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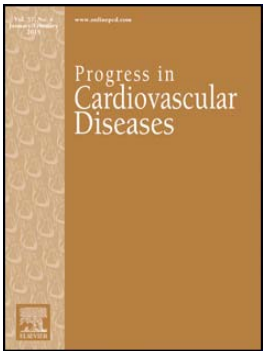

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Invited Review

Oral Anticoagulant Therapy in Atrial Fibrillation Patients at High Stroke and Bleeding Risk

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Conflict of Interest/Disclosures:

Prof Lip has served as a consultant for Bayer, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic

Dr Potpara has received speaker fees from Bayer, Pfizer, Boehringer Ingelheim and Gedeon Richter.

Abbreviations:

AF- Atrial fibrillation

ARR-Absolute risk reduction

CKD-Chronic kidney disease

CMB-Cerebral microbleeds

CrCL- Creatinine clearance

CV-Cardiovascular

ESRD-End stage renal disease

FFP-Fresh frozen plasma

GI-Gastrointestinal

HR-Hazard ratio

ICH-Intra cranial hemorrhage

INR-International Normalized Ratio

MRI-Magnetic resonance imaging

NOAC-Non-vitamin K antagonist oral anticoagulant

OAC-Oral anticoagulant

OR-Odds ratio

PCC-Prothrombin complex concentrate

RR-Relative risk

TTR-Time in therapeutic range

VKAs-Vitamin K antagonists

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Abstract

Atrial fibrillation (AF) is associated with a 5-fold greater risk of ischemic stroke or systemic embolism compared with normal sinus rhythm. Cardioembolic AF-related strokes are often more severe, fatal or associated with greater permanent disability and higher recurrence rates than strokes of other aetiologies. These strokes may be effectively prevented with oral anticoagulant (OAC) therapy, using either vitamin K antagonists (VKAs) or non-vitamin K antagonist oral OACs (NOACs) such as the direct thrombin inhibitor dabigatran or direct factor Xa inhibitors rivaroxaban, apixaban or edoxaban. Most AF patients have a positive net clinical benefit from OAC, excluding those with AF and no conventional stroke risk factors. Balancing the risks of stroke and bleeding is necessary for optimal use of OAC in clinical practice, and modifiable bleeding risk factors must be addressed. Concerns remain over 'non-changeable' bleeding risk factors such as older age, significant renal or hepatic impairment, prior stroke(s) or prior bleeding event(s) and active malignancies. Such AF patients are often termed 'special' AF populations, due to their 'special' risk profile that includes increased risks of both thromboembolic and bleeding events, and due to fear of bleeding complications these AF patients are often denied OAC. Evidence shows, however, that the absolute benefits of OAC are the greatest in patients at the highest risk, and NOACs may offer even a greater net clinical benefit compared to warfarin particularly in these high risk patients.

In this review article, we summarize available data on stroke prevention in AF patients at increased risk of both stroke and bleeding and discuss the use of NOACs for thromboprophylaxis in these 'special' AF populations.

Introduction

Atrial fibrillation (AF) is associated with a 5-fold greater risk of thromboembolic events compared with normal sinus rhythm (NSR) [1]. Without treatment, approximately one in three AF patients would ultimately suffer an ischemic stroke, most often of cardioembolic or far less commonly of atherothrombotic origin [2, 3]. Cardiembolic AF-associated events predominantly result from dissemination of thrombus formed in the left atrial appendage, and such strokes are often more severe, more fatal or associated with greater permanent disability and higher recurrence rates than strokes of other aetiologies [3-5].

Cardioembolic AF-related strokes may be effectively prevented with oral anticoagulant (OAC) therapy, using either vitamin K antagonists (VKAs) or non-vitamin K antagonist OACs (NOACs) such as the direct thrombin inhibitor ,dabigatran, or direct factor Xa inhibitors, rivaroxaban, apixaban or edoxaban [6-10]. Treatment with VKAs provides a positive net clinical benefit in almost all AF patients (excluding those with no conventional stroke risk factors), regardless of the bleeding risk level [11, 12]. Compared with VKAs, NOACs may offer even a greater net clinical benefit, particularly in AF patients at increased risk of bleeding [13, 14].

Balancing the stroke and bleeding risks is necessary for optimal use of OAC in clinical practice [15-19], and modifiable bleeding risk factors such as poorly controlled hypertension, low quality of VKA treatment (as reflected through labile International Normalized Ratios [INR]), co-medication (e.g., antiplatelet or non-steroidal anti-inflammatory drugs) or alcohol abuse must be corrected [20, 21]. Concerns remain over ‘non-changeable’ bleeding risk factors such as older age, significant renal or hepatic disease, prior stroke(s) or prior bleeding event(s) and malignancy. Such AF patients are often termed ‘special’ AF populations, due to their ‘special’ risk profile that includes increased risks of both thromboembolic and bleeding events [17]. In these populations the use of OAC might be challenging and more data are needed to better define optimal stroke prevention and diminish often unjustified underuse of OAC in the high-risk AF patients [22].

In this review article, we summarize available data on stroke prevention in AF patients at increased risk of both stroke and bleeding and discuss the use of NOACs for thromboprophylaxis in these ‘special’ AF populations.

Elderly patients with AF

Over a half of AF patients are >75 years old [23]. Advancing age is among the strongest independent stroke risk factors, with relative risk (RR) of 1.5 per decade (95% Confidence Interval [CI], 1.3-1.7) [24, 25] and stroke rates of up to 36.2% at age of 80-89 years [26]. The lifetime AF-related stroke incidence sharply increases during the sixth decade of life, reaching the threshold for OAC at 65 years even in the absence of other risk factors [17-19].

Recently a significant overall decline in the annual stroke rates (from 2.09% to 1.66%, $p<0.001$) in AF patients taking warfarin has been reported, but the risk was still higher in elderly (≥75 years) compared with younger patients [27]. The rates of warfarin-related major bleeding (including intracranial haemorrhage [ICH]) also increased with aging (from 4.7% in those younger than 80 years to 13.1% per 100 patient-years in older patients) [28], and each year at least 1% of the latter are hospitalized due to gastrointestinal (GI) bleeding [29]. VKAs are often underused in older AF patients [30, 31] and, when warfarin is prescribed, those ≥80 years old were more likely to discontinue the drug within the first year of treatment (26%) [28].

A recent report from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry suggests that antiplatelet therapy (mainly aspirin, alone or in combination with OAC) is still frequently prescribed in clinical practice (30.7%), particularly in patients at high risk of stroke (as measured by the CHA_2DS_2-VASc score of ≥2) or bleeding (the use of antiplatelet drugs increased from 8.7% in patients with a HAS-BLED=0 to 29.4% in those with a HAS-BLED=4) [32]. This persistent misperception of lower bleeding risk with aspirin compared to OAC most likely stems from results of the historical randomized trials on warfarin vs. aspirin for stroke prevention in AF [6]. A meta-analysis of participants aged ≥75 years showed a 2.2% lower risk of ischemic stroke at the cost of a 1.7% greater risk of major bleeding with warfarin, but older patients were significantly under-represented in those trials [33].

In contrast to these historical data, a contemporary, adequately powered, randomized, controlled trial on adjusted-dose warfarin (target INR of 2.0-3.0) vs. aspirin 75mg daily for stroke prevention in elderly AF patients (all ≥75 years old, mean age 81.5 years) showed no significant difference in the rates of haemorrhagic strokes (0.5% vs. 0.4%), other ICH (0.2% vs. 0.1%) or

extracranial bleeding (1.4% vs. 1.6%) with warfarin vs. aspirin (all p>0.05) [23]. Overall, there was no difference in the annual rates of major bleedings (1.9% vs. 2.0%, RR 0.97; 95%CI, 0.53-1.75), and the primary endpoint of fatal or disabling stroke, other ICH or arterial embolism was significantly reduced by warfarin in comparison to aspirin (RR 0.48; 95%CI, 0.28-0.80, p=0.003), with no significant interaction between age and treatment [23]. Aspirin was also associated with more adverse events (including bleeding) than warfarin in another trial on octogenarians with AF [34].

In the absence of formal contraindications, warfarin is often denied to older AF patients due to concerns such as frailty and the risk of falling, or anticipated non-adherence to therapy (secondary to the need for regular INR monitoring or cognitive impairment) [35-37] resulting in a poor quality of warfarin therapy as measured by the time in therapeutic range (TTR), thus increasing the risk of both thromboembolic and bleeding events [38, 39]. With respect to falling, however, it has been estimated that an elderly patient taking warfarin would have to fall 295 times per year for the risk of warfarin-related bleeding to outweigh the benefit from cardioembolic stroke prevention [40]. Indeed, the overall benefit from warfarin was positive in elderly AF patients at risk of fall, even in the setting of an increased risk of bleeding [41, 42]. A recent 'real world' study reported that a small proportion of AF patients actually did have a history of prior falls (1.1% of >7000 patients) [43]. A history of falls was associated with increased risk of stroke, bleeding and all-cause mortality (all p<0.05), but there was no significant association of prior falls and the risk of haemorrhagic stroke under OAC (p=0.16).

Overall, randomized trials of NOACs vs. warfarin showed that NOACs were non-inferior (dabigatran 110mg twice daily, rivaroxaban 20mg once daily, edoxaban both 60mg and 30mg once daily) or better than warfarin (dabigatran 150mg twice daily, apixaban 5mg twice daily) for the prevention of any stroke or systemic embolism in AF patients [7-10]. Although pertinent subanalyses [44-48] uniformly showed higher rates of cardiovascular (CV) events and bleeding in patients aged ≥75 years (as compared to those <75 years old) in *all* treatment arms, there was no significant treatment-by-age interaction with respect to the efficacy (i.e., NOACs were as effective in elderly AF patients as in the main trials) [44-47, 49, 50].

Regarding the primary safety outcome of major bleeding, NOACs were as safe as warfarin (dabigatran 150mg, rivaroxaban) or safer (dabigatran 110mg, apixaban, edoxaban in both doses)

in the main trials, but all NOACs significantly reduced the risk of haemorrhagic stroke or any intracranial bleeding compared with warfarin [7-10]. However, there was a significant treatment-by-age interaction with dabigatran regarding *extracranial* bleeding. Compared with warfarin, dabigatran110mg was associated with a lower risk of major bleeding in patients aged <75 years and similar risk in those ≥75 years old, whilst dabigatran 150mg was associated with lower risk of major bleeding in patients younger than 75 years and a trend towards greater risk in older patients (p=0.07, interaction p<0.001) [44]. A significant interaction has been also reported for rivaroxaban, with higher rates of clinically relevant non-major bleeding in the rivaroxaban arm compared with warfarin in AF patients aged ≥75 years (15.6% vs. 9.2%), whilst the rates were similar in both treatment arms in patients <75 years old (9.2% vs. 9.9%), interaction p=0.01 [48, 49]. All other effects of rivaroxaban were consistent to the main trial in all age groups.

There was no significant treatment-by-age interaction either for the efficacy or the safety of apixaban [47]. Apixaban effects were consistent across all subgroups of patients aged ≥75 years (e.g., different levels of chronic kidney disease, warfarin-naive patients, etc.), with significant interaction only between treatment and individual TTR (the reduction in major bleeding with apixaban vs. warfarin was greater in elderly patients with low vs. high predicted TTR, interaction p=0.029). Importantly, there was no significant interaction of treatment and apixaban dose (790 patients aged ≥75 years received a reduced dose of 2.5mg twice daily) [47].

In the AVERROES trial comparing apixaban with aspirin for stroke prevention in AF patients unsuitable for warfarin, apixaban significantly reduced the risk of stroke or systemic embolism (Hazard Ratio [HR] 0.45; 95%CI, 0.32-0.62, p<0.001), with no difference in the risk of major bleeding (HR 1.13; 95%CI, 0.74-1.75, p=0.57) or ICH (HR 0.85; 95%CI, 0.38-1.90, p=0.69) between the treatment arms, and the effects of apixaban were consistent in all age groups [51].

The ENGAGE-AF trial compared edoxaban 60mg once daily (high-dose) and 30mg once daily (low-dose) vs. dose-adjusted warfarin for stroke prevention in non-valvular AF; however, in both treatment arms edoxaban dose was halved for patients with any of the following conditions: body weight <60kg, creatinine clearance <50ml/min or verapamil or quinidine use (25.4% of patients received the reduced dose at randomization in both edoxaban treatment arms) [10]. There was no significant interaction between age and treatment effects of edoxaban.

A pooled meta-analysis of the trials comparing NOACs vs. warfarin for thromboprophylaxis in patients with non-valvular AF showed no significant interaction of the NOACs effects with age [52]. Hence, age itself should not preclude the use of OAC in AF patients. Due to a greater risk of stroke in elderly AF patients, any OAC should be preferred over aspirin or no therapy, and NOACs may offer a greater net clinical benefit than VKAs in this patient population, due to significantly lower risk of haemorrhagic stroke or any other ICH with NOACs compared to warfarin. Individual patient and drug characteristics should influence the choice of particular NOAC for a given patient.

Patients with chronic kidney disease

Nearly a third of patients with chronic kidney disease (CKD) have AF [53], and up to 50% of AF patients may have some degree of renal dysfunction [54]. The incidence and prevalence of AF increase with increasing severity of renal dysfunction [55, 56] and incident AF further increases the risk of end-stage renal disease (ESRD), with HR of 1.67 (95%CI, 1.46-1.91) [57].

Patients with CKD or AF carry a larger burden of associated CV diseases compared to individuals with normal heart rhythm and normal renal function [53, 58]. In addition, patients with both AF and CKD have higher mortality than those with AF or CKD only [59]. Both AF and CKD are associated with increased annual risk of ischemic stroke (5% and 4%, respectively) [1, 60], and stroke risk increases with the severity of CKD (Table 1) [60]. Whilst the occurrence of AF in non-end-stage CKD patients clearly adds to the risk of stroke [59, 61], data on the association of incident AF with an additional increase in the (already high) risk of stroke in patients with ESRD requiring dialysis are inconsistent [57, 59, 61-65]. Although AF patients with stage III/IV CKD (Table 1) have sufficiently high absolute stroke risk to warrant oral anticoagulation, such therapy may be challenging for a number of considerations including the greater risk of bleeding compared to patients with normal renal function [53, 59, 66]. Indeed, in a large outpatient cohort, stage IV CKD has been identified as a multivariable predictor of major haemorrhage during warfarin therapy [67].

Mild to moderate CKD (Stages II-III) in AF patients.

In a subgroup analysis of a randomized trial adjusted-dose warfarin significantly reduced the relative risk of stroke by 76% (95%CI, 42-90) compared with aspirin plus low doses warfarin in AF patients with stage III CKD [68]. However, in a large observational trial, the use of warfarin in AF patients with non-ESRD was associated with stroke reduction at the cost of increased bleeding risk (HR 1.36; 95%CI, 1.17-1.59, p<0.001), particularly in patients aged ≥65 years (HR 1.61; 95%CI, 1.35-1.95) [59]. Of note, aspirin was also associated with increased bleeding risk but, in contrast to warfarin, there was no benefit with aspirin for reducing thromboembolism in the trial cohort.

Subgroup analyses of the NOACs trials uniformly reported greater thromboembolic and bleeding rates in AF patients with mild to moderate CKD compared to those with normal renal function in *all* treatment arms [69-72], and the risk of major bleeding increased with decreasing creatinine clearance (CrCl) [45, 46]. NOACs are eliminated via the kidneys to a variable extent, with a proportional prolongation of their half-lives relative to the degree of renal dysfunction [7-10]. Dabigatran has the greatest extent of renal elimination (80% of the dose) [73]. Patients with severe CKD (CrCl of <25-30mL/min) were excluded from the NOACs trials [7-10, 51]. There was also a drug dose adjustment in patients with moderate CKD in ROCKET-AF and ENGAGE-AF, as well as in the ARISTOTLE, and AVERROES and ENGAGE-AF trials, where the apixaban dose was halved to 2.5mg twice daily if increased serum creatinine of ≥133μmol/l was combined with age ≥80 years and/or body weight ≤60kg) [8-10, 51]. No dose adjustment on basis of renal function was performed in RELY, although CrCl <30mL/min was an exclusion criteria.

With respect to the primary efficacy endpoint of any stroke or systemic embolism, there was no statistically significant interaction between treatment and renal (dys)function (NOACs were as effective in patients with mild to moderate CKD as in the main trials) [69-72]. Regarding the primary safety endpoint, there was a significant interaction between the effect of apixaban and renal dysfunction in the way that apixaban was even safer in patients with mild, and particularly with moderate CKD (the major bleeding rates in this subgroup were halved with apixaban compared to warfarin) [71]. There were no significant safety interactions relative to renal function with other NOACs [69, 70, 72], including edoxaban (as per the primary publication of

the trial results) [10]. Importantly, rivaroxaban and apixaban dose reduction in AF patients with moderate CKD did not affect their efficacy and safety in these patients [70-72].

Overall, in a pooled individual patient data meta-analysis, NOACs as a whole were better than warfarin in the reduction of any stroke or systemic embolism in patients with moderate CKD (RR 0.79; 95%CI, 0.65-0.96), with similar major bleeding risk in both treatment groups (RR 0.74; 95%CI, 0.52-1.05), and there was no significant treatment interaction with renal function (interaction p 0.12 and 0.57, respectively) [52]. Regarding the comparison of apixaban with aspirin, apixaban was as effective and safe in patients with moderate CKD as in all other AF patients unsuitable for aspirin in the AVERROES trial [72]. All NOACs consistently reduced the risk of ICH compared with either warfarin or aspirin, irrespective of the renal function [69-72]. Given these advantages of NOACs, these drugs should clearly be preferred over warfarin (or aspirin) for stroke prevention in patients with AF and mild-to-moderate renal dysfunction.

Advanced CKD in AF patients.

Whilst being excluded from the RE-LY, ROCKET-AF and ENGAGE-AF trials, small numbers of patients with stage IV CKD (CrCl of 25-29 mL/min) participated in the ARISTOTLE and AVERROES trials (n=270 and n=70, respectively), but no results from these subsets have been published [9, 72]. Rivaroxaban 15mg once daily has been approved for AF patients with stage IV CKD in the United States of America and Europe, whilst dabigatran 75mg twice daily has been approved in this setting only in the United States. Among the NOACs, only apixaban has been recently approved for the use in ESRD patients on haemodialysis (the recommended dose of 5mg twice daily should be halved in patients with body weight of ≤60kg and or age ≥80 years).

Data from randomized trials are also lacking for the use of VKAs in AF patients with stage IV-V CKD [74], and observational data on the effects of VKAs in such patients are conflicting. Retrospective analyses of 3 large databases of ESRD patients on dialysis failed to show a benefit of warfarin in those with AF [62, 75, 76], whilst warfarin (but not aspirin) treatment was associated with a significant reduction of stroke or systemic embolism (HR 0.44, 95%CI, 0.26-0.74, p=0.002) in AF patients requiring renal-replacement therapy in a retrospective large cohort study [59]. However, the risk of bleeding among such patients was significantly increased.

Overall, the net clinical effect of warfarin therapy in this patient population requires careful individual patient assessment [17-19, 77-79]. Importantly, AF patients with ESRD and prior stroke are at such high risk of recurrent stroke that the use of well managed warfarin with careful INR monitoring seems justified, but patient values and preferences should also be taken into account [80, 81]. There is an urgent need for randomized clinical trials of optimal stroke prevention in AF patients with ESRD [82].

Patients with prior ischemic stroke

Previous ischemic stroke (or TIA) is the single most powerful independent risk factor for recurrent stroke in patients with non-valvular AF, conferring a 2.5-fold greater risk of new brain ischemic event compared to patients without history of stroke [24, 25]. Recurrent strokes are often more disabling (or fatal) and costly compared with index stroke [83]. Importantly, prior stroke/TIA is also an independent risk factor for bleeding complications of OAC [84].

Aspirin is not effective in long-term secondary prevention of ischemic stroke in patients with AF (HR 0.83; 95%CI, 0.65-1.05) [85]. Combined aspirin and clopidogrel are generally more effective than aspirin alone (RR 0.72; 95%CI, 0.62-0.83), but with more major bleeding (RR 1.57; 95%CI, 1.29-1.92) as shown in AF patients unsuitable for VKAs (however, only 13% of patients in that trial had a history of stroke or TIA) [86].

Two randomized trials investigated the efficacy and safety of warfarin vs. control (aspirin [85] or indobufen [87]) in patients with a previous stroke or TIA, and the results were consistent with those in the primary prevention of AF-related stroke [6, 83]. There was an impressive reduction of recurrent stroke with warfarin (OR 0.49; 95%CI, 0.33-0.72) at the cost of increased risk of major extracranial bleeding (OR 5.2; 95%CI, 2.1-12.8), as compared to antiplatelet therapy [83, 85]. Aspirin plus clopidogrel was also less effective than warfarin (RR 2.13; 95%CI, 1.23-3.69) [88]. Overall, the absolute benefits of warfarin therapy in the older trials were the greatest in patients at the highest risk of stroke [6, 11].

Approximately 20% of AF patients included in the recent NOACs clinical trials had a history of prior stroke or TIA [52]. The rates of both thromboembolic and bleeding events were higher in

this subgroup compared with patients without previous stroke/TIA but the relative efficacy and safety of NOACs compared to warfarin (or aspirin) were consistent in patients with and without previous stroke/TIA [89-92]. Importantly, all four NOACs were far safer than warfarin in this high-risk AF patient population, in terms of the impressive reduction in the risk of cerebral haemorrhage and other ICH events [10, 89-91].

In contrast to individual NOACs trials, which were not sufficiently powered to reliably detect the presence (and significance) of differences in NOACs effects compared with warfarin in various AF patient subgroups, a meta-analysis of 14,527 AF patients with previous stroke/TIA from the RE-LY, ROCKET-AF and ARISTOTLE trials revealed a significant reduction of any stroke or systemic embolism with NOACs relative to warfarin (OR 0.85; 95%CI, 0.74-0.99), with absolute risk reduction (ARR) of 0.7% and number needed to treat (NNT) of 134 (over 1.8-2.0 years) [93]. NOACs were also associated with a significant reduction in major bleeding events (OR 0.86; 95%CI, 0.75-0.99), with ARR of 0.8% and NNT of 125, and the effect was mostly driven by the significant reduction of the haemorrhagic stroke rates (OR 0.44; 95%CI, 0.32-0.62), with ARR of 0.7% and NNT of 139 [93].

Compared to warfarin, the absolute benefits of NOACs are greater in the secondary stroke prevention, due to the higher baseline risk of both thromboembolic and bleeding events in this subgroup [93, 94]. Accordingly, even patients with AF and prior stroke/TIA who are unsuitable or unwilling to take VKAs should be offered a NOAC instead of aspirin, since in the AVERROES trial, for example, apixaban was superior to aspirin, with comparable bleeding risk and better tolerability [51, 92].

When to start a NOAC after recent brain ischemia?

The risk of a recurrent stroke within the first two weeks after the index ischemic event averages 5%-10% [95, 96]. However, within the first 48 hours of acute cardioembolic stroke there was no mortality or disability benefit of anticoagulant therapy compared with aspirin (OR 1.14; 95%CI, 0.95-1.38) or placebo (OR 0.90; 95%CI, 0.62-1.22) [97]. Overall, there was a trend towards recurrent stroke reduction (OR 0.68; 95%CI, 0.44-1.06, p=0.09, NNT 53), at the cost of significantly increased risk of symptomatic ICH (OR 2.89; 95%CI, 1.19-7.01, p=0.02, NNT 55)

and no mortality benefit with anticoagulants versus control (OR 1.01; 95%CI, 0.82-1.24, p=0.9) [97].

Recent stroke was among the exclusion criteria in all trials of NOACs for stroke prevention in AF, with the cut-off set at 30 days (ENGAGE-AF), 14 days (RE-LY and ROCKET-AF) or 7 days (ARISTOTLE) prior to randomization [7-10]. Of note, a small number of AF patients (n=21) were randomized to apixaban 8-14 days after an acute stroke in the ARISTOTLE trial and there were no secondary bleeding events in this subgroup. However, the time from randomization to treatment is unknown, and most probably those were patients with minor strokes [94, 98]. A recent small study of 41 AF patients in whom a NOAC (dabigatran, n=37 or rivaroxaban, n=4) was started 1-6 days (median 2 days) post acute ischemic stroke reported no recurrent thromboembolic events or bleeding complications during a 3-month follow-up, thus suggesting that early NOAC initiation after an ischemic stroke in AF patients might be safe [99].

Until more data are available, decision about the timing of NOACs initiation in AF patients post acute ischemic stroke should include assessment of the index stroke severity (and resulting risk of haemorrhagic transformation) and the risk of recurrent thromboembolic event [100]. Whilst a NOAC should be initiated immediately after a TIA, the use of NOACs most likely should be postponed for 3-5, 7-14 and ≥14 days post mild-to-moderate, moderate-to-severe and severe large strokes, respectively [100, 101]. Antiplatelet drugs should be discontinued at the time of NOACs initiation unless there is a strong indication other than secondary stroke prevention for their continuous use.

Patients with prior intracranial bleeding

The term ICH encompasses several subtypes of bleeding within the skull – *intracerebral bleeding* (a haemorrhage directly into the brain parenchyma; when causing focal neurological symptoms and signs, such bleeding is termed *hemorrhagic stroke*), *subdural haematoma* and *subarachnoid haemorrhage*. Intracerebral bleeding accounts for 10%-20% of all strokes and generally has worse prognosis than cerebral ischemia [102]. ICH is the most feared and devastating complication of OAC, occurring in 0.2%-1% of patients taking OAC [7-10, 27, 50, 51, 103, 104] and resulting with fatal outcome in ≥40% of cases, whilst at least half of the

survivors permanently remain severely disabled [105]. Anticoagulation-associated ICH generally has worse prognosis than a spontaneous ICH [106, 107].

The annual rates of ICH in AF patients taking VKAs ranged from 0.33% to 0.85% in recent randomized trials comparing warfarin to other antithrombotic drugs [7-10, 27, 51], with a pooled rate of 0.61% (95%CI, 0.48-0.73) per year [27]. Observational studies mostly report higher annual rates of anticoagulation-associated ICH, reaching up to 2.5% per year in the inception cohorts and elderly AF patients [11, 28, 108-111]. Patients with intracerebral haemorrhage during warfarin therapy often present with larger haematoma and have worse functional outcomes than patients with normal coagulation status [112, 113]. At presentation, most patients with anticoagulation-associated intracerebral bleeding have a therapeutic INR (2.0-3.0) [106, 107, 114], although supratherapeutic INRs have been also associated with increased 30-day mortality [107, 115]. The prevalence of warfarin-associated intracerebral bleeding is still increasing, most likely due to increasing use of OAC [116]. Whilst the overall mortality from intracerebral bleeding has declined, warfarin-associated intracerebral bleeding mortality is unchanged [116]. For example, in an AF cohort, of 72 patients with warfarin-associated intracerebral haemorrhage 76% had died or were severely disabled at hospital discharge, whilst the mortality from warfarin-associated major extracranial bleeding was only 3% [105].

Compared with warfarin, NOACs impressively reduced the risk of ICH in AF patients (Table 2), with pooled RR of 0.48 (95%CI, 0.39-0.59) [52], and the effect was consistent across all patient subgroups in all NOACs trials [7-10, 51]. A more detailed analysis of the RE-LY and ROCKET-AF trials with respect to ICH [50, 117] showed that NOAC-related ICHs mostly were spontaneous intracerebral bleedings with higher mortality than those of traumatic origin. In the RE-LY trial, 108 of 154 ICHs (70%) were spontaneous and associated with higher mortality (42%) than traumatic ICHs (24%) [117]. Intracerebral bleeds accounted for 46% of all ICHs (n=71), most often were spontaneous (89%) and associated with higher mortality (52%) than traumatic intracerebral bleeds (25%), which were infrequent (n=8) and mostly occurred after a major head trauma. In the ROCKET-AF trial, 127 of 172 ICHs (73.8%) were intracerebral bleedings, of which only 9 (7%) were caused by trauma. ICH-associated 30- and 90-day mortality was 43% and 51%, respectively [50]. Whilst the case fatality of ICH was lower with both doses of dabigatran, and similar with rivaroxaban compared to warfarin, there were no

significant differences in the ICH-associated mortality among the treatment groups (i.e., warfarin and both doses of dabigatran or rivaroxaban) [50, 117].

Clinical trials provided strong evidence of much lower incidence of ICH with NOACs relative to warfarin, whilst ICH-associated mortality rates were similar with dabigatran, rivaroxaban and warfarin. A recent analysis of a health insurance database also confirmed similar in-hospital mortality from anticoagulant-associated ICH in patients taking warfarin or dabigatran [118]. Nonetheless, specific clinical data on the effects of NOACs on the intracerebral bleeding volume, haematoma expansion and functional outcome are lacking [119]. Both experimental and clinical evidence suggest that patients with warfarin-associated ICH have a larger haematoma size at presentation, with fluid blood inside the haematoma, a smaller early perihaematomal oedema and a higher rate of delayed haematoma expansion resulting in a worse clinical outcome compared to ICH patients with normal coagulation status [105, 106, 119-123]. Experimental randomized studies consistently showed less detrimental effects of therapeutic levels of dabigatran and rivaroxaban on haematoma expansion and functional outcome compared to warfarin [124-126]. However, most experiments are run on healthy anticoagulated animals with artificially induced ICH and experimental data should be translated with caution into clinical setting, wherein ICH commonly occur in elderly AF patients with some comorbidities.

Evidence suggests a frequent occurrence of cerebral microbleeds (CMB) in AF patients taking warfarin and positive correlation between higher CHA_2DS_2-VASc scores and increasing rates of CMBs [127]. CMBs have been shown to be an independent risk factor for anticoagulation-associated symptomatic ICH [128-130]. CMBs identified by brain magnetic resonance imaging (MRI) provide direct evidence of blood leakage from pathologically fragile small vessels, and their distribution likely reflects the nature of underlying small vessel disease – strictly lobar CMBs localized cortically-to-subcortically are characteristic of cerebral amyloid angiopathy, whilst deep CMBs rather reflect hypertensive arteriopathy [111]. Although the former seems to be a stronger risk factor for recurrent symptomatic ICH, there are no clear criteria for reliable recognition of patients at higher risk of anticoagulation-associated ICH based on MRI [131]. Whilst clinical evidence suggest that the occurrence of CMBs in patients taking OAC increases the risk of anticoagulation-associated ICH [128-130], experimental data failed to confirm their expansion into large parenchymal haematoma under warfarin treatment [119], and there was no

increase in the CMBs volume after standard doses of dabigatran and rivaroxaban [124, 126]. Importantly, CMBs have been associated with increased risk not only of recurrent ICH, but of ischemic stroke as well [132].

Available experimental and clinical data provided some insight into the differences in pathophysiology of ICH occurring during dabigatran or rivaroxaban anticoagulation compared to warfarin. In vitro studies showed that deficiencies of the coagulation factors II (thrombin), VII and X result in delayed clot formation, with slow propagation and reduced clot strength, thus facilitating prolonged bleeding, whilst only a partial restoration of thrombin enabled almost normal clot formation [133]. VKAs extensively alter coagulation by affecting factors II, VII, IX and X, thus compromising the formation of the complex of tissue factor (factor III) and activated factor VII (VIIa), which is the primary cellular driver of coagulation that provides physiological haemostatic protection from various injuries. In contrast, dabigatran and rivaroxaban reversibly interfere only with one coagulation factor (i.e., factor IIa and Xa, respectively), not affecting the formation of tissue factor-VIIa complexes. In addition, dabigatran binds only to the active site of the thrombin molecule, leaving the two exosites available for interaction with other components of the haemostatic system, and neither dabigatran nor rivaroxaban substantially penetrates the blood-brain barrier [125, 126, 134-136]. In brief, it seems that selective inhibition of a single coagulation factor allows for feedback mechanisms within the coagulation cascade to maintain the necessary haemostasis, thus preventing excessive intracerebral haematoma growth [137].

Given that anticoagulation-associated ICH is characterized by prolonged bleeding with delayed formation of a fragile clot, and the size of haematoma is a major prognostic determinant of ICH, a key therapeutic aim in ongoing ICH is to prevent continued haematoma growth [131]. A rapid reversal of anticoagulation to prevent extensive haematoma enlargement is strongly recommended [138], although no evidence from randomized clinical trials is available to support the expert opinion [119, 131]. Treatment options include *vitamin K* (reconstitutes the hepatic synthesis of the vitamin K-dependent coagulation factors, but anticoagulation reversal occurs only after hours to days), *fresh frozen plasma* (FFP; mostly not available immediately because it is stored in blood banks, requires blood compatibility testing, the infusion takes several hours and there is some volume overload, which may be challenging in patients with heart failure, for example), *prothrombin complex concentrates* (PCCs; reverse anticoagulation by replacement of

coagulation factors, are readily available, the infusion takes minutes, provide faster reversal of anticoagulation, with lower red cell transfusion requirement and have fewer adverse effects than FFP [139]) and *recombinant factor VIIa*, which is thought to provide a localized enhancement of thrombin generation with a more stable clot formation at the site of injury [140].

Observational studies suggest that PCCs correct increased INR more rapidly than does FFP, and recombinant factor VIIa corrects INR more reliably than do PCCs [141-143]. Reduction of INR has been associated with reduced haematoma size, and randomized experimental studies suggest that rapid anticoagulation reversal could prevent extensive haematoma enlargement and improve functional outcome of anticoagulation-associated intracerebral bleeding [144-146]. The reversal of warfarin effect may be easily monitored at bedside, using the point-of-care-devices for INR measurement. In patients taking NOACs, however, administration of haemostatic agents has variable effects on the coagulation tests, and the extent of laboratory tests reversal is not a reliable indicator of sufficient haemostasis to halt anticoagulant-associated bleeding [119, 147]. Experimental studies and randomized studies in healthy individuals suggest that both FFP and PCC reduce the size of intracerebral haematoma during dabigatran and rivaroxaban anticoagulation, whilst recombinant factor VII reduced haematoma size during rivaroxaban anticoagulation, but was ineffective in dabigatran-treated animals [148-150].

Resumption of OAC after ICH.

Most AF patients have sufficient thromboembolic risk to warrant long-term OAC, which would result in positive net clinical benefit at any bleeding risk level [11, 13]. However, patients with anticoagulation-associated acute intracerebral bleeding have a transient short-term risk of haematoma expansion and persistent long-term risk of ICH recurrence, both of which are highly fatal events [131]. Immediate withdrawal of OAC at the onset of an ICH is mandatory, but it leaves the patient at increased risk of ischemic stroke and other thrombotic events (e.g., pulmonary embolism, deep vein thrombosis, etc.).

Unfortunately, there is only limited evidence of whether and when it is safe to restart OAC after an intracerebral bleeding. Data from observational case series and stroke registries uniformly report high mortality rates in patients with anticoagulation-associated ICH, regardless of whether or not warfarin therapy was restarted (in the Canadian Stroke Registry, for example, overall 30-

day and 1-year mortality was 47% and 57%, respectively) [151]. Not surprisingly, mortality from subdural haematoma was lower than mortality from intracerebral bleeding (32% and 52%, respectively) [152]. Warfarin therapy has been restarted in about a third of ICH survivors, and the rates of recurrent ICH were either similar or higher in patients with OAC compared to those without OAC in the two registries (15% each and 14% vs. 8%, respectively), whilst thromboembolic event rates were variable (0.8% vs. 0.5% in the Canadian Registry, and 2% vs. 18% in another registry) [151, 152]. Differences in the thromboembolic event rates most likely could be attributed to different patient risk profiles in the registries (e.g., different proportion of patients with mechanical valves, AF, etc.).

In the absence of sufficient quality data and explicit formal recommendations to inform clinical decision about resumption of OAC in AF patients who survived an anticoagulation-associated ICH, careful patient selection is critical. Although the thromboembolic risk can be lowered by resumption of OAC, net clinical benefit may be substantially offset by an increased risk of recurrent ICH, which strongly depends on the underlying pre-existent cerebrovascular disease and is much higher in patients with lobar intracerebral bleeding than in those who suffered a deep cerebral haemorrhage [119]. It has been suggested that the risk of recurrent ICH and mortality is sufficiently high to preclude OAC resumption in patients who survived a lobar ICH, whilst AF patients post deep cerebral haemorrhage may be considered for OAC in the presence of a very high risk of ischemic stroke (e.g., with a CHA_2DS_2-VASc score of ≥ 5, although this approach has not been formally tested) [153, 154]. Until more data are available, the presence of CMBs on MRI should not be used as an absolute exclusion criterion for OAC resumption post ICH. The optimal timing of OAC re-initiation post ICH is poorly defined, and available evidence suggest that the descending risk of recurrent bleeding crosses the imaginary line of thromboembolic risk somewhere at 10 weeks post index anticoagulation-associated ICH (a time point when the risks become balanced) [152, 154].

Once the decision to restart OAC has been made, NOACs should be considered rather than warfarin due to their favourable safety profile with respect to ICH. Strict blood pressure control is important, and regular clinical follow-up is strongly advised, with renal function assessment (with NOACs therapy) and strict INR control (with warfarin). In AF patients with highly unfavourable risk/benefit ratio antiplatelet drugs should not be considered as an alternative to

OAC, due to their marginal efficacy [6] and no true safety benefit [51, 88], whilst the left atrial appendage occlusion could be a viable alternative to OAC in such patients [17].

Patients with prior GI bleeding

Clearly,GI bleeding may be a serious medical condition, particularly in elderly AF patients with complex co-morbidities [155]. The estimated annual risk of GI bleeding in these patients ranges between 0.3% and 0.5% even without antithrombotic therapy [156]. Warfarin is associated with a 3-fold greater risk of major GI bleeding compared to placebo, whilst the combination of warfarin and aspirin doubles the risk of GI bleeding compared to warfarin monotherapy [156]. Antiplatelet drugs (such as aspirin or thienopyridines) cause bleeding by creating erosions and/or ulcers within the GI tract, and anticoagulant drugs (e.g., VKAs, heparins) may facilitate bleeding from pre-existing GI lesions [157, 158].

A meta-analysis of 43 randomized controlled trials that compared NOACs to standard care (depending on the indication for OAC) in a total of 151,578 patients reported an increased overall risk of GI bleeding in patients taking NOACs (OR of 1.45; 95%CI, 1.07-1.97), but substantial heterogeneity was observed among the trials [159]. Of note, GI bleeding risk was the highest in patients treated for arterial thrombosis (i.e., acute coronary syndrome), in whom NOACs were co-administered with other antithrombotic drugs (OR 5.21; 95%CI, 2.58-10.53), intermediate in patients with venous thrombosis (OR 1.59; 95%CI, 1.03-2.44) or AF (OR 1.21; 95%CI, 0.91-1.61) and the lowest in patients receiving NOACs for thromboprophylaxis after orthopaedic surgery (OR 0.78; 95%CI, 0.31-1.96). Compared to standard care, the drug-specific risk of GI bleeding tended to be lower with edoxaban (OR 0.31; 95%CI, 0.01-7.69), was similar to standard care with apixaban (OR 1.23; 95%CI, 0.56-2.73) and increased with dabigatran (OR 1.58; 95%CI, 1.29-1.93) or rivaroxaban (OR 1.48; 95%CI, 1.21-1.82) [159].

A pooled individual patient data meta-analysis of the trials comparing NOACs vs. warfarin in AF patients showed the increased risk of GI bleeding with NOACs as a whole compared to warfarin (RR 1.25; 95%CI, 1.01-1.55, p=0.043) [52]. The drug-specific GI bleeding rates in the trials of NOACs for stroke prevention in non-valvular AF are shown in Table 3.

In the main RE-LY trial report, dabigatran 110mg twice daily was associated with similar GI bleeding rates as warfarin, whilst the rates were significantly higher with dabigatran 150mg twice daily compared to warfarin (Table 3) [7]. The use of dabigatran 150mg twice daily during 1 year would have resulted in 5 additional GI bleedings per thousand of patients [160]. GI bleeding rates were higher with concomitant use of antiplatelet drugs (i.e., aspirin and/or clopidogrel) or with decreasing creatinine clearance [44]. There was a significant interaction between age and GI bleeding risk with dabigatran 110mg twice daily in the RE-LY trial: whilst the risk of GI bleeding was similar with dabigatran 110mg or warfarin in patients younger than 75 years (RR 0.82; 95%CI, 0.58-1.15), dabigatran 110mg was associated with significantly greater risk of GI bleeding in patients ≥75 years old (RR 1.39; 95%CI, 1.03-1.98), p for interaction 0.02 [44]. Overall, dabigatran was associated with a higher percentage of lower GI bleedings than warfarin (53% vs. 25%, respectively) [44]. Of note, a recent nationwide analysis of AF patients taking dabigatran reported no increase in GI bleeding rates compared to warfarin (indeed, the rates of GI bleeding were lower with dabigatran 110mg and similar with dabigatran 150mg compared to warfarin) [161].

The ROCKET-AF trial included older AF patients with more comorbidities (and a higher bleeding risk) compared with other NOAC trials in AF [8]. Rivaroxaban was associated with higher rates of GI bleeding events than warfarin [8, 162], resulting in 8 additional GI bleeds annually, per 1000 patients [160]. The anatomic sites of GI bleeding were not specified in the ROCKET-AF trial, and increased risk of GI bleeding was associated with age, concomitant antiplatelet drug therapy, lower creatinine clearance, anaemia, smoking, chronic obstructive pulmonary disease, male gender, diastolic blood pressure and prior GI bleeding [45]. Indeed, there was a significant interaction between the effects of rivaroxaban and history of prior GI bleeding (interaction p=0.002) – patients taking rivaroxaban were at increased risk of GI bleeding compared to those on warfarin if they had a history of prior GI bleed (HR 2.33; 95%CI, 1.39-3.88), whilst the risk was comparable in patients with no history of prior GI in both treatment groups (HR 1.00; 95%CI, 0.86-1.16) [45].

The rates of GI bleeding were similar in the apixaban and warfarin arms of the ARISTOTLE trial [9], as well as in the apixaban and aspirin arms of the AVERROES (Table 3) [51]. Two-thirds of all GI bleeding events in the ARISTOTLE trial were located in the upper GI tract, with no

significant difference between apixaban and warfarin (Table 3) [46]. Factors associated with an increased risk of major haemorrhage were older age, prior haemorrhage, prior stroke or TIA, diabetes, lower creatinine clearance, decreased hematocrit level and the use of aspirin or non-steroidal anti-inflammatory drugs [46].

High-dose edoxaban was associated with significantly higher GI bleeding rates than warfarin, whilst the GI bleeding rates were lower with low-dose edoxaban compared to the warfarin treatment group (Table 3) [10]. In contrast to dabigatran, and similar to apixaban, about two thirds of GI bleeding events associated with edoxaban were located in the upper GI tract [10, 44, 46].

Restarting OAC after a major GI bleeding.

Prior GI bleeding is a risk factor for future bleeding events in patients taking OAC [20]. However, given a positive net clinical benefit of OAC in most AF patients [11-14], the history of GI bleeding itself should not be considered as an absolute contraindication for OAC. Indeed, it has been reported that cessation of warfarin therapy was associated with increased risk of thrombosis and death in patients who had experienced a GI bleeding [163]. Importantly, the timing of OAC resumption following a major GI haemorrhage should be guided by the cause and severity of GI bleeding and the individual patient stroke risk [160]. After resection of solid GI tumors, for example, the risk of bleeding returns to baseline as soon as haemostasis has been achieved, whilst the risk of recurrent GI bleeding events remains increased in patients with multiple GI angiectasias [16, 164]. In general, following a major GI haemorrhage OAC should be restarted after haemostasis has been secured and some GI lesion(s) healing has occurred [160], and gastric protection with proton pump inhibitors or H2 receptor blockers should be considered [100].

Patients with hepatic insufficiency

Impairment of liver function in patients taking OAC may increase the risk of bleeding by diminished synthesis of coagulation factors (both pro- and anticoagulant ones) and by altered anticoagulant drug metabolism and elimination. The liver has a high compensatory capacity

(hence, the degenerative decrease in liver function that occurs with increasing age usually does not become clinically relevant), but chronic liver diseases (such as hepatitis B or C, excessive alcohol ingestion, etc.) ultimately may result in sufficient destruction of liver parenchyma (i.e., liver cirrhosis) to cause clinically relevant hepatic insufficiency[165].

Although reduction in pro- and anticoagulant factors and qualitative and quantitative platelet defects in hepatic failure correlate with severity of liver insufficiency, the prolongation of coagulation times (especially the prothrombin time and activated partial thromboplastin time as excellent markers of liver dysfunction) might not reliably reflect the extent of reduced coagulation, due to concomitant deficiency in the anticoagulant liver-dependent proteins which re-balances haemostasis and may protect from spontaneous bleeding. Thrombin is the final enzyme in the coagulation cascade and therefore global coagulation assays (e.g., thrombin generation) may better indicate the coagulation capacity in patients with hepatic insufficiency [166].

Worsening liver function has been associated with subsequent bleeding in patients taking warfarin [167]. A recent retrospective study reported a 2-fold greater risk of bleeding and a lower mean time in therapeutic range in patients with chronic liver disease compared to those without (53.5% vs. 61.7%, $p<0.001$), and serum albumin or creatinine were the strongest predictors of both outcomes [168]. Since all NOACs undergo some hepatobiliary metabolism (dabigatran ~20%, rivaroxaban ~34%, apixaban 75%, and edoxaban ~65%) hepatic impairment can affect the NOACs' disposition and, hence, the intensity of their anticoagulation effect [169]. However, only a few patients with significant chronic liver disease were included in the landmark trials of NOACs in AF [7-10, 51], and data are lacking for the safety of NOACs in patients with liver dysfunction.

The Child-Pugh scale is the most commonly used to describe the extent of chronic hepatic impairment by combining two symptoms (ascites and encephalopathy) with three laboratory parameters (serum albumin, serum bilirubin and prothrombin time), thus categorizing chronic liver disease into mild, moderate or severe hepatic dysfunction (i.e., grades A, B and C, respectively). Available data suggest that dabigatran [170], rivaroxaban [171], apixaban [172] and edoxaban [169] can be used in patients with mild hepatic impairment (Child-Pugh A), dabigatran and apixaban can be given with caution in moderate hepatic dysfunction (Child-Pugh

B) and normal levels of the liver enzymes, but all three drugs should be avoided in patients with severe liver impairment (Child-Pugh C) [169].

A recent meta-analysis of 29 phase III randomised controlled trials evaluating a total of 152,116 patients taking dabigatran, rivaroxaban, apixaban, edoxaban or darexaban versus control treatment (i.e., vitamin K antagonists, low molecular weight heparin or placebo) reported similar risk of drug-induced liver injury with NOACs as a whole compared to control therapy (RR 0.90; 95%CI, 0.72-1.13) [173]. Similar results were obtained on individual NOAC analyses compared to VKAs or other control therapies (drug-induced liver injury was defined as transaminase and total bilirubin elevations of >3-fold and >2-fold the upper limit of normal, respectively, and all included trials were rated as having low risk of bias).

Until more data are available, OAC should be used with a caution in patients with mild to moderate liver function impairment. Regular clinical follow-up on every few months and careful laboratory monitoring of liver function seem prudent in this population of AF patients.

Patients with malignancy

Patients with malignancies have an increased baseline risk of bleeding, dependent on the cancer type and stage, renal and liver function and the presence or absence of thrombocytopenia. In addition, bleeding risk could also be aggravated by chemotherapy. The risk of clinically relevant bleeding without anticoagulation in patients with advanced cancer is estimated to be around 10%, although data are lacking [174].

Available data on OAC in patients with a malignancy mostly come from clinical randomized trials on deep venous thromboembolism. These data suggest there is a comparable risk of major bleeding with VKAs and low molecular weight heparins (around 6% during the 3-6-month treatment period), and a pooled analysis of NOACs vs. warfarin revealed no significant difference in major bleeding (HR 1.03; 95%CI, 0.44-2.39) or clinically relevant bleeding (HR 0.95; 95%CI, 0.71-1.29) between the treatment groups [174]. However, data on the use of OAC in AF patients with cancer are sparse, and individual risk assessment is necessary. Of note, it has been shown that cancer patients with recent bleeding (within the last 30 days) or CrCl of less

than 30mL/min, those with immobility of ≥4 days and patients with metastatic disease have significantly greater risk of OAC-associated bleeding compared to other patients with a malignancy [175].

Selection of optimal thromboprophylaxis in AF in clinical practice

An overview of antithrombotic drugs is presented in Table 4. Overall, many issues in the field of thromboprophylaxis in AF patients are still to be solved. Until more information on optimal thromboprophylaxis in various AF populations is acquired, a proposal for clinical decision-making is shown in Figures 1 and 2. In general, when choosing between NOACs and VKAs, the decision could be aided by reliable prediction of the quality of anticoagulation with VKAs in terms of individual TTR. Recently, a relatively simple clinical risk score with an acronym SAMe-TT_2R_2 (Figure 3) has been formulated and several observational studies showed that the score had a good ability to identify patients who will have good TTR, whilst a SAMe-TT_2R_2 value of >2 was predictive of poor TTR, all-cause mortality and composite endpoint of thromboembolic events, major bleeding and mortality [176-180]. It has been postulated that OAC-naive AF patients with a SAMe-TT_2R_2 score of 0 to 2 could be assigned to a VKA, whilst patients with a SAMe-TT_2R_2 score of >2 should start a NOAC straightforward (Figure 3).

Conclusions

Most AF patients are indicated for oral anticoagulant therapy to prevent stroke or systemic embolism, and increased risk of bleeding complications should not preclude consideration of adequate thromboprophylaxis. Available evidence shows that any oral anticoagulant therapy is better than no therapy or aspirin in almost all AF patients, regardless of the bleeding risk level. NOACs offer a significant safety advantage over VKAs, particularly in patients at increased risk of bleeding events such as the elderly and patients with impaired renal function or prior stroke or TIA, whilst more information is needed to inform better use of oral anticoagulant drugs in patients with prior ICH, end-stage renal disease, severe hepatic insufficiency or active malignant disease. Patients at increased risk of both stroke and bleeding events should be prescribed oral

anticoagulant therapy whenever possible, and regular clinical follow-up of these patients is mandatory.

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Table 1. Stages of chronic kidney disease [181] and eGFR stratified risk of stroke [60, 181].

CKD	**Stage I** Normal or increased GFR	**Stage II** Mild	**Stage IIIa/IIIb** Moderate	**Stage IV** Severe	**CKD Stage V** End-stage	
eGFR ml/min/1.73m^2	≥90	60-89	45-59 / 30-44	15-29	<15	
eGFR stratified stroke risk HR (95%CI)	eGFR>60 1.07 (0.98-1.56)		eGFR 40-60 1.28 (1.04-1.56)	eGFR <40 1.77 (1.32-2.38)		

CKD: chronic kidney disease; GFR: glomerular filtration rate; HR: Hazard Ratio; CI: Confidence Interval.

Table 2. Intracranial bleeding event rates in randomized phase III trials of NOACs vs. Warfarin (or aspirin) for stroke prevention in patients with non-valvular AF.

Trial	**Annualized ICH rates with a NOAC vs. Warfarin (or Aspirin)**						
RE-LY [117]	**Warfarin**	**Dabigatran 150mg bid**	**RR (95%CI) Dabigatran 150mg bid vs. Warfarin**	**P**	**Dabigatran 110mg bid**	**RR (95%CI) Dabigatran 110mg bid vs. Warfarin**	**P**
All ICHs (n=154)	90 (0.76)	37 (0.31)	0.40 (0.27-0.59)	<0.001	27 (0.23)	0.30 (0.19-0.45)	<0.001
ROCKET-AF [50]	**Warfarin**	**Rivaroxaban**	**HR (95%CI)**	**P**			
All ICHs (n=172)	84 (0.7)	55 (0.5)	0.67 (0.47-0.93)	0.02			
ARISTOTLE [9]	**Warfarin**	**Apixaban**	**HR (95%CI)**	**P**			
All ICHs (n=174)	122 (0.80)	52 (0.33)	0.42 (0.30-0.58)	<0.001			
ENGAGE-AF [10]	**Warfarin**	**Edoxaban 60mg OD**	**HR (95%CI)**	**P**	**Edoxaban 30mg OD**	**HR (95%CI)**	**P**
All ICHs (n=234)	132 (0.85)	61 (0.39)	0.47 (0.34-0.63)	<0.001	41 (0.26)	0.30 (0.21-0.43)	<0.001
AVERROES [51]	**Aspirin**	**Apixaban**	**HR (95%CI)**	**P**			
All ICHs (n=24)	13 (0.41)	11 (0.35)	0.85 (0.38-1.90)	0.69			

NOAC: Non-vitamin K oral anticoagulant; AF: Atrial fibrillation; ICH: Intracranial haemorrhage; RR: Relative Risk; HR: Hazard Ratio; CI: Confidence Interval.

RE-LY - Randomized Evaluation of Long-term Anticoagulant Therapy; ROCKET AF - Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE - Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 48 - Effective Anticoagulation with factor Xa next Generation in Atrial Fibrillation; AVERROES - Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment.

Table 3. Major gastrointestinal bleeding event rates in randomized phase III trials of NOACs vs. Warfarin (or aspirin) for stroke prevention in patients with non-valvular AF.

Trial	**Annualized GI bleeding rates with a NOAC vs. Warfarin (or Aspirin)**						
RE-LY	**Warfarin**	**Dabigatran 150mg bid**	**RR (95%CI) Dabigatran 150mg bid vs. Warfarin**	**P**	**Dabigatran 110mg bid**	**RR (95%CI) Dabigatran 110mg vs. Warfarin**	**P**
Main trial report [7]	1.02	1.51	1.50 (1.19-1.89)	<0.001	1.12	1.10 (0.86-1.41)	0.43
Subanalysis [44]	1.25	1.85	1.49 (1.21-1.84)	0.002	1.36	1.09 (0.87-1.36)	0.44
ROCKET-AF	**Warfarin**	**Rivaroxaban**	**HR (95%CI) Rivaroxaban vs. Warfarin**	**P**			
Main trial report [8]	2.2	3.2		<0.001			
Subanalysis [162]	1.24	2.00	1.61 (1.30-1.99)	<0.001			
ARISTOTLE	**Warfarin**	**Apixaban**	**HR (95%CI) Apixaban vs. Warfarin**	**P**			
Main trial report [9]	0.86	0.76	0.89 (0.70-1.15)	0.37			
Subanalysis: [46]	0.88	0.78	0.89 (0.70-1.14)	0.35			
Upper GI bleeding	0.56	0.43	0.76 (0.55-1.05)	0.09			
Lower GI bleeding	0.24	0.25	1.06 (0.67-1.67)	0.80			
ENGAGE-AF	**Warfarin**	**Edoxaban 60mg OD**	**HR (97%CI) Edoxaban 60mg OD vs. Warfarin**	**P**	**Edoxaban 30mg OD**	**HR (97%CI) Edoxaban 30mg OD vs. Warfarin**	**P**
Main trial report[10]	1.23	1.51	1.23 (1.02-1.50)	0.03	0.82	0.67 (0.53-0.83)	<0.001
Upper GI bleeding	0.71	0.91	1.27 (0.99-1.63)	0.06	0.56	0.78 (0.59-1.03)	0.08
Lower GI bleeding	0.52	0.62	1.20 (0.89-1.61)	0.23	0.28	0.54 (0.37-0.77)	<0.001
AVERROES	**Aspirin**	**Apixaban**	**HR (95%CI) Apixaban vs. Aspirin**	**P**			
Main trial report [51]	0.4	0.4	0.85 (0.38-1.90)	0.69			

NOAC: non-vitamin K oral anticoagulant; AF: atrial fibrillation; GI: gastrointestinal; RR: Relative Risk; HR: Hazard Ratio; CI: Confidence Interval.

RE-LY - Randomized Evaluation of Long-term Anticoagulant Therapy; ROCKET AF - Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation;

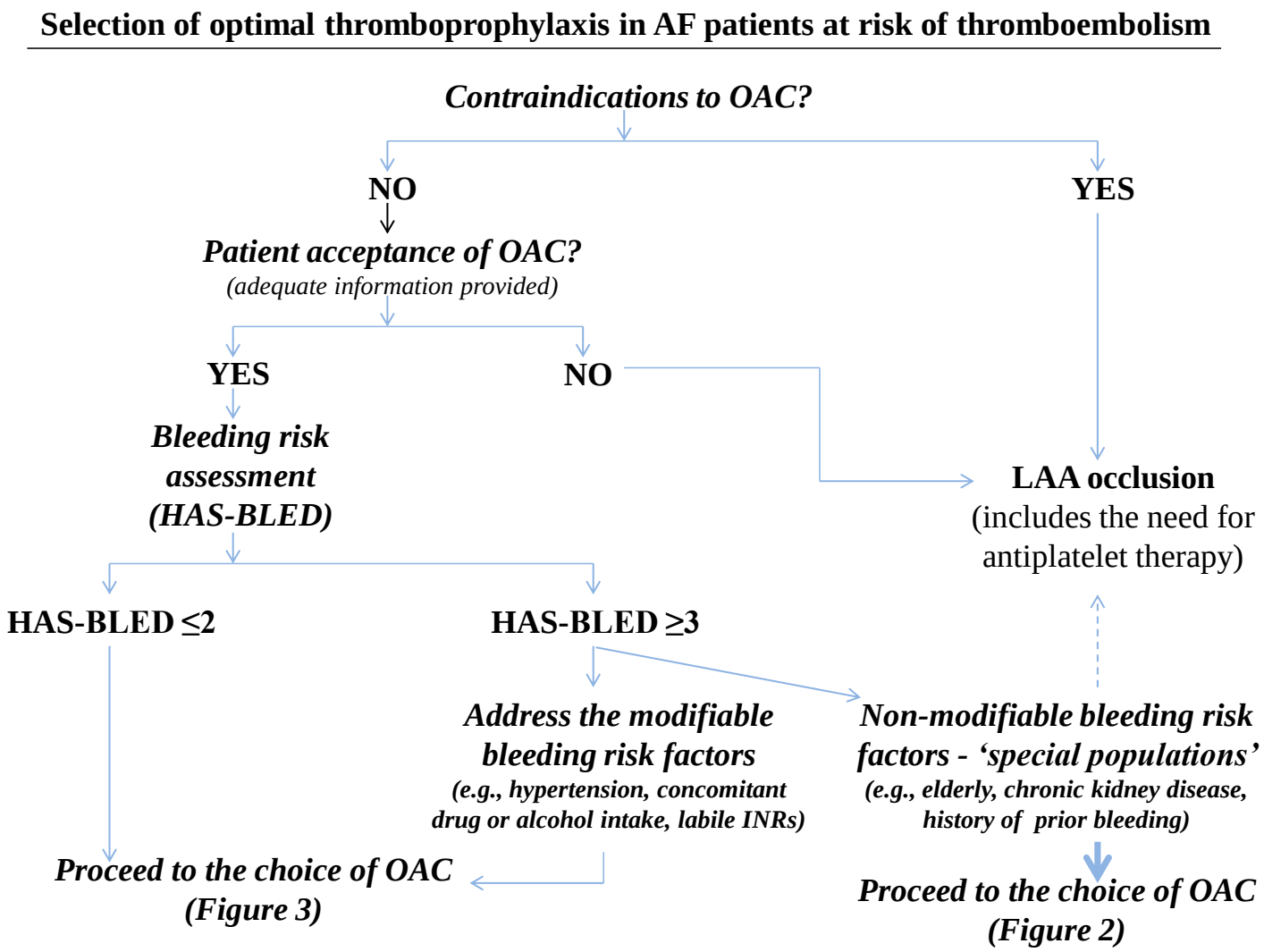
ARISTOTLE - Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF-TIMI 48 - Effective Anticoa**g**ulation with factor Xa next G**e**neration in Atrial Fibrillation; AVERROES - Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment.

Table 4. Pharmacological thromboprophylaxis in atrial fibrillation – an overview.

Drug	Comparator	Stroke reduction (95% CI)	Comment
Antiplatelet drugs			
Aspirin (meta-analysis) [6]	Placebo	All strokes: 19% (-1% to 35%) Ischemic strokes: 21% (-1% to 38%)	• Aspirin slightly better than placebo (no statistical significance) • Only 325mg daily shown to be beneficial (lower doses were similar to placebo) • Aspirin was not effective in patients ≥75 years and in the prevention of severe strokes
Aspirin + Clopidogrel (ACTIVE A) [182]	Aspirin	28%; RR 0.72 (0.62 to 0.84)	• The combination of aspirin plus clopidogrel was associated with >50% higher risk of major bleeding compared with aspirin alone (RR 1.56; 95%CI, 1.28%-1.89%) • Major bleeding rates were comparable with the rates in some warfarin trials
VKAs			
Warfarin (meta-analysis) [6]	Placebo	All strokes: 64% (49% to 74%) Ischemic strokes: 67% (54% to 77%)	• A 26% (3%-43%) reduction in all-cause mortality with warfarin
Warfarin (meta-analysis) [6]	Aspirin	37% (23% to 48%)	• The risk of ICH was doubled with warfarin, but the absolute risk increase was small (0.2% per year)
Warfarin (ACTIVE W) [183]	Aspirin + Clopidogrel	40% (18% to 56%)	• The trial was stopped early, because of clear evidence of oral VKA superiority over clopidogrel plus aspirin
NOACs			
Apixaban (AVERROES) [51]	Aspirin	Stroke or SE: 55%; RR 0.45 (0.32 to 0.62) Ischemic stroke: 63%; RR 0.37 (0.25 to 0.55)	• No significant difference in major bleeding with apixaban vs. aspirin (RR 1.13, 0.74-1.75) • No significant difference in ICH (RR 0.85, 0.38-1.90) • Lower risk of permanent drug discontinuation with apixaban (RR 0.88, 0.78-0.99)
NOACs (meta-analysis) [52]	Warfarin	Stroke or SE: 19%; RR 0.81 (0.73 to 0.91) Ischemic stroke 8%; RR 0.92 (0.83 to 1.02)	• Significant reduction of haemorrhagic stroke (RR 0.49, 0.38-0.64) • Significant reduction of ICH (RR 0.48, 0.39-0.59) • Significant reduction of all-cause mortality (RR 0.90, 0.85-0.95) • Increased risk of GI bleeding (RR 1.25, 1.01-1.55)

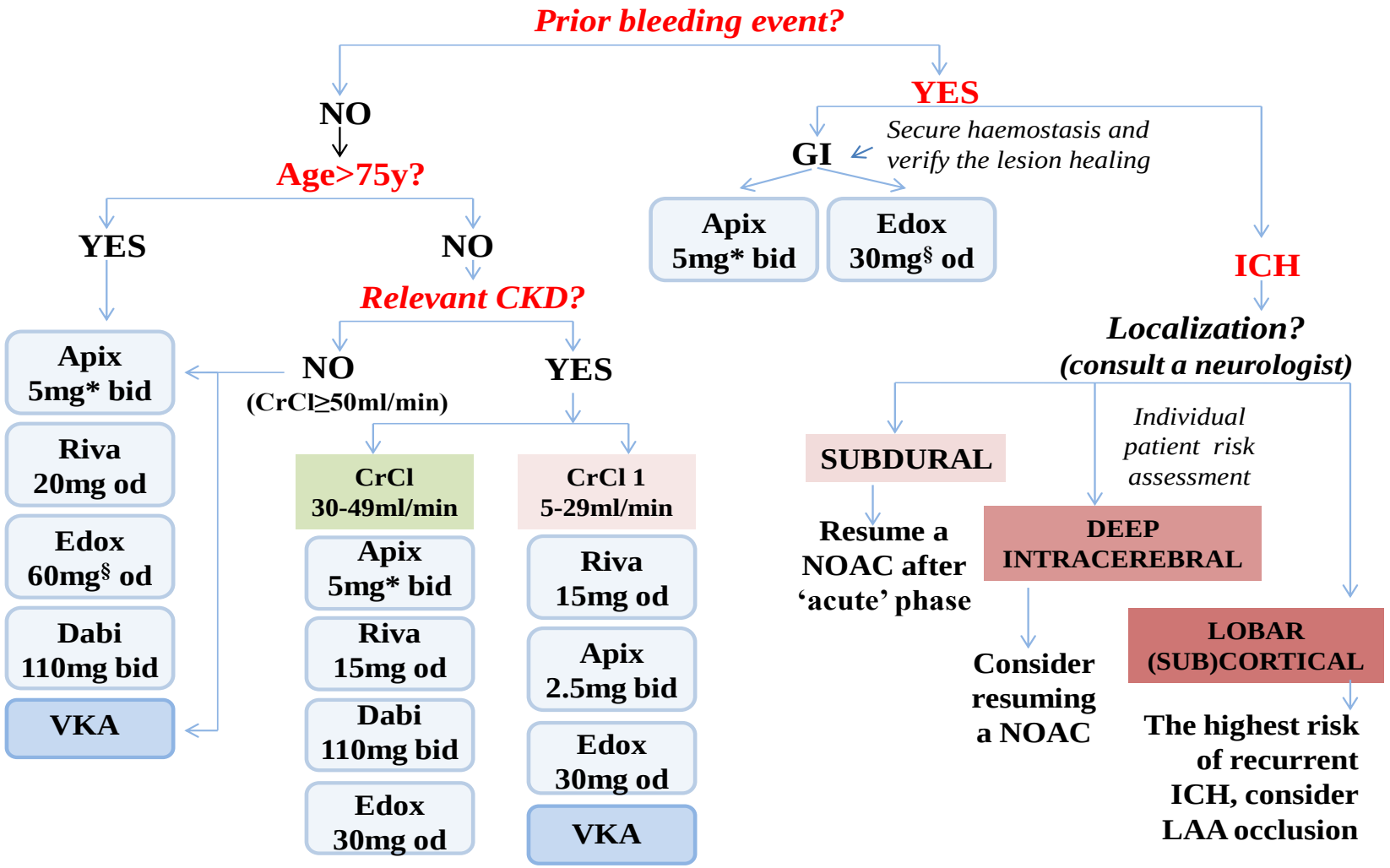
CI: Confidence Interval; ACTIVE A: Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events Aspirin; RR: Relative Risk; VKA: Vitamin K antagonist; ACTIVE W: Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events Warfarin; ICH: Intracranial haemorrhage; NOAC: Novel oral anticoagulants; AVERROES: Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment; GI: Gastrointestinal.

Figure 1. Selection of optimal thromboprophylaxis in AF.



OAC: oral anticoagulation; LAA: left atrial appendage.

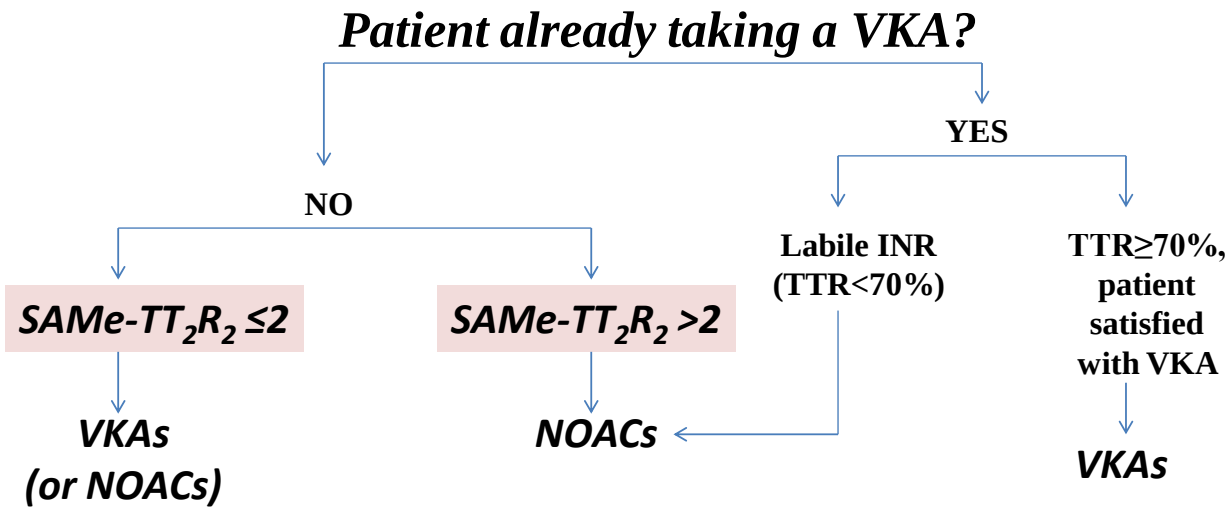
Figure 2. Selection of OAC in 'special' AF populations.



*Apixaban dose should be halved to 2.5mg bid in the presence of 2 of the following criteria: increased serum creatinine of ≥133µmol/l, age ≥80 years and/or body weight ≤60kg; [§]Edoxaban dose should be halved in the presence of any of the following: body weight <60kg, creatinine clearance <50ml/min or verapamil or quinidine use.

CKD: chronic kidney disease; GI: gastrointestinal; ICH: intracranial haemorrhage, NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin-K antagonist; LAA: left atrial appendage; bid: twice daily; od: once daily.

Figure 3. The choice of OAC for thromboprophylaxis in AF.



	Component	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history*	1
T	Treatment (interacting drugs, e.g., amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2

*More than two of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease.

VKA: vitamin K antagonist; NOAC: non-vitamin K antagonist; INR: international normalized ratio; TTR: time in therapeutic range.