTE. Four drugs are currently approved for these indications in Europe: dabigatran, apixaban, rivaroxaban, and edoxaban. Dabigatran is a direct thrombin inhibitor (15), while the other NOACs target Factor Xa (16–18). Phase III trials of the NOACs compared to VKA therapy demonstrate non-inferiority, and in some cases superiority, of these agents for reducing the risk of stroke/thromboembolic events in AF patients and in reducing the risk of recurrence in VTE patients. All NOACs have also been shown to be non-inferior or superior to VKAs for key safety outcomes, including the risk of bleeding. These agents have a predictable dosing profile, fewer drug and dietary interactions than VKAs, and do not require anticoagulation monitoring (19–21).

However, the safety profile associated with anticoagulant use varies within these populations. Patients with either AF or VTE are heterogeneous in nature, and characterised by multiple risk factors for bleeding or thromboembolism. Factors such as age, renal function, body weight, frailty, and the presence of comorbid disease may influence the response to NOACs and the subsequent safety of these agents. As a result, there is a growing need for appreciation of the safety features of NOACs to be comprehensively reviewed, in order to direct or tailor therapy in specific patient sub-populations and in specific care contexts (22,23).

Aim

The aim of this paper was to provide an overview of the current evidence base in order to characterise how NOACs can be used safely within the clinical setting. To meet this aim, the following objectives were met:

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- Comparison of safety outcomes for NOACs and alternative anticoagulants
- Evaluation of safety in specific clinical scenarios and patient groups
- Consideration of NOAC dosing and practical administration.

Methods

A comprehensive, systematic literature search was completed to provide an overview of the safety of NOACs in clinical practice. This search was conducted using multiple online databases, including papers published up to the 31st March 2017. Primary data sets were used for analysis wherever possible, while the summary of product characteristics (SmPC) for each NOAC was consulted to ensure accurate dosing information. Once the final data set was identified, these papers were critically appraised, and key evidence was extracted in order to provide a synthesis of safety data.

This report was composed in collaboration with an international panel of eight experts in the field of AF or VTE (inclusive of two chairpersons) in order to ensure the clinical relevance of all expert statements. A consensus process was employed based on a modified Delphi technique, wherein all experts were asked to contribute their clinical expertise in defining key clinical questions, as well as in the generation of expert statements. This strategy took place in a series of 'rounds', consistent with the iterative nature of the process. Specifically, once the key clinical topics were identified, all experts were asked to complete questionnaires and indicate their agreement with evidence statements. Based on the level of agreement noted for all experts these statements were revised and the process was repeated, if necessary. This was continued until a consensus was achieved, defined as agreement of

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at least 70% of the experts. Where there was continued disagreement among the experts, the chairpersons had a final say over the direction of any expert statements.

For each expert statement, the strength of available research evidence is presented, based on the criteria noted in table 1. Level I evidence comprises meta-analyses or RCTs and high-quality RCTs. Level II evidence comprises quasi-experimental studies and controlled studies (non-randomised). Level III evidence comprises descriptive studies (e.g. comparative, correlation or case-control methodologies). Finally, Level IV evidence suggests that there is a lack of formal research in this area, and that expert opinions or reports form the basis for this level of evidence (24).

Following determination of the existing level of support, for each expert statement the strength of the statement (SOS) was determined. The SOS is a marker for the overall degree to which the evidence supports the assertion of the expert statement. Two categories were used for the sake of simplicity: strong and weak statements. Strong statements included more definitive wording (i.e., “it is advised that” or “strongly advised that”), while weak statements were represented in a less authoritative manner (i.e., “should be”). When consensus was used to achieve the statement, the percentage agreement was recorded along with the SOS, to highlight the level of agreement between experts. Where consensus was not considered necessary, based on the quality of available data, the “% agreement” component is absent from the expert statement.

Results and expert statements

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The results of the combined literature search and consensus process are presented according to three categories: patient safety outcomes; specific patient groups; and practical issues in prescribing. For each of these categories the statements are presented, with a supporting summary of the available evidence. Statements where consensus was required are clearly noted. In total, 44 statements were formulated, 22 of which were based on expert consensus due to a lack of available evidence or conflicting data.

Patient safety outcomes

This paper focused on five main patient safety outcomes: major or clinically relevant non-major (CRNM) bleeding; intracranial bleeding; gastrointestinal bleeding; bleeding mortality; and cardiovascular mortality. Statements are presented in table 2.

Major or CRNM bleeding

Phase III trials in patients with AF (25–28) demonstrate that all NOACs are associated with similar or reduced risks of major or CRNM bleeding compared to warfarin therapy. For dabigatran, there was a dose-dependent effect on major bleeding, with 110 mg twice daily associated with a statistically significantly lower rate of bleeding compared to warfarin ($p=0.003$), but comparable bleeding rates with 150 mg twice-daily dabigatran and warfarin. For rivaroxaban, the rate of major bleeding was comparable to that seen with warfarin ($p=0.35$). Apixaban was associated with a statistically significant reduction in major bleeding compared to warfarin ($p<0.001$). Finally, edoxaban was associated with a significant reduction in all major bleeding compared to warfarin, regardless of the edoxaban dose ($p<0.001$).

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For the phase III trials of NOACs versus VKA therapy in patients with VTE, the major safety outcome was CRNM bleeding or composite bleeding outcomes (29–33). The data from these trials suggest that all NOACs are at least non-inferior to warfarin for this safety outcome. For dabigatran 110 mg twice daily, a composite endpoint of major and CRNM bleeding suggested a lower rate of bleeding with dabigatran, although statistical significance was not reported. Similarly, the rate of major bleeding was reduced by 69% with apixaban compared to warfarin, and the rate of major or CRNM bleeding was significantly reduced. There was no significant difference between the rates of first major or CRNM bleeding for rivaroxaban compared to warfarin in either the EINSTEIN-DVT or EINSTEIN-PE studies. Edoxaban was shown to be superior to warfarin for CRNM bleeding in a statistically significant manner (p=0.004).

It has been recommended that major or CRNM bleeding should be considered an important factor in guiding NOAC selection versus VKA therapy (34). However, other factors need to be taken into account to ensure patient safety. Expert consensus supported the identification of modifiable risk factors prior to anticoagulant use. However, bleeding risk is highly dynamic, and hence regular reassessment of modifiable bleeding risk factors is needed in patients 'flagged up' for review, with suitable follow-up (35).

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Intracranial bleeding

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The risk of intracranial bleeding with anticoagulation therapy is important, as it is strongly associated with poor patient outcomes. In phase III trials with AF patients, there was a significant reduction in intracranial bleeding associated with NOAC use compared to warfarin. For dabigatran, both 110 mg and 150 mg twice-daily doses were associated with statistically significant reductions in intracranial bleeding compared to warfarin ($p<0.001$ for both). Similarly, intracranial bleeding was significantly lower with rivaroxaban compared to warfarin ($p=0.02$). Apixaban was associated with a significant reduction in intracranial bleeding compared to warfarin. The investigation of intracranial bleeding rates in patients treated with NOACs for VTE demonstrated a significantly lower rate of intracranial bleeding associated with NOAC therapy compared to warfarin therapy.

The evidence suggests that NOACs are likely to be preferable to VKA therapy for the prevention of intracranial bleeds. Important considerations pertain as to when best to restart OAC after a presentation with an intracranial bleed, as such patients were excluded from clinical trials (36).

Gastrointestinal bleeding

A meta-analysis of NOAC studies found that the NOACs are associated with a higher rate of gastrointestinal bleeding than warfarin therapy, with similar rates observed with low-dose NOAC regimens and warfarin use (37). However, the rates of gastrointestinal bleeding varied and were comparable with apixaban and warfarin (0.76% vs 0.86%, HR 0.89, 95% CI 0.70–1.15, $p=0.37$). The rate of gastrointestinal bleeding with the high-dose edoxaban regimen (60 mg) was not statistically different to that seen with warfarin therapy. In the VTE trials, the rate of gastrointestinal bleeding was similar with the NOACs compared to warfarin, with the exception

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of apixaban, for which the rate was significantly lower. A meta-analysis of phase III trial data suggests that the risk of major gastrointestinal bleeding did not differ significantly between the NOACs and warfarin (38). Consequently, the use of either NOACs or VKA therapy should prompt a risk assessment for gastrointestinal bleeding in eligible patients to ensure safety.

Fatal bleeding

Although bleeding events were extensively documented in phase III trials, the incidence of fatal bleeding was not consistently noted in the RE-LY or ARISTOTLE trials (life-threatening bleeding in combination with major bleeding was here used as an outcome). Edoxaban (at both doses) and rivaroxaban were associated with a reduction in fatal bleeding events compared to warfarin. Data on dabigatran and apixaban are available from additional analyses, although the statistical significance of these events is uncertain. Fatal bleeding in VTE studies was generally infrequent, and none of the studies showed a significant difference between fatal bleeding rates for any NOAC compared to warfarin. A meta-analysis (39) of randomised trials of AF and VTE patients receiving NOAC therapy showed that the rate of fatal bleeding events was generally lower with the NOACs, although the effect was more pronounced in AF patients.

Despite the benefits of NOACs in reducing fatal bleeding compared with VKA therapy, expert consensus determined that fatal bleeding risk alone was not sufficient to justify the use of NOACs over VKA, as a multifactorial analysis of bleeding and thrombosis risk should be used to guide treatment choice.

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Cardiovascular mortality

The phase III NOAC trials in patients with AF explored cardiovascular outcomes of the NOACs compared to warfarin therapy. Only the ENGAGE AF-TIMI 48 trial (edoxaban) demonstrated a statistically significant reduction in cardiovascular mortality associated with edoxaban compared to warfarin. A non-significant reduction in cardiovascular deaths was observed in the ROCKET-AF trial with rivaroxaban compared to warfarin. Neither the RE-LY nor ARISTOTLE trials provide detailed data on cardiovascular mortality. However, the RE-LY study demonstrated a lower level of cardiovascular mortality with the higher dose of dabigatran compared to warfarin, while the ARISTOTLE study reported comparable mortality due to cardiovascular causes in both treatment groups (1.80% per year with apixaban and 2.02% per year with warfarin). Cardiovascular mortality has not been explored in detail for patients with VTE in phase III NOAC trials, largely due to the low rate of cardiovascular deaths seen with either NOACs or warfarin in these trials. In all phase III VTE trials cardiovascular mortality was low with NOACs and there is no discernible difference between the findings for individual NOACs.

Based on these data, expert consensus is that cardiovascular risk alone does not justify NOAC use over VKA use in either AF or VTE patients, but cardiovascular risk factor identification and management should be prompted prior to either therapy.

Specific patient groups

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Specific patient groups were selected on the basis that they may be associated with alterations in the safety profile of anticoagulant use in both AF and VTE. Expert statements for the defined patient groups are presented in table 3.

Elderly and fragile patients

Patients aged over 75 years are at overall high risk of stroke irrespective of the presence of AF (40), and have been shown to have an increased risk of adverse events associated with AF or VTE, as well as with the anticoagulation strategy used for these indications. The efficacy and safety of the NOACs in older patients has been noted in trial subgroup analyses for both AF and VTE patients, suggesting that both outcomes are comparable to or better than those seen with warfarin therapy.

For patients with VTE, trial data suggest that the safety of each NOAC is preserved in older patient subgroups. However, only a small proportion of patients were aged ≥75 years in these trials, and the presence of comorbidities in trial populations may be lower than that seen in clinical practice populations (41). Only rivaroxaban and edoxaban trials have reported specific analyses of the fragile population. An analysis of the EINSTEIN-PE and EINSTEIN-DVT trials defined fragile patients as those who were elderly, had moderate or severe renal impairment, or low body weight. According to this definition, the rate of bleeding was higher in fragile patients compared to the general study population.

Rivaroxaban demonstrated superior safety compared to standard therapy for fragile patients, with a significant reduction in major bleeding (HR, 0.27; 95% CI, 0.13–0.54; P= 0.011), which was not the case in non-fragile patients (42). In the HOKUSAI-VTE trial

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(29), 1,421 patients were classified as fragile (CrCl 30–50 mL/min, age ≥75 years of age, or body weight ≤50 kg). Comparable rates of clinically relevant bleeding were observed in fragile and non-fragile patients, showing that edoxaban maintained superiority for safety compared to standard therapy. An analysis of dose-reduced edoxaban (30 mg) in VTE patients has shown comparable safety and efficacy compared with the 60 mg dose, but improved safety compared with warfarin (43).

For elderly patients, it is recommended that NOACs should be considered as viable alternatives to VKA therapy. Age alone should not be universally considered a sufficient justification for dose reduction of NOACs, however, and specific guidelines for dose reduction are reported in the specific SmPCs. Dose reductions to maintain safety should be specifically based on published guidance. However, real world data on elderly patients with AF are needed (44).

Patients with active cancer

Cancer is known to be a hypercoagulable state, increasing the risk of VTE in patients (45,46). It is estimated that patients with active cancer have a 4 to 8-fold increased risk of VTE compared to the general population (47,48). Patients with AF and active cancer have an increased risk of bleeding and thrombosis compared to the general AF population (49).

A systematic review and meta-analysis of data for VTE management in cancer patients suggested that NOACs may be beneficial compared to warfarin, although these findings did not approach statistical significance due to small numbers of patients in these trials (50). Furthermore, data comparing NOACs with LMWH for the prevention of thrombosis are minimal. The data comparing

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NOACs to warfarin in patients with AF and cancer are also limited by exclusion criteria in phase III trials, including life expectancy of patients. It can be expected that drug-drug interactions (including common chemotherapy regimens), bleeding risk and thrombosis risk all contribute towards the suitability of NOACs versus warfarin in this group. Therefore, pending further data, patients with active cancer should be thoroughly assessed to determine their bleeding risk and risk of VTE or stroke/SEE. However, given that warfarin is the standard therapy in patients with AF, the presence of cancer in AF patients is not, at the moment, a contraindication to the use of a NOAC.

Overall, expert consensus noted that VTE guidelines should be followed, with NOACs only considered when patients cannot tolerate LMWH, with NOACs representing alternatives to VKA therapy. In patients with cancer bleeding risk factors and drug-drug interactions should be carefully considered when selecting NOACs, while dose reductions are recommended in patients with impaired renal function, low body weight and/or advancing age. However, recent data from the Hokusai VTE cancer study (51) found that the combination of LMWH (minimum of 5 days) followed by edoxaban 60 mg once daily was non-inferior to the use of subcutaneous dalteparin (200 IU per kg body weight for one month followed by 150 IU per kg body weight) in patients with cancer-associated VTE (P=0.006). The primary outcome in this study was composite recurrent VTE or major bleeding during 12 months following randomisation: the lower rate of recurrent VTE with edoxaban (7.9% vs 11.3%) was offset by the higher rate of major bleeding with edoxaban (6.9% vs 4.0%). Therefore, edoxaban may be considered as an alternative to LMWH in patients with cancer-associated VTE and optimisation of control of modifiable bleeding risk factors should be emphasised.

Patients with renal impairment

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Renal impairment is an independent risk factor for haemorrhage (52), potentially increasing the risk of adverse bleeding events in patients on oral anticoagulant therapy. VKA therapy is associated with a poor safety record in patients with renal impairment (53), hence NOACs may be a good alternative to warfarin. However, the NOACs undergo renal clearance to varying degrees and therefore there is the potential for increased drug exposure in renal impairment.

In AF patients, numerous analyses have been conducted on NOAC efficacy and safety based on renal function (54). Data from the RE-LY trial showed that stroke/SEE rates were lower with dabigatran 150 mg twice daily compared to warfarin, regardless of renal function (55), but significant reductions in major bleeding were only seen in patients with CrCl ≥80 mL/min. In the ROCKET-AF trial, patients with CrCl 30–49 mL/min received a reduced dose of 15 mg once daily rivaroxaban, which was associated with comparable safety and efficacy outcomes to warfarin therapy and a lower rate of fatal bleeding (56). In the ARISTOTLE trial, apixaban was dose-reduced to 2.5 mg twice daily in patients with 2 or 3 risk factors (serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤60 kg) (57). Subgroup analyses showed that patients with CrCl 30–50 mL/min or lower, had a greater reduction in major bleeding with apixaban compared to warfarin. A recent analysis (58) of edoxaban versus warfarin in patients with CrCl ≤50 mL/min or >50 mL/min showed that higher-dose edoxaban regimen (60 mg/30 mg) was associated with a lower bleeding rate compared to warfarin, regardless of CrCl. Furthermore, the net clinical benefit of higher-dose edoxaban remained favourable compared to warfarin across all CrCl values (58).

For VTE, a pooled analysis of the NOAC trials suggested that safety outcomes (clinically relevant bleeding) were consistent in patients with and without renal impairment (defined as CrCl 30–50 mL/min) (59). However, in the AMPLIFY trial only 6% of patients

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in the apixaban arm had a CrCl <50 mL/min (30). Similarly, in the Hokusai-VTE trial only 7% of patients had a CrCl of 30–50 mL/min (29). Therefore, the generalisability of these findings to the practice VTE population may be limited. It is important to consider labelling recommendations in addition to trial data, however. For instance, rivaroxaban was used without dose adjustment in patients with renal impairment in the EINSTEIN trials, but now consideration of dose reduction is suggested in rivaroxaban labelling in this context. This applies to multiple aspects of pharmacological dosing, particularly as more data become available.

There are sufficient data to suggest that renal impairment demands modification of NOAC doses in some settings and careful consideration of NOAC use. Published guidelines should be adhered to in this context.

Other patient groups

Obese patients may demonstrate alterations in NOAC pharmacokinetics and exposure and have an increased risk of hypertension and cardiovascular disease compared to the non-obese population (60). However, limited data are available regarding NOAC therapy in obese patients (60). The RE-LY study noted a 20% decrease in trough concentrations of dabigatran in patients over 100 kg in weight (25). However, dosing adjustments for obese patients are not currently recommended (55). Similarly, for rivaroxaban and apixaban no changes in dosing are recommended in obese patients, although the ARISTOTLE trial only stratified patients as weighing less than or greater than 60 kg, limiting the ability to draw conclusions regarding efficacy in obesity (26). Data on edoxaban suggest that dose adjustment based on obesity may not be warranted (61). Expert consensus recommends avoiding dose adjustments due to obesity. Patients with low body weight have been considered elsewhere in the literature (60) and current recommendations for dose reductions, based on product labels, should be adhered to in such patients.

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Whether or not patients with a single stroke risk factor i.e. CHA_2DS_2-VASc = 1 (men) or 2 (women) require oral anticoagulation remains controversial. These patients are considered at low-risk for thrombotic events, but may still have preventable morbidity and mortality associated with stroke risk. These patients are under-represented in clinical trials but observational studies have suggested a net clinical benefit of NOACs versus aspirin (a treatment alternative that is not widely recommended) or no antithrombotic therapy in patients with one additional CHA_2DS_2-VASc stroke risk factor (excluding sex) (62–64). However, confounding factors may have influenced these findings, including variation in bleeding risk or disease severity in patients initiated on anticoagulation. Data from the SPORTIF trials suggest that patients with one additional stroke risk factor have a high rate of major adverse events (stroke/SEE and mortality), even when oral anticoagulation was used (65). Expert consensus agrees with published ESC guidelines, recommending anticoagulation in men with CHA_2DS_2-VASc = 1 and women with CHA_2DS_2-VASc = 2, depending on individual risk factors,

Previous cerebral ischaemic events in patients with AF are associated with an increased risk of future events (66–68) but a highly relevant question is when to reinitiate OAC after presentation with an ischaemic stroke (69). Phase III NOAC trials found that patients with previous stroke/transient ischaemic attack (TIA) had a higher rate of stroke than patients without a history of stroke/TIA. Subgroup analyses of trials exploring the use of dabigatran, rivaroxaban and apixaban found similar efficacy and safety with these NOACs, regardless of stroke/TIA history (70–72). A meta-analysis of apixaban, dabigatran, and rivaroxaban found that NOACs were comparable to warfarin for the prevention of stroke/SEE in patients with a history of stroke/TIA, while the rate of intracranial bleeding was lower with NOACs compared with warfarin in this subgroup (73). Edoxaban has also been shown to have

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a lower rate of bleeding compared to warfarin for primary and secondary stroke prevention (74). Therefore, NOACs are recommended for use in patients with or without previous history of stroke/TIA.

The bleeding risk of an individual patient is an important consideration prior to NOAC therapy, as all forms of anticoagulation may be associated with a risk of bleeding. Bleeding risk scores may be used to inform clinicians of the risk of haemorrhage in patients with AF. The appropriate use and misuse of bleeding risk scores has recently been discussed (35). The use of over-simplified bleeding risk scores (e.g. ORBIT, ATRIA) may result in many patients with a high bleeding risk not being identified appropriately (75).

The HAS-BLED score has been shown to outperform alternative bleeding risk scores in real-world and trial patient populations and has practical advantages over other scoring systems (76,77), suggesting that it should be preferentially used in practice. Since VKAs are most widely used worldwide, other scores that do not account for labile INR or poor TTR would perform suboptimally in predicting bleeding risk (78,79). However, other bleeding risk scores may play an important role in evaluating bleeding risk (major and clinically relevant non-major bleeding), and no preference is indicated in recent European guidelines. Therefore, the use of any bleeding risk score can be considered a means of flagging up high risk patients to be brought back for review and more careful follow-up, and for identifying modifiable risk factors for bleeding; the key issue is identifying these risk factors and addressing them, as appropriate. In the pursuit of individualised approaches to patient risk assessment and anticoagulant therapy, consideration of individual risk factors may be more important than general risk factor scores for justifying dose-reduced NOAC therapy (80). Expert consensus advises individual risk factor assessment and the use of bleeding scores to assist in this process.

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Clinically relevant non-major bleeding poses a challenge to healthcare professionals and patients and is defined as bleeding that does not meet major bleeding criteria, but which requires healthcare intervention, contact with physicians, interruption of the study drug, discomfort or impacts of activities of daily living. The findings of large clinical trials suggest NOACs have a similar level of safety for major and clinically relevant non-major bleeding compared with warfarin therapy. Therefore, pending further data, the same recommendations may apply to the use of NOACs with both types of bleeding as safety outcomes.

Nuisance bleeding should also be recognised as a clinical problem, encompassing minor bleeding, which is often temporary, but which may prompt patient dissatisfaction and physician medication switching (34,81). Nuisance bleeding may account for uncontrolled treatment interruptions initiated by the patient. These bleeding events may include gum bleeding or nosebleeds, and patients should be advised of strategies to minimise these events (e.g., the use of soft toothbrushes, or of an electric razor when shaving). Ultimately, nuisance bleeding is not a sufficient justification for switching oral anticoagulants and modifiable risk factors should be addressed.

Dual antiplatelet therapy is an important clinical challenge in NOAC use. The combination of AF and coronary artery disease (CAD) is common in the practice setting (82) and adds complexity to the management of AF patients due to the higher risk of mortality and the increased risk of bleeding noted with the use of anticoagulation and antiplatelet therapy (81). Combination therapy is often inappropriately prescribed in the setting of AF, and mostly in the presence of concomitant vascular disease, under the wrong belief that antiplatelet agents are the default best option in such patients (83). It is estimated that the risk of bleeding increases roughly 60–80% when combining anticoagulants with single antiplatelet therapy, and by at least 130% with dual antiplatelet therapy (84). Phase III trials failed to show any effect of previous myocardial infarction or the use of dual antiplatelet therapy on safety outcomes

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when comparing NOACs and VKA therapy for AF management. However, the PIONEER AF-PCI trial (85) showed that the use of reduced dose rivaroxaban plus dual antiplatelet therapy led to significantly reductions in bleeding compared to VKA therapy in combination with dual antiplatelet therapy. Furthermore, the REDUAL trial showed that dabigatran plus P2Y12 inhibitor therapy was associated with a lower bleeding risk post-PCI compared with combined warfarin, P2Y12 inhibitor and aspirin therapy (86).

Recent guidance suggests that the use of dual antiplatelet therapy in combination with oral anticoagulation is required after PCI and should be limited in duration to minimise excessive bleeding risks (81,87), although It may also be, based on the PIONEER-AF study, that the use of aspirin in the presence of 15 mg/day rivaroxaban may be safely omitted (85). However, this study was not powered to show any difference in efficacy, suggesting further data are needed to confirm this finding.

There is no evidence to suggest that the benefits of prolonged antiplatelet therapy lead to clinical benefits, and NOAC monotherapy should be advised in patients with stable vascular disease (≥1 year after an acute coronary syndrome). Ultimately, the decision to combine NOACs and single or dual antiplatelet therapy should be based on a comprehensive evaluation of cardio-embolic risk, bleeding risk and athero-thrombotic risk.

Incidental or unsuspected VTE can be defined as the detection of either DVT or PE during imaging studies for unrelated reasons (e.g., cancer staging) (88). Due to a lack of prospective interventional studies assessing the optimal management approach in incidental VTE, the benefit of anticoagulation and the selection of specific agents remain controversial. There is presently a lack of evidence to suggest any negative effects of therapeutic anticoagulation with NOACs in patients with incidental VTE, provided there

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are no other contraindications to therapy. However, confirmation of the diagnosis should be sought prior to initiating treatment, where possible, in order to ensure that NOACs are used appropriately (89).

Practical issues in prescribing

There are instances where the practical use of NOACs may be associated with variations in patient safety, including the use of NOACs and reversal agents during acute bleeding, switching from VKA therapy to NOACs, and with or without a heparin lead-in for VTE management. The expert statements for practical issues of NOAC safety are presented in table 4.

Managing acute bleeding

One of the major sources of concern regarding broad uptake of the NOACs is the lack of specific reversal agents (90). Warfarin can be effectively monitored through INR determinations and the anticoagulant effects reversed, albeit slowly with vitamin K_1 administration (91). However, the short half-life of NOACs suggests that in most instances doctors need only to wait for bleeding to stop without the need for an antidote. The indications for when antidotes are needed should be clarified, without overreliance on these measures in cases of bleeding that is not severe or life-threatening.

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Idarucizumab is the first specific reversal agent for NOACs to be approved, and irreversibly binds to dabigatran neutralising its activity (92). Its approval was based on the reduction in unbound dabigatran and the rapid normalisation of coagulation parameters in healthy volunteers in the context of emergency procedures and life-threatening or uncontrolled bleeding (93). Reassuring data are now also available from a phase IIIb 'real world' study with this agent (94).

Andexanet alfa, a recombinant modified human factor Xa decoy protein, is currently under investigation as a potential reversal agent for factor Xa inhibitors (95). Ciraparantag is currently in clinical development, and may act as a universal reversal agent, based on its potential to bind edoxaban, rivaroxaban, apixaban and dabigatran, as well as heparins, in preclinical models (96). Reversal of edoxaban effects is also evident in the literature (97).

Specific reversal agents should be used according to the protocol proposed by the International Society on Thrombosis and Haemostasis (98). A general approach to the management of bleeding patients has also been discussed in a recent white paper from the Anticoagulation Education Task Force (99). This should include discontinuation or delay of NOAC use in minor bleeding (bleeding that does not fulfil criteria for major or non-major clinically relevant bleeding), and fluid support, mechanical compression and transfusion in moderate or severe cases of bleeding (100). Non-specific reversal agents may also play a role in severe or life-threatening bleeding events on NOACs, including PCC and rVIIa, although the evidence for the latter is weak (100). A graduated approach to bleeding is advised by the expert panel, reserving specific reversal agents for life-threatening or severe bleeding.

Switching from VKA to NOACs

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The potential for NOACs to essentially replace VKA therapy in eligible patients has led to important questions regarding which patients should be switched to NOACs and how the transition process should be managed. The phase III clinical trials of NOACs do not explore this issue in depth, but provide an insight into the safety of NOACs when administered in patients who have received previous VKA therapy or those who are VKA-naïve. For all of the AF trials, the efficacy and safety of NOACs was comparable in either VKA-experienced or naïve patients (25–28).

Switching from VKA therapy to a NOAC is associated with minimal changes of the pharmacokinetics and pharmacodynamics of the NOACs. Recently it has been shown that the risk of bleeding is low during and in the short term following this transition (101). A randomised trial investigating the switch from warfarin to edoxaban found that edoxaban administered 24 hours after the last dose of warfarin was safe and well tolerated (102). Data from the Dresden NOAC registry suggested that, in 716 switched from VKA therapy to NOACs, the 30-day rate of cardiovascular events or major bleeding events was very low, regardless of INR testing prior to switching (103).

The decision to switch to a NOAC from VKA therapy should be based on pragmatic decision-making, taking into account the available clinical evidence, the patient's comorbidities and clinical status, and patient's wishes. Once the decision to switch has been made, the process of switching is important to minimise time spent out of an effective anticoagulant state. According to the SmPC for each NOAC, switching may be directed based on the most recent INR value obtained while the patients end their VKA therapy. A NOAC should be started when the INR is ≤3 for rivaroxaban, ≤2.5 for edoxaban, and ≤2 for apixaban and dabigatran. It has been uniformly recommended in the EHRA Practical Guide that an INR of 2.0–2.5 justifies initiating NOAC therapy on the next

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day (81). Where the INR is >2.5, further considerations of the actual INR value and the half-life of the VKA should be noted before switching.

Heparin lead-in for VTE therapy

The use of the heparin lead-in for patients with VTE is based on the delay in achieving optimal anticoagulation with warfarin therapy and the elevated risk of thrombosis associated with the transition to warfarin use (104). The high level of heterogeneity in the study populations, as well as the procedures applied, complicates the process of comparing VTE trials of NOACs. The RE-COVER (105) and Hokusai-VTE (29) trials both employed heparin lead-ins, lasting a median of 6 and 7 days, respectively. The EINSTEIN-PE (31) and EINSTEIN-DVT (32) trials excluded patients who received parenteral anticoagulation for greater than 48 hours. The AMPLIFY study excluded patients who received more than one day of LMWH or 36 hours of continuous intravenous heparin (30). However, 80-90% of patients in the EINSTEIN and AMPLIFY trials received a pre-randomisation dose of parenteral heparin. A subgroup analysis of patients who received either rivaroxaban monotherapy or initial parenteral therapy and rivaroxaban did not suggest any differences in outcomes (32).

Current recommendations suggest that rivaroxaban and apixaban may be used without the heparin lead-in, while edoxaban and dabigatran should include the heparin lead-in phase in the initial and long-term treatment of VTE, reflecting the design of phase III trials (89). Expert consensus advises the use of heparin lead-in as per clinical trial protocols, pending further data.

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Additional considerations

The attitudes and prescribing characteristics of the physician are significant factors in determining the uptake of new agents in clinical practice (106). Individual physicians may be reluctant to prescribe NOACs in preference to VKA therapy due to the long history of VKA prescribing and the perceived safety and benefits of this therapy, particularly in elderly or frail patients , although comparative data do not support this perception (107). However, it is important to combat clinical inertia by reviewing the evidence and considering the practical needs and preference of patients.

The simplicity of dosing regimens of the NOACs and the lack of need for routine anticoagulation monitoring suggest that NOACs may facilitate earlier and more effective transfer of care from secondary to primary or community care settings. This is particularly the case with VTE management, where primary care transfer is often delayed due to the use of initial parenteral anticoagulation (108).

When patients are transferred from the community or the primary care setting to receive an intervention, interruption NOAC therapy may be required. This has been described in detail in the EHRA Practical Guide, which should be referred to for a detailed overview of the topic in patients with AF (81). Peri-operative bridging with LMWH is generally not necessary when long term oral anticoagulants are interrupted for elective procedures in patients with a low or moderate thromboembolic risk and may be associated with poorer safety outcomes, including an elevated bleeding risk (109). This strategy is also supported by the results of the Dresden NOAC registry, in which major cardiovascular events were consistent in patients regardless of the receipt of bridging

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therapy during an invasive procedure (110). The expert panel does not recommend routine use of peri-operative LMWH bridging, although individualised decisions should be made in this context.

The off-label use of NOACs may take a number of forms, including those that are clinically inappropriate, such as use in patients with mechanical prosthetic heart valves (111). The early terminated RE-ALIGN trial suggested that dabigatran was associated with an increased risk of stroke, myocardial infarction, thrombosis and bleeding compared to warfarin in patients with mechanical heart valves (112). There is no evidence to support NOAC use in patients with mechanical heart valves at present, and this practice should be actively discouraged. Use in other indications that have not been explored in extensive trials should not be considered without careful consultation. The expert panel advises NOAC use only in situations defined by product labelling, to ensure patient safety.

On the other hand, NOACs can safely be used in all types of native valvular heart disease accompanied by AF (113), with the exception of mitral stenosis (114).

The justification for dose reduction of NOACs is based on a multitude of phase II and III trials and the support for off-label use of NOACs in published guidelines (115). Drug labelling guidelines differ from published guidance (e.g., the EHRA practical guide) and therefore disparities can lead to low-dose NOAC use in situations not supported by drug labelling. Off-label dose reductions have the potential to lead to undertreatment of patients with AF or VTE. The ORBIT-AF II registry (116) showed that of 5,738 patients treated with NOACs, 9.4% were underdosed and 3.4% overdosed compared to product labelling. Off-label dosing was more likely in patients who were older, had higher thrombosis risk scores, were of female sex, and had higher bleeding risk scores. The use of

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NOACs in accordance with the 2016 European Society of Cardiology AF Guideline recommendations (117) has been demonstrated to lead to optimal efficacy and safety outcomes, as noted in a post-hoc analysis of the RE-LY trial (118). Therefore, current indications and dosing recommendations for NOACs need to be reinforced in practice to avoid unnecessary risk to patients, as advised by the expert panel.

At present, NOACs fall into two categories with respect to daily dosing requirements: once-daily agents (edoxaban and rivaroxaban), and twice-daily agents (dabigatran and apixaban). When considering the choice of NOAC, one potential factor may be the frequency of dosing, particularly in patients with a high pre-existing pill burden. Indeed, where once-daily regimens are used in the context of cardiovascular medication, adherence may be improved compared to twice-daily regimens (119). However, it should also be considered that all drug dosing regimens rely on good patient adherence, but this is of particular importance with once-daily dosing, as missing one dose can lead to a longer period without anticoagulation compared to the same lapse with a twice-daily dosing schedule (115). Adherence appears to be maintained slightly better in patients taking once-daily NOACs in practice (120,121). Patients most likely to benefit from once-daily dosing include those with an already high pill burden and patients with a good level of adherence. For all of the NOACs, dosing should be based on existing guidance, with adherence optimised regardless of once- or twice-daily dosing regimens.

Morning or evening dosing is generally considered acceptable for all NOACs. A recent study (122) has shown that evening dosing of rivaroxaban is associated with prolonged exposure, better matching the morning hypofibrinolysis observed as part of the circadian rhythm. Therefore, evening intake of rivaroxaban may potentially improve safety and efficacy profiles of this drug, though further studies are needed to confirm this potential.

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For all of the NOACs, with the exception of rivaroxaban, intake may be accompanied with or without food without significantly affecting the bioavailability of the drug. In the case of rivaroxaban, the bioavailability of the drug decreases significantly from close to 100% to 66% without food (25). Dabigatran, apixaban and edoxaban may represent more convenient options for long-term anticoagulation in some patients, due to the fact that these drugs may be taken without considering meal times (124–126). For patients requiring anticoagulation through enteral feeding tubes, it should be noted that rivaroxaban can be given as oral solution or via nasogastric tube, but that larger doses require co-administration of a nutritional supplement, while enteral tubes must not be distal to the stomach (127,128). Apixaban may be administered as an oral solution or via nasogastric/gastric tubes, and recent data suggests that the bioavailability of crushed tablets with or without food is acceptable (125). The large variation in exposure noted with crushed dabigatran tablets precludes the use of this NOAC through feeding tubes (128). Recent data suggest that the pharmacokinetics of edoxaban tablets crushed and administered either by nasogastric tube or in apple puree is not altered (data/manuscript submitted).

Conclusion

We have here provided a summary of contemporary evidence regarding NOAC safety, focusing on safety compared with VKA therapy and safety between the NOACs. Although clinical trial data support the use of NOACs as an effective and safe alternative to VKA therapy in both AF and VTE contexts, there is a need to consider the individual clinical profile and risk factors of patients prior to NOAC initiation. The role of dose reductions to enhance NOAC safety in certain patient subgroups is becoming clearer.

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Where data were lacking, we have developed consensus statements to guide contemporary practice. These statements are largely consistent with available clinical guidelines, emphasising the complexity of decision-making in patients with AF or VTE, while highlighting the emerging clinical issues relating to NOAC safety in practice (table 5).

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Conflicts of interest

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References

1. Murphy NF, Simpson CR, Jhund PS, Stewart S, Kirkpatrick M, Chalmers J, et al. A national survey of the prevalence, incidence, primary care burden and treatment of atrial fibrillation in Scotland. Heart Br Card Soc. 2007 May;93(5):606–12.
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006 Jul 11;114(2):119–25.
3. Watanabe H, Tanabe N, Watanabe T, Darbar D, Roden DM, Sasaki S, et al. Metabolic Syndrome and Risk of Development of Atrial Fibrillation: The Niigata Preventive Medicine Study. Circulation. 2008 Mar 11;117(10):1255–60.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991 Aug 1;22(8):983–8.
5. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007 Oct;98(4):756–64.
6. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: A population-based cohort study in patients without active cancer: Thromb Haemost. 2014 Apr 3;112(2):255–63.
7. Ensor J, Riley RD, Moore D, Snell KIE, Bayliss S, Fitzmaurice D. Systematic review of prognostic models for recurrent venous thromboembolism (VTE) post-treatment of first unprovoked VTE. BMJ Open. 2016;6(5):e011190.
8. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013 Dec;110(6):1087–107.
9. Sjögren V, Grzymala-Lubanski B, Renlund H, Friberg L, Lip GYH, Svensson PJ, et al. Safety and efficacy of well managed warfarin. A report from the Swedish quality register Auricula. Thromb Haemost. 2015 Jun;113(6):1370–7.
10. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. Thromb Res. 2009 May;124(1):37–41.
11. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008 Nov 11;118(20):2029–37.
12. van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systematic review and metaregression. Chest. 2006 May;129(5):1155–66.
13. Sandén P, Renlund H, Svensson PJ, Själander A. Bleeding complications and mortality in warfarin-treated VTE patients, dependence of

ACCEPTED MANUSCRIPT

INR variability and iTTR. Thromb Haemost. 2017 Jan 5;117(1):27–32.
14. Kooistra HAM, Veeger NJGM, Khorsand N, Kluin-Nelemans HC, Meijer K, Piersma-Wichers M. Long-term quality of VKA treatment and clinical outcome after extreme overanticoagulation in 14,777 AF and VTE patients. Thromb Haemost. 2015 Apr;113(4):881–90.
15. Mungall D. BIBR-1048 Boehringer Ingelheim. Curr Opin Investig Drugs Lond Engl 2000. 2002 Jun;3(6):905–7.
16. Pinto DJP, Orwat MJ, Koch S, Rossi KA, Alexander RS, Smallwood A, et al. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor Xa. J Med Chem. 2007 Nov 1;50(22):5339–56.
17. Perzborn E, Strassburger J, Wilmen A, Pohlmann J, Roehrig S, Schlemmer K-H, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939--an oral, direct Factor Xa inhibitor. J Thromb Haemost JTH. 2005 Mar;3(3):514–21.
18. Furugohri T, Isobe K, Honda Y, Kamisato-Matsumoto C, Sugiyama N, Nagahara T, et al. DU-176b, a potent and orally active factor Xa inhibitor: in vitro and in vivo pharmacological profiles. J Thromb Haemost JTH. 2008 Sep;6(9):1542–9.
19. Husted S, de Caterina R, Andreotti F, Arnesen H, Bachmann F, Huber K, et al. Non-vitamin K antagonist oral anticoagulants (NOACs): No longer new or novel. Thromb Haemost. 2014 May 5;111(5):781–2.
20. Weitz JI, Harenberg J. New developments in anticoagulants: Past, present and future. Thromb Haemost. 2017 Jun 28;117(7):1283–8.
21. Beyer-Westendorf J, Ageno W. Benefit-risk profile of non-vitamin K antagonist oral anticoagulants in the management of venous thromboembolism. Thromb Haemost. 2015 Feb;113(2):231–46.
22. Diener H-C, Aisenberg J, Ansell J, Atar D, Breithardt G, Eikelboom J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1. Eur Heart J. 2017 Mar 21;38(12):852–9.
23. Diener H-C, Aisenberg J, Ansell J, Atar D, Breithardt G, Eikelboom J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. Eur Heart J. 2017 Mar 21;38(12):860–8.
24. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: Developing guidelines. BMJ. 1999 Feb 27;318(7183):593–6.
25. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139–51.
26. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981–92.
27. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28;369(22):2093–104.
28. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883–91.
29. The Hokusai-VTE Investigators. Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism. N Engl J

ACCEPTED MANUSCRIPT

Med. 2013 Oct 10;369(15):1406–15.
30. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med. 2013 Aug 29;369(9):799–808.
31. The EINSTEIN–PE Investigators. Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism. N Engl J Med. 2012 Apr 5;366(14):1287–97.
32. The EINSTEIN investigators. Oral Rivaroxaban for Symptomatic Venous Thromboembolism. N Engl J Med. 2010 Dec 23;363(26):2499–510.
33. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. N Engl J Med. 2009 Dec 10;361(24):2342–52.
34. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H-C, Hacke W, 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 Oct;17(10):1467–507.
35. Lip GYH, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. J Thromb Haemost. 2016 Sep;14(9):1711–4.
36. Paciaroni M, Agnelli G. Should oral anticoagulants be restarted after warfarin-associated cerebral haemorrhage in patients with atrial fibrillation? Thromb Haemost. 2014 Jan;111(1):14–8.
37. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. The Lancet. 2014 Mar;383(9921):955–62.
38. Caldeira D, Barra M, Ferreira A, Rocha A, Augusto A, Pinto FJ, et al. Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants. Aliment Pharmacol Ther. 2015 Dec;42(11–12):1239–49.
39. Caldeira D, Rodrigues FB, Barra M, Santos AT, de Abreu D, Gonçalves N, et al. Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis. Heart. 2015 Aug 1;101(15):1204–11.
40. Guo Y, Wang H, Tian Y, Wang Y, Lip GYH. Multiple risk factors and ischaemic stroke in the elderly Asian population with and without atrial fibrillation. An analysis of 425,600 Chinese individuals without prior stroke. Thromb Haemost. 2016 Jan;115(1):184–92.
41. Cohen AT, Imfeld S, Rider T. Phase III Trials of New Oral Anticoagulants in the Acute Treatment and Secondary Prevention of VTE: Comparison and Critique of Study Methodology and Results. Adv Ther. 2014 May;31(5):473–93.
42. Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J.

ACCEPTED MANUSCRIPT

2013;11(1):21.
43. Verhamme P, Wells PS, Segers A, Ageno W, Brekelmans MPA, Cohen AT, et al. Dose reduction of edoxaban preserves efficacy and safety for the treatment of venous thromboembolism. An analysis of the randomised, double-blind HOKUSAI VTE trial. Thromb Haemost. 2016 Sep 27;116(4):747–53.
44. Avgil-Tsadok M, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Behlouli H, et al. Dabigatran use in elderly patients with atrial fibrillation: Thromb Haemost. 2015 Sep 10;115(1):152–60.
45. Tafur AJ, Caprini JA, Cote L, Trujillo-Santos J, Del Toro J, Garcia-Bragado F, et al. Predictors of active cancer thromboembolic outcomes. RIETE experience of the Khorana score in cancer-associated thrombosis. Thromb Haemost. 2017 Jun 2;117(6):1192–8.
46. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016 Sep 21;37(36):2768–801.
47. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000 Mar 27;160(6):761–8.
48. Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006. Br J Cancer. 2010 Sep 28;103(7):947–53.
49. van der Hulle T, den Exter PL, Kooiman J, van der Hoeven JJM, Huisman MV, Klok FA. Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism. J Thromb Haemost. 2014 Jul;12(7):1116–20.
50. Larsen TB, Nielsen PB, Skjøth F, Rasmussen LH, Lip GYH. Non-Vitamin K Antagonist Oral Anticoagulants and the Treatment of Venous Thromboembolism in Cancer Patients: A Semi Systematic Review and Meta-Analysis of Safety and Efficacy Outcomes. Fukumoto Y, editor. PLoS ONE. 2014 Dec 5;9(12):e114445.
51. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med. 2018 Feb 15;378(7):615–24.
52. Friberg L, Benson L, Lip GYH. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J. 2015 Feb 1;36(5):297–306.
53. Kooiman J, van Rein N, Spaans B, van Beers KAJ, Bank JR, van de Peppel WR, et al. Efficacy and Safety of Vitamin K-Antagonists (VKA) for Atrial Fibrillation in Non-Dialysis Dependent Chronic Kidney Disease. Eller K, editor. PLoS ONE. 2014 May 9;9(5):e94420.
54. Nielsen PB, Lane DA, Rasmussen LH, Lip GYH, Larsen TB. Renal function and non-vitamin K oral anticoagulants in comparison with warfarin on safety and efficacy outcomes in atrial fibrillation patients: a systemic review and meta-regression analysis. Clin Res Cardiol Off J Ger Card Soc. 2015 May;104(5):418–29.

ACCEPTED MANUSCRIPT

55. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014 Mar 4;129(9):961–70.
56. Fox KAA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011 Oct 1;32(19):2387–94.
57. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012 Nov;33(22):2821–30.
58. Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EM, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 TrialClinical Perspective. Circulation. 2016 Jul 5;134(1):24–36.
59. Sardar P, Chatterjee S, Herzog E, Nairooz R, Mukherjee D, Halperin JL. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. Can J Cardiol. 2014 Aug;30(8):888–97.
60. De Caterina R, Lip GYH. The non-vitamin K antagonist oral anticoagulants (NOACs) and extremes of body weight-a systematic literature review. Clin Res Cardiol Off J Ger Card Soc. 2017 Aug;106(8):565–72.
61. Stacy ZA, Call WB, Hartmann AP, Peters GL, Richter SK. Edoxaban: A Comprehensive Review of the Pharmacology and Clinical Data for the Management of Atrial Fibrillation and Venous Thromboembolism. Cardiol Ther. 2016 Jun;5(1):1–18.
62. Lip GYH, Skjøth F, Rasmussen LH, Nielsen PB, Larsen TB. Net Clinical Benefit for Oral Anticoagulation, Aspirin, or No Therapy in Nonvalvular Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA2DS2-VASc Score (Beyond Sex). J Am Coll Cardiol. 2015 Jul;66(4):488–90.
63. Lip GYH, Skjøth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. Thromb Haemost. 2015 Oct;114(4):826–34.
64. Fauchier L, Clementy N, Bisson A, Ivanes F, Angoulvant D, Babuty D, et al. Should Atrial Fibrillation Patients With Only 1 Nongender-Related CHA2DS2-VASc Risk Factor Be Anticoagulated? Stroke. 2016;47(7):1831–6.
65. Proietti M, Lip GYH. Major Outcomes in Atrial Fibrillation Patients with One Risk Factor: Impact of Time in Therapeutic Range Observations from the SPORTIF Trials. Am J Med [Internet]. 2016 Apr [cited 2016 Sep 15]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002934316303527
66. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006 Mar;151(3):713–9.
67. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE. Comparison of Risk Stratification Schemes to Predict

ACCEPTED MANUSCRIPT

Thromboembolism in People With Nonvalvular Atrial Fibrillation. J Am Coll Cardiol. 2008 Feb;51(8):810–5.
68. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012 Jun 2;33(12):1500–10.
69. Paciaroni M, Agnelli G, Ageno W, Caso V. Timing of anticoagulation therapy in patients with acute ischaemic stroke and atrial fibrillation. Thromb Haemost. 2016 30;116(3):410–6.
70. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, et al. Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. Lancet Neurol. 2012 Jun;11(6):503–11.
71. Diener H-C, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, et al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. Lancet Neurol. 2010 Dec;9(12):1157–63.
72. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012 Apr;11(4):315–22.
73. Sardar P, Chatterjee S, Wu W-C, Lichstein E, Ghosh J, Aikat S, et al. New Oral Anticoagulants Are Not Superior to Warfarin in Secondary Prevention of Stroke or Transient Ischemic Attacks, but Lower the Risk of Intracranial Bleeding: Insights from a Meta-Analysis and Indirect Treatment Comparisons. Meisel A, editor. PLoS ONE. 2013 Oct 25;8(10):e77694.
74. Masjuan J, DeFelipe A. Secondary prevention in non-valvular atrial fibrillation patients: a practical approach with edoxaban. Int J Neurosci. 2016 Sep 20;1–10.
75. Lip GYH, Lane DA. Assessing bleeding risk in atrial fibrillation with the HAS-BLED and ORBIT scores: clinical application requires focus on the reversible bleeding risk factors. Eur Heart J. 2015 Sep 8;ehv415.
76. Roldán V, Marín F, Fernández H, Manzano-Fernandez S, Gallego P, Valdés M, et al. Predictive Value of the HAS-BLED and ATRIA Bleeding Scores for the Risk of Serious Bleeding in a "Real-World" Population With Atrial Fibrillation Receiving Anticoagulant Therapy. Chest. 2013 Jan;143(1):179–84.
77. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GYH. Performance of the HEMORR2HAGES, ATRIA, and HAS-BLED Bleeding Risk–Prediction Scores in Patients With Atrial Fibrillation Undergoing Anticoagulation. J Am Coll Cardiol. 2012 Aug;60(9):861–7.
78. Senoo K, Proietti M, Lane DA, Lip GYH. Evaluation of the HAS-BLED, ATRIA, and ORBIT Bleeding Risk Scores in Patients with Atrial Fibrillation Taking Warfarin. Am J Med. 2016 Jun;129(6):600–7.
79. Proietti M, Senoo K, Lane DA, Lip GYH. Major Bleeding in Patients with Non-Valvular Atrial Fibrillation: Impact of Time in Therapeutic Range on Contemporary Bleeding Risk Scores. Sci Rep. 2016 Apr 12;6:24376.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

80. Alings M. Individualising Anticoagulant Therapy in Atrial Fibrillation Patients. Arrhythmia Electrophysiol Rev. 2016 Aug;5(2):102–9.
81. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H-C, Hacke W, 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: Executive summary. Eur Heart J. 2016 Jun 9;ehw058.
82. Senoo K. PREVALENCE AND INCIDENCE OF CORONARY ARTERY DISEASE IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION. J Am Coll Cardiol. 2013 Mar;61(10):E1190.
83. De Caterina R, Ammentorp B, Darius H, Le Heuzey J-Y, Renda G, Schilling RJ, et al. Frequent and possibly inappropriate use of combination therapy with an oral anticoagulant and antiplatelet agents in patients with atrial fibrillation in Europe. Heart Br Card Soc. 2014 Oct;100(20):1625–35.
84. Oldgren J, Wallentin L, Alexander JH, James S, Jonelid B, Steg G, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J. 2013 Jun 2;34(22):1670–80.
85. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med. 2016 Dec 22;375(25):2423–34.
86. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med. 2017 Oct 19;377(16):1513–24.
87. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016 Jan 14;37(3):267–315.
88. Khorana AA, O'Connell C, Agnelli G, Liebman HA, Lee AYY, Subcommittee on Hemostasis and Malignancy of the SSC of the ISTH. Incidental venous thromboembolism in oncology patients. J Thromb Haemost JTH. 2012 Dec;10(12):2602–4.
89. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease. Chest. 2016 Feb;149(2):315–52.
90. Sarich TC, Seltzer JH, Berkowitz SD, Costin' J, Curnutte JT, Gibson CM, et al. Novel oral anticoagulants and reversal agents: Considerations for clinical development. Am Heart J. 2015 Jun;169(6):751–7.
91. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition: Guideline. Br J Haematol. 2011 Aug;154(3):311–24.
92. Glund S, Moschetti V, Norris S, Stangier J, Schmohl M, van Ryn J, et al. A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran: Thromb Haemost. 2015 Mar 19;113(5):943–51.
93. Pollack CV, Reilly PA, Bernstein R, Dubiel R, Eikelboom J, Glund S, et al. Design and rationale for RE-VERSE AD: A phase 3 study of

ACCEPTED MANUSCRIPT

idarucizumab, a specific reversal agent for dabigatran: Thromb Haemost. 2015 May 28;114(1):198–205.
94. Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015 Aug 6;373(6):511–20.
95. Connolly SJ, Milling TJ, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016 Sep 22;375(12):1131–41.
96. Ansell JE, Bakhru SH, Laulicht BE, Steiner SS, Grosso M, Brown K, et al. Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban. N Engl J Med. 2014 Nov 27;371(22):2141–2.
97. Ansell JE, Bakhru SH, Laulicht BE, Steiner SS, Grosso MA, Brown K, et al. Single-dose ciraparantag safely and completely reverses anticoagulant effects of edoxaban. Thromb Haemost. 2017 Jan 26;117(2):238–45.
98. Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost. 2016 Mar;14(3):623–7.
99. Ageno W, Büller HR, Falanga A, Hacke W, Hendriks J, Lobban T, et al. Managing reversal of direct oral anticoagulants in emergency situations: Anticoagulation Education Task Force White Paper. Thromb Haemost [Internet]. 2016 Aug 4 [cited 2016 Oct 19];116(5). Available from: http://www.schattauer.de/index.php?id=1214&doi=10.1160/TH16-05-0363
100. Ruff CT, Giugliano RP, Antman EM. Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents. Circulation. 2016 Jul 19;134(3):248–61.
101. Bouillon K, Bertrand M, Maura G, Blotière P-O, Ricordeau P, Zureik M. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. Lancet Haematol. 2015 Apr;2(4):e150–9.
102. Mendell J, Noveck RJ, Shi M. A randomized trial of the safety, pharmacokinetics and pharmacodynamics of edoxaban, an oral factor Xa inhibitor, following a switch from warfarin: Edoxaban PK/PD after warfarin. Br J Clin Pharmacol. 2013 Apr;75(4):966–78.
103. Beyer-Westendorf J, Gelbricht V, Förster K, Ebertz F, Röllig D, Schreier T, et al. Safety of switching from vitamin K antagonists to dabigatran or rivaroxaban in daily care - results from the Dresden NOAC registry: Switching from VKA to NOAC in daily care. Br J Clin Pharmacol. 2014 Oct;78(4):908–17.
104. Heit JA. Predicting the risk of venous thromboembolism recurrence. Am J Hematol. 2012 May;87(S1):S63–7.
105. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al. Treatment of Acute Venous Thromboembolism With Dabigatran or Warfarin and Pooled Analysis. Circulation. 2014 Feb 18;129(7):764–72.
106. Lublóy Á. Factors affecting the uptake of new medicines: a systematic literature review. BMC Health Serv Res [Internet]. 2014 Dec [cited 2016 Oct 14];14(1). Available from: http://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-14-469
107. Camm AJ, Pinto FJ, Hankey GJ, Andreotti F, Hobbs FDR. Non-vitamin K antagonist oral anticoagulants and atrial fibrillation guidelines

ACCEPTED MANUSCRIPT

in practice: barriers to and strategies for optimal implementation. Europace. 2015 Jul;17(7):1007–17.
108. Gross PL, Weitz JI. New Anticoagulants for Treatment of Venous Thromboembolism. Arterioscler Thromb Vasc Biol. 2008 Mar 1;28(3):380–6.
109. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015 Aug 27;373(9):823–33.
110. Beyer-Westendorf J, Gelbricht V, Forster K, Ebertz F, Kohler C, Werth S, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014 Jul 2;35(28):1888–96.
111. Price J, Hynes M, Labinaz M, Ruel M, Boodhwani M. Mechanical Valve Thrombosis With Dabigatran. J Am Coll Cardiol. 2012 Oct;60(17):1710–1.
112. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus Warfarin in Patients with Mechanical Heart Valves. N Engl J Med. 2013 Sep 26;369(13):1206–14.
113. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease. J Am Coll Cardiol. 2017 Mar 21;69(11):1363–71.
114. De Caterina R, Camm AJ. What is "valvular" atrial fibrillation? A reappraisal. Eur Heart J. 2014 Dec 14;35(47):3328–35.
115. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. Europace. 2015 Apr 1;17(4):514–23.
116. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes. J Am Coll Cardiol. 2016 Dec;68(24):2597–604.
117. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct 7;37(38):2893–962.
118. Lip GYH, Clemens A, Noack H, Ferreira J, Connolly SJ, Yusuf S. Patient outcomes using the European label for dabigatran: A post-hoc analysis from the RE-LY database. Thromb Haemost. 2013 Dec 11;111(5):933–42.
119. Coleman CI, Roberts MS, Sobieraj DM, Lee S, Alam T, Kaur R. Effect of dosing frequency on chronic cardiovascular disease medication adherence. Curr Med Res Opin. 2012 May;28(5):669–80.
120. Márquez-Contreras E, Martell-Carlos N, Gil-Guillén V, De La Figuera-Von Wichmann M, Sanchez-López E, Márquez-Rivero S, et al. Therapeutic compliance with rivaroxaban in preventing stroke in patients with non-valvular atrial fibrillation: CUMRIVAFA study. Curr Med Res Opin. 2016 Dec;32(12):2013–20.
121. Forslund T, Wettermark B, Hjemdahl P. Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation. Eur J Clin Pharmacol. 2016 Mar;72(3):329–38.
122. Brunner-Ziegler S, Jilma B, Schörgenhofer C, Winkler F, Jilma-Stohlawetz P, Koppensteiner R, et al. Comparison between the impact of

ACCEPTED MANUSCRIPT

morning and evening doses of rivaroxaban on the circadian endogenous coagulation rhythm in healthy subjects. J Thromb Haemost. 2016 Feb;14(2):316–23.
123. Stampfuss J, Kubitza D, Becka M, Mueck W. The effect of food on the absorption and pharmacokinetics of rivaroxaban. Int J Clin Pharmacol Ther. 2013 Jul;51(7):549–61.
124. Mendell J, Tachibana M, Shi M, Kunitada S. Effects of Food on the Pharmacokinetics of Edoxaban, an Oral Direct Factor Xa Inhibitor, in Healthy Volunteers. J Clin Pharmacol. 2011 May;51(5):687–94.
125. Song Y, Chang M, Suzuki A, Frost RJA, Kelly A, LaCreta F, et al. Evaluation of Crushed Tablet for Oral Administration and the Effect of Food on Apixaban Pharmacokinetics in Healthy Adults. Clin Ther. 2016 Jul;38(7):1674–1685.e1.
126. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet. 2008;47(5):285–95.
127. Moore KT, Krook MA, Vaidyanathan S, Sarich TC, Damaraju CV, Fields LE. Rivaroxaban crushed tablet suspension characteristics and relative bioavailability in healthy adults when administered orally or via nasogastric tube. Clin Pharmacol Drug Dev. 2014 Jul;3(4):321–7.
128. Peterson JJ, Hoehns JD. Administration of Direct Oral Anticoagulants Through Enteral Feeding Tubes. J Pharm Technol. 2016 Oct 1;32(5):196–200.

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Appendices

Table 1. Hierarchy of evidence for the formulation of expert statements (24).

Level of evidence	Source data
Level I	Meta-analysis of RCTs High-quality RCTs
Level II	Controlled studies, without randomisation
Level III	Descriptive studies (comparative, correlation, case-control)
Level IV	Expert opinion or reports from medical bodies/organisations

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Table 2. Expert statements for patient safety outcomes (combined expert consensus and evidence-based statements).

CRNM bleeding, clinically-relevant non-major bleeding

Clinical topic	Expert statement	SOS	% expert agreement	Level of evidence
Major/CRNM bleeding	The rates of major bleeding and clinically-relevant non-major bleeding with NOACs are favourable compared to VKA therapy in both AF and VTE patients. However, basing clinical decision-making on this factor alone is not advisable due to the heterogeneity in bleeding risk on an individual patient basis.	Weak	-	I
	A thorough bleeding risk assessment must be used to guide the identification of modifiable risk factors to minimise major bleeding events.	Strong	100%	II
Intracranial bleeding	The use of NOACs in preference to VKA therapy reduces the likelihood of intracranial bleeds.	Strong	-	I
	A thorough risk factor assessment must be used to identify modifiable risk factors for intracranial bleeding and these should be addressed prior to the use of any oral anticoagulant.	Strong	-	IV
Gastrointestinal bleeding	A thorough gastrointestinal bleeding risk assessment should be conducted before initiating anticoagulation in either AF or VTE patients.	Weak	-	IV
Bleeding mortality	NOACs reduce the risk of fatal bleeding compared to warfarin in both AF and VTE contexts. However, a multifactorial analysis of bleeding risk, balanced	Weak	71%	IV

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	with stroke risk, should be used to guide therapy, rather than this single factor alone.			
Cardiovascular mortality	At present, evidence suggests that NOACs in general should be selected over VKA therapy on the basis that they are safer through a reduction in cardiovascular mortality alone.	Weak	71%	IV
	Optimisation of cardiovascular risk factors is advised irrespective of anticoagulation for AF or VTE.	Strong	100%	IV

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Table 3. Expert statements for specific patient groups (combined consensus and evidence-based statements).

Clinical topic	Expert statement	SOS	% expert agreement	Level of evidence
Elderly and fragile	Elderly patients are at an increased risk of bleeding with anticoagulant therapy, but the NOACs (with the exception of dabigatran) demonstrate comparable safety in this group compared to the general study population suggesting that they are viable anticoagulant choices in VTE and AF patients aged ≥75 years.	Strong	-	I
	Age alone should only be used to justify dose modifications of NOACs in specific cases e.g. dabigatran dose reduction to 110 mg twice daily in patients aged >80 years.	Weak	86%	I
	It is advised that dose reduction of NOACs in patients with AF or VTE be performed in accordance with published guidance, taking into account factors that may increase drug exposure and thereby increase the risk of bleeding.	Strong	-	IV
Patients with active cancer	Consistent with VTE guidelines (134,135), NOACs should only be considered in active cancer patients who cannot tolerate LMWH. (However, recent data suggest that edoxaban is non-inferior to LMWH in these patients.)	Weak	71%	IV
	When chronic anticoagulation is needed in patients with active cancer, and	Strong	86%	I

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	LMWH is not suitable, NOACs are advised as alternative agents to warfarin			
	NOAC use in patients with AF and cancer must be based on an appraisal of known bleeding and thrombosis risk factors, in addition to potential drug-drug interactions.	Strong	100%	IV
	Dose-reduced NOACs are advised in active cancer patients with impaired renal function, low body weight and/or advancing age, according to published AF guidelines.	Strong	86%	IV
Patients with renal impairment	Renal function is a key factor in determining drug exposure levels of NOACs and it is advised that renal function is routinely assessed prior to NOAC use.	Strong	-	III
	NOACs are not advised for use in patients with CrCl <15 ml/min (<30 ml/min for dabigatran).	Strong	-	III
	Consideration of dose-adjusted NOAC therapy is advised for all patients with renal impairment, according to practical guidelines, for the management of AF. This may be considered for VTE therapy, but is not advised for rivaroxaban or apixaban.	Strong	-	IV
	Renal function must be considered in concert with additional risk factors for increased drug exposure (low body weight, advancing age) when determining the suitability and dose of NOACs.	Strong	-	III
Obese patients	There is insufficient evidence to suggest that NOAC dose adjustments are justified in obese patients; this practice is not advised.	Strong	71%	IV
Single stroke risk	It should be considered that contemporary guidelines are used and that	Strong	86%	IV

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factor (CHA_2DS_2-VASc =1 in men, 2 in women)	individual patient risk factors should be taken into account in borderline instances, where CHA_2DS_2-VASc = 1 for men, when determining the need for anticoagulation with NOACs.			
	Where CHA_2DS_2-VASc = 2 in women, it is advised that anticoagulation is initiated, as per published ESC guidelines.	Strong	86%	IV
Primary vs secondary stroke prevention	NOACs are advised in patients with a previous history of stroke/TIA as they have a lower risk of bleeding compared to warfarin therapy.	Strong	-	IV
Patients with an increased bleeding risk	Bleeding risk scores may be used to identify modifiable risk factors for bleeding and prompt routine review of patients, rather than as tools to select suitability for NOAC/VKA use or to justify dose adjustments to NOAC therapy. However, individual bleeding risk factor identification is essential and must be performed, regardless of the use of these scoring systems.	Strong	71%	IV
Dual antiplatelet therapy	Dual antiplatelet therapy in combination with NOACs should be minimised to avoid excessive bleeding risks, lasting for one month following elective PCI and up to six months following acute coronary syndrome management.	Weak	-	IV
	Dose reductions of NOACs should be pursued cautiously depending on the individual patient bleeding and thromboembolic risk factors.	Weak	-	IV
Incidental VTE	In cases of incidental VTE, therapeutic anticoagulation must be considered unless there are contraindications to therapy.	Strong	-	IV
	Where incidental VTE is noted in patients already on NOAC therapy, diagnostic confirmation and full risk factor assessment is advised to guide	Strong	-	IV

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	future anticoagulation therapy.			

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Table 4. Expert statements for practical use of NOACs (combined consensus and evidence-based statements).

Clinical topic	Expert statement	SOS	% expert agreement	Level of evidence
Once daily dosing	Once-daily dosing with NOACs should be considered in patients already taking a number of medications, although twice-daily dosing may not be problematic in patients already on similar regimens.	Strong	100%	IV
	The safety of once-daily dosing relies on optimal patient adherence and it is advised that patients are educated on the importance of taking their drug at the prescribed frequency and what to do if a dose is missed.	Strong	100%	III
	Either evening or morning intake of once-daily NOACs is considered acceptable based on expert consensus; for some patients it may be optimal to time drug intake in accordance with concomitant medications to maximise adherence. Rivaroxaban may be preferably taken in the evening with food.	Strong	100%	IV
NOAC administration	Edoxaban and apixaban may be safely taken with or without food; dabigatran and rivaroxaban should be taken with food due to the risk of gastrointestinal upset and poor drug bioavailability, respectively.	Strong	-	II
	When NOACs need to be delivered through a feeding tube, dabigatran should be avoided. Apixaban may be administered on an empty stomach and rivaroxaban may be administered with or without food (a nutritional supplement is advised with larger doses). More data are needed on	Strong	-	III

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	edoxaban (currently submitted).			
Off-label use	Off-label use of NOACs is not generally advised.	Strong	100%	II
Off-label dose reductions	Dose-reduced NOAC therapy is advised only in line with current product labelling.	Strong	86%	II
Prescribing experience and transfer of care	NOACs can lead to earlier discharge and effective use in the primary care/community setting and careful patient evaluation is needed to determine those who would benefit the most.	Strong	-	IV
	Specific guidance on NOAC management during transfer of care is essential for patients and prescribers- this should be reflected on a local policy level.	Strong	-	IV
	Peri-operative bridging with LMWH is generally not required for patients on NOAC therapy, although individual risks of thromboembolism or bleeding should be taken into account.	Strong	86%	III
Switching patients from VKA to NOACs	The decision to switch from VKA therapy to NOAC therapy must be based on individual patient factors.	Strong	-	IV
	Patients with end stage renal disease should not be switched (<30 mL/min for dabigatran, <15 mL/min for other NOACs).	Strong	-	IV
	When the decision to switch has been made, INR values should be recorded prior to NOAC initiation. A NOAC should be started when the INR is ≤3 for rivaroxaban, ≤2.5 for edoxaban, and ≤2 for apixaban and dabigatran. EHRA guidance on switching may also be applied.	Strong	-	III
Heparin lead-in for	The heparin lead-in (parenteral therapy) must be used for edoxaban and	Strong	85%	I

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VTE	dabigatran in patients with VTE, but is not necessary for rivaroxaban or apixaban.			
	The benefits of the heparin lead-in for all NOACs are not established; trial regimens should be followed in practice pending further data.	Weak	71%	IV
Managing acute bleeding	A graduated approach to bleeding management is advised in patients prescribed NOACs; specific reversal agents are limited for all NOACs and their use is advised for life-threatening or severe bleeding.	Strong	100%	I

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Table 5. Priority areas for further research regarding NOAC safety

Key area	Implications/importance
Off-label dose reduction in patients at risk of high exposure	If the effect of NOACs is measurable, off-label use may be considered. Off-label dose reductions when exposure may be increased are also justifiable.
Heparin lead-in for all NOACs	The role of the heparin lead-in is questionable, as this was largely based on practice prior to NOAC introduction in the VTE setting. The value for the lead-in for all NOACs should be explored and vice versa.
NOAC dose adjustment in obese patients	Obesity affects a significant proportion of the population and there are limited data on dosing of NOACs in this subgroup; obesity may affect drug exposure, leading to suboptimal effects. More pharmacokinetic data is warranted.
Risk factor assessment and treatment	In some patient, even 'weak' risk factors for poor outcomes (e.g. hypertension) may justify the use of NOACs, which have good safety profiles.
NOAC use in patients with active cancer	Chronic LMWH use is not feasible and VKA therapy is associated with poorer prevention of recurrent VTE and a significant bleeding risk; more trials of NOACs in this population are needed to explore the effects of cancer therapy and physiology on safety.
Borderline cases or patients with bleeding and/or dose reduction risk factors	In patients with one criterion for dose reduction (e.g. low body weight) the presence of an additional bleeding risk factor may justify dose reduction. Data are needed to explore variations in exposure in these instances, to justify dose adjustment.
Bleeding management cost	The use of specific bleeding reversal agents may be justified in all cases of significant bleeding-costs inhibit this in practice. Cost-effectiveness analyses are justified.