Stroke Prevention with Anticoagulant in Cardiovascular Problem: Focus in Atrial Fibrillation

Ismail Setyopranoto[1(✉)], Punik Mumpuni Wijayanti[2], and Utami[3]

[1] Department of Neurology, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia
[2] Department of Public Health, Faculty of Medicine, Islamic University of Indonesia, Yogyakarta, Indonesia
[3] STIKES Husada Jombang, Kabupaten Jombang, Indonesia
ismail.setyopranoto@ugm.ac.id

Abstract. Cardiovascular problems such as atrial fibrillation is a serious and growing health problem in the global community. The presence of atrial fibrillation increases the risk of stroke, which in turn has its own problems and impact. Data have shown that the use of warfarin reduces the risk of stroke in patients with atrial fibrillation, yet this drug has been historically underutilized due to challenges with its use.

New oral anticoagulants (NOACs) are easier to use, have a lower risk of major bleeding, and have been shown to be non-inferior, and in some cases, superior to warfarin. NOACs have started to replace warfarin as the first choice anticoagulant in clinical practice. Optimal strategies to reduce stroke and risk of major bleeding in subsets of atrial fibrillation patients undergoing Percutaneous Coronary Intervention (PCI) and ablation will continue to evolve. When evaluating patients with AF, care should be taken to address the risk of stroke and provide recommendations on the use of anticoagulation to reduce it.

As atrial fibrillation becomes the most prevalent arrhythmia that is associated with an increased risk of ischemic stroke, stroke prevention is crucial for management of atrial fibrillation patients. The NOACs, such as dabigatran, rivaroxaban, apixaban and edoxaban, are at least as effective as warfarin in reducing ischemic stroke with a lower rate of major bleeding. This review article provides evidence on the performance of NOACs in AF patients with different clinical conditions. Despite the evidence from recent trials, further research is necessary for patients undergoing PCI, bioprosthetic valve replacement, transcatheter aortic valve intervention, mitraclip and for those requiring long-term antiplatelet therapy over anticoagulation.

Keywords: Stroke Prevention · Anticoagulant · Cardiovascular Problem · Atrial Fibrillation

1 Introduction

Cardiogenic cerebral embolism is responsible for approximately 20% of all ischemic stroke events. There is a history of nonvalvular atrial fibrillation in about 50% of all

H. Nurdiyanto et al. (Eds.): ICCvD 2021, AHSR 52, pp. 269–292, 2023.
https://doi.org/10.2991/978-94-6463-048-0_32

cases, then a history of valvular heart disease in about 25% and due to mural thrombus in the left ventricle in the remainder [1, 2].

Fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated activation with consequent deterioration of atrial mechanical function. On electrocardiographic (ECG) examination, atrial fibrillation is characterized by a consistent alternation of waves with oscillatory or fibrillatory waves that vary in amplitude, shape and timing, and are all associated with an irregular, often rapid ventricular response during atrioventricular (AV) conduction still intact [3]. The ventricular response to atrial fibrillation depends on the electrophysiological examination of the AV node and other conducting tissues, the level of vagal and sympathetic tone, the presence or absence of accessory conduction pathways, and the action of the drug [4]. Atrial fibrillation in the regular cardiac cycle (R-R interval) can occur in the presence of AV block, ventricular tachycardia or AV junctional. In patients with pacemakers, the diagnosis of atrial fibrillation requires temporary inhibition of the pacemaker [5]. The presence of rapid, irregular, continuous tachycardia, a widened QRS complex, is a strong feature of atrial fibrillation with excessive conduction in the accessory pathway or atrial fibrillation with underlying bundle-branch block, as well as the presence of an extreme mean velocity frequency (>200 x/min) indicates the presence of an accessory pathway or ventricular tachycardia.

Atrial fibrillation is the most common continuous heart rhythm disorder, and its incidence increases with age, and is often associated with structural heart disease, although most patients have no detectable heart disease. Hemodynamic disturbances and thromboembolic events due to atrial fibrillation are significantly associated with morbidity, mortality and costs [6]. Patients with atrial fibrillation, a history of previous stroke or TIA are at increased risk for stroke, and there is controversy over whether to administer intravenous heparin or a non-vitamin K antagonist oral anticoagulant (NOAC). Non-vitamin K antagonist oral anticoagulant (NOAC) is currently considered by several atrial fibrillation guidelines worldwide as the preferred anticoagulant for preventing stroke in atrial fibrillation patients [7–10].

The term NOAC is still used today by the European Society of Cardiology (ESC) Atrial Fibrillation Guidelines [10], and is widely recognized. Although some literature refers to these drugs as direct oral anticoagulants (DOACs) [11], however, in this review, the term Non-Vitamin K antagonist oral anticoagulant (NOAC) is still used. Finally, the two terms are understandable, referring to the direct factor Xa inhibitors, namely apixaban, edoxaban, and rivaroxaban, as well as the direct thrombin inhibitor, dabigatran.

NOAC has a better efficacy/safety ratio, and a predictable anticoagulant effect without the need for routine coagulation monitoring [12, 13]. However, the proper use of NOAC requires careful and careful consideration. Each available NOAC will be accompanied by instructions for appropriate use in clinical situations which are also explained, for example a summary of product characteristics and also information leaflets for patients and doctors, however, there are often differences in each country, and this can sometimes cause confusion, so it is necessary to clarify.

In addition, there are still some inaccurate uses of NOAC, related to side effects and interactions with other drugs, however, this drug is still relevant for use by specialists in heart and blood vessel disease, neurologists, specialists in internal medicine, geriatric

consultants, and general practitioners in practice daily. Therefore, the European Heart Rhythm Association (EHRA) coordinates in an integrated manner to provide information to doctors about the use of NOAC in the form of a practical guide (Practical Guide). The first edition of the practical guide was published in 2013 [14], then the first update was carried out in 2015 [15], then the new version was revised in 2018 [16, 17]. The purpose of publishing the EHRA Practical Guide is to provide support for the safe and effective use of NOAC in daily practice, so that it will further complement the guidelines of the European Society of Cardiology (ESC) and other international guidelines, especially on scientific evidence of atrial fibrillation therapy with anticoagulants. General, and NOAC in particular [7–10].

The purpose of writing this review is to provide understanding to doctors regarding ischemic stroke prevention with anticoagulation in atrial fibrillation patients.

2 Epidemiology of Ischemic Stroke Associated Atrial Fibrillation

The incidence of ischemic stroke due to atrial fibrillation is 1–2% per year in patients treated with Non-Vitamin K Antagonist Oral Anticoagulant (NOAC). In patients with atrial fibrillation, although the patient's level of adherence to therapy is good, stroke can still occur because the concentration of NOAC in the plasma cannot be optimal, and this correlates well with the severity of stroke, as well as the INR value in patients with vitamin K antagonists (VKA) and great vessel occlusion [18]. There are case series reports and observational studies that reveal adequate doses of NOAC at the onset of ischemic stroke are associated with less severity and better outcomes compared to stroke patients without non-anticoagulant therapy with risk factors for atrial fibrillation [19, 20]. Intracerebral hemorrhage accounts for 8–15% of all stroke events in Europe and the United States, and 15–25% of all patients with intracerebral hemorrhage are associated with oral anticoagulant drugs [21, 22]. There are several randomized controlled trials that report the incidence of intracerebral hemorrhage ranging from 0.13–0.37% per year in atrial fibrillation patients treated with NOAC, while the incidence of intracranial hemorrhage (including subarachnoid, epidural and subdural hemorrhage) is in the range of 0.23–0.55% per year [23–27].

It was reported in a retrospective analysis of the Guidelines-Stroke in the United States and the Japanese national database, that a better outcome was found with NOAC therapy than with VKA, and this result contrasts with previous studies that used the same outcome but with a mortality rate of 25–40%. After NOAC therapy and is associated with intracerebral hemorrhage [28, 29]. All stroke patients treated with NOAC need an explanation from a stroke consultant or neurologist to decide the best therapy that can be given.

3 Use of CHA2DS2-VASC to Assess Stroke Risk Factors

Despite its simplicity, the CHADS2 score does not cover many of the common stroke risk factors, and this makes it limited [30, 31]. Even patients classified as low risk by CHADS2 in the original validation study had a mean stroke rate of 1.9% per year [32]. It was reported that patients with a CHADS2 score of 0 were not all at low risk,

even though the decision to give anticoagulation or not was only based on a CHADS2 score of 0 (a category recommended not to give antithrombotics or aspirin according to guidelines), and this may not avoid the occurrence of stroke due to thromboembolism in atrial fibrillation patients [33].

Data from cohort studies around the world provide information that independent predictive values of female sex, age 65 to 74 years, and vascular disease are proven risk factors for stroke [33, 34]. Whereas it is known that congestive heart failure (C in CHADS2) is not a consistent risk factor for stroke [34], while moderate to severe increase in systolic blood pressure is an independent risk factor [35].

Because several risk factors must be paid more attention to, the CHA2DS2-VASc score has been added to which several risk factors have been added (Table 1), with scores ranging from 0 to 9 [37]. The CHA2DS2-VASc further clarifies the importance of age 75 years as an additional single risk factor for stroke with a score of 2 points, and this

Table 1. Assessment of stroke risk factors (CHA2DS2-VASc)36 and bleeding risk (HAS-BLED)37 in atrial fibrillation patients

CHA2DS2-VASc	Score	HAS-BLED	Score
– *Congestive heart failure*	1	– Hypertension (TDS > 160 mm Hg)	1
– Hypertension	1	– Abnormal renal and liver function*	1 or 2
– Age ≥ 75 years	2	(1 point each)	1
– Diabetes mellitus	1	– Stroke	1
– Stroke/TIA/Thromboemboli	2	– Bleeding tendency/predisposition*	1
– Vascular disease (prior MI, PAD, or	1	– Labile of INR (jika dengan	1
aortic plaque)	1	warfarin)*	1 or 2
– Aged 65–74 years	1	– Elderly (>65 tahun)	
– Sex category (female)		– Drugs or alcohol (1 point each)*	
Maximum Score	…..	Maximum Score	…..

Notes:

TIA: transient ischemic attack; TE: thromboembolic; INR: international normalized ratio; MI: myocardial infarction; dan PAD: peripheral artery disease.

– CHA2DS2-VASc score 0: recommends no antithrombotic therapy

– CHA2DS2-VASc score 1: recommends antithrombotic therapy with antiplatelet or oral anticoagulants, but oral anticoagulants are preferred.

– CHA2DS2-VASc score 2: recommend oral anticoagulants. [38]

– HAS-BLED score 3 indicates that caution is required when prescribing oral anticoagulants and routine examination is recommended. [38]

**Classified as abnormal kidney function is if the patient is on chronic dialysis, kidney transplantation, or serum creatinine 200 mmol/L.*

**Abnormal liver function was defined as chronic liver disease (eg cirrhosis) or biochemical evidence of significant hepatic impairment (bilirubin 2 to 3 times the upper limit of normal, associated aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 times the upper limit of normal, etc.).*

**Bleeding history or predisposition (anemia), labile INR (ie, time in therapeutic range < 60%).*

** Concurrent use of antiplatelet or nonsteroidal anti-inflammatory drugs, or excessive alcohol consumption.*

shows that age is not a phenomenon with a simple "yes or no" answer because the risk of stroke increases with age, especially from 65 years and over [34, 39]. The CHA2DS2-VASc also combines vascular disease, including myocardial infarction, aortic plaque, and peripheral vascular disease, and an increased risk of stroke in women with atrial fibrillation [34].

4 Use of HAS-BLED to Assess Bleeding Risk in Patients with Atrial Fibrillation

The abbreviation HAS-BLED represents each risk factor for bleeding and is assigned 1 point if there are these risk factors, namely hypertension with uncontrolled systolic blood pressure > 160 mmHg, abnormal kidney and/or liver function, history of previous stroke, history or predisposition to bleeding, unstable international normalized ratios (INR), advanced age, and excessive drug and/or alcohol consumption [37]. The HAS-BLED score ranges from 0 to 9, and a score > 3 indicates a high risk of bleeding, and is recommended for be careful and check regularly. Based on validation by Euro Heart Survey [37], reported that the predictive accuracy of the HAS-BLED score was compared with other bleeding risk scores, e.g. HEMORR2HAGES [40], with C statistics are 0.72 and 0.66, respectively. In an analysis among patients who did not receive antithrombotic or antiplatelet therapy, HAS-BLED showed better accuracy in predicting the risk of major bleeding (with C statistics 0.85 and 0.91, respectively). The HAS-BLED score has also been validated in several different cohort studies, including large population clinical trials, such as the European Consensus Document [41]. Overall, the HAS-BLED score predicts bleeding better than other bleeding risk scores [42].

In addition, the advantage of the HAS-BLED score over other bleeding risk scores is that it is easier to use and its components consist of clinical information that is routinely obtained from patients before therapy is started (except for INR values), so that the HAS-BLED is easier to apply clinically.

HAS-BLED should not be used alone to justify a patient not being given oral anticoagulant therapy, however, a clinician should identify risk factors for bleeding and correct modifiable risk factors, namely by controlling blood pressure, delaying antiplatelet therapy or administering anti-inflammatory drugs. Concomitant non-steroidal drugs, and advise the patient to stop drinking alcohol. Therefore, the bleeding risk assessment with the HAS-BLED score should not be used as a reason not to give oral anticoagulants, but rather to encourage doctors to be more careful and advise patients to continue taking medication and have regular check-ups.

5 Eligibility of Non-Vitamin K Antagonist Oral Anticoagulant (NOAC)

NOAC has been approved for stroke prevention therapy in patients with non-valvular atrial fibrillation, and has passed a Phase III clinical trial with a Randomized Clinical Trial (RCT). Because of its consistent efficacy and safety, the indications for NOAC therapy were extended to patients eligible for anticoagulant therapy based on the CHA2DS2-VASc score (Table 2).

Table 2. Indications and contraindications for NOAC in patients with atrial fibrillation

Condition	NOAC Eligibility	Notes
Mechanical prosthetic valve	Contraindications	Excluded from RCTs, data show poorer outcome. [46, 47]
Moderate to severe mitral stenosis (usually rheumatic)	Contraindications	Excluded from RCTs, few reasons for lower efficacy and safety than VKA
Other mild to moderate valvular disease, eg, degenerative aortic stenosis, mitral regurgitation, etc.	Included in the NOAC trial	Overall efficacy and safety data are consistent with patients without valvular heart disease.[44, 48–53]
Bio-prosthetic valve/valve repair	Acceptable	Single RCT showed no inferiority to VKA.54 Patients without atrial fibrillation are usually given ASA after 3–6 months postoperatively, so NOAC therapy can be given to prevent stroke if atrial fibrillation is diagnosed.
Severe aortic stenosis	Limited data (except on RE-LY)	There is no pathophysiological reason for low efficacy and safety, most will undergo intervention
Trans-catheter aortic valve implantation	Acceptable	Single RCT + observational data, may require combination with antiplatelet. [55, 56]
Percutaneous transluminal aortic valvuloplasty	Carefully	No prospective data, may require combination with antiplatelet
Cardiomyopathic hypertrophy	Acceptable	No reason for lack of efficacy and safety vs VKA, positive observational data for NOAC. [57–60]

To avoid confusion, the use of the term non-valvular is strongly discouraged by the European Society of Cardiology (ESC) guidelines on the management of patients with atrial fibrillation, and references are made to specific underlying valvular heart disease [10, 43, 44]. However, the term is still unclear. Found in the brochures of individual NOAC products, as these were the original terms used in the RCT exclusion criteria on which the regulatory approvals were based. The term non-valvular atrial fibrillation refers to atrial fibrillation without a mechanical prosthetic heart valve or moderate to severe mitral stenosis, usually from rheumatic heart disease (Table 2) [10, 44, 45], being the exclusion criteria for all phase III trials of administration NOAC vs. warfarin in atrial fibrillation.

However, there have been no RCT studies reporting that NOAC is less efficacious in patients with rheumatic mitral stenosis, nor is there a rational basis for comparing differences in response between NOAC and VKA. Currently INVICTUS 9iis investigating the use of VKA, rivaroxaban and aspirin in patients with rheumatic heart disease. So that until the study is completed, patients should still be given VKA as standard therapy.

However, if therapy with VKA is really not possible, for example there is no monitoring tool or the INR value is unstable, then the use of NOAC can be an option, but doctors should evaluate it carefully, given the lack of research on this matter, and doctors still have to consider the factors of safety and effectiveness, and of course with the consent of the patient regarding the off-label use of NOAC.

In patients with atrial fibrillation with a valvular etiology, such as severe mitral stenosis undergoing mechanical mitral valve replacement, NOAC therapy should be avoided and patients should be given VKA for stroke prevention [46, 47]. In patients with degenerative valvular heart disease in phase III studies, It was reported that NOAC demonstrated comparable efficacy and safety with warfarin in valvular patients compared with those without valvular disease, except for a higher bleeding risk with rivaroxaban versus warfarin in a post hoc analysis of Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) [44, 48–53, 57]. Therefore NOAC can be used in patients with atrial fibrillation, and mostly for valvular heart disease (Table 2) [10, 44].

Until now, the administration of oral anticoagulants in patients with atrial fibrillation and biologic valves or after valve repair is still controversial, although these patients were included as subjects of several NOAC studies [44, 48, 50, 51]. In the Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation (RIVER) study), reported that rivaroxaban was not inferior to warfarin in terms of the mean time to the combined end point of mortality, major cardiovascular events, or major hemorrhage in a 12-month follow-up of 1005 patients with atrial fibrillation or flutter who underwent mitral valve replacement bioprosthetics [54].

Edoxaban was also not inferior in terms of efficacy and safety in a study of 220 patients in the Efficacy and Safety trial of edoxabaN in Patients After Heart Valve Repair or Bioprosthetic valve Replacement (ENAVLE), and NOAC is the drug of choice for the management of atrial fibrillation, especially 8 to 12 weeks after surgery.

In patients after transcatheter aortic valve implantation (TAVI), who have indications for therapy with anticoagulants, for example in patients with atrial fibrillation, there was an RCT of 157 patients comparing oral anticoagulants alone with a combination of oral anticoagulants and clopidogrel, reported that oral anticoagulants alone more beneficial in terms of reducing the risk of bleeding without ignoring ischemic events [55]. Greater advantages were reported for the use of NOAC over VKA in this study, however, this study was unable to answer several controversial questions. Based on observational data, it was also found that the rate of thromboembolic events and early bleeding (and all-cause mortality) was lower in NOAC than in VKA after TAVI, although there may still be confounding factors [56, 62].

There are ongoing studies on the efficacy and safety of NOAC, namely the Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) [63] and EdoxabaN vs. standard of care and their effects on clinical outcomes in patients having undergonE Transcatheter Aortic Valve Implantation–Atrial Fibrillation (ENVISAGE-TAVI) [64]. Monotherapy with oral anticoagulant drugs, including NOAC may be considered after TAVI in patients with atrial fibrillation, and oral anticoagulants may not be given to patients without clear indications [65].

In both obstructive and non-obstructive hypertrophic cardiomyopathy, atrial fibrillation is associated with high rates of thromboembolism [66, 67]. Although there are currently no RCT studies, there is increasing evidence from studies showing that NOAC is safer and more effective [57–60]. There is no mechanistic reason why NOAC is inferior to warfarin in hypertrophic cardiomyopathy, on the other hand atrial fibrillation in hypertrophic cardiomyopathy has much in common with atrial fibrillation associated with Heart failure with preserved ejection fraction (HfpEF), i.e. NOAC is not inferior to VKA [68–70]. In addition NOAC is also more efficacy than VKA in other high-risk subgroups, for example patients with high CHA2DS2VASc scores. Thus patients with hypertrophic cardiomyopathy are eligible for NOAC therapy.

NOAC is contraindicated in pregnancy, and if NOAC is to be administered to women of childbearing age, contraception may be considered. Pediatric patients were excluded from RCTs for stroke prevention, and the incidence of atrial fibrillation requiring oral anticoagulation was rare in children. NOAC therapy is not recommended in children, but may be considered in adolescent adults weighing more than 50 kg.

There are reports of studies on weight-adjusted therapy with rivaroxaban that have been shown to be safe and effective for children with acute venous thromboembolism compared with standard anticoagulation given for 3 months. Beneficial as a secondary therapy for the prevention of venous thromboembolism in children aged 3 months to 18 years [72]. Patients with non-valvular atrial fibrillation and the antiphospholipid syndrome were better treated with VKA than NOAC, because the rates of thromboembolic events and major bleeding were higher with rivaroxaban than with warfarin in these patients [73].

6 Dose

There are four NOACs currently available with different doses for different indications and with different dose reduction criteria, making identification of the beard dose more complicated. Table 3 shows an overview of currently available NOACs and their dosages in different indications, as well as the relevant dose reduction criteria.

6.1 Time Range on Missed NOAC Dose

The time range for the missed dose from the time the drug should be taken can be taken until half the time interval that should have taken the drug has elapsed. Therefore for NOAC on a twice-daily dosing regimen or intake every 12 h, the allowable time range for the missed full dose may be up to 6 h after the scheduled drug intake. As for NOAC

Table 3. Oral anticoagulants and approved doses according to indications

Prevention of stroke in patients with atrial fibrillation		
NOAC	Standard dosage	Note/dose reduction
Apixaban[24]	5 mg (2x/day)	2.5 mg (2×/day) if 2 of 3 are met, i.e. body weight ≤ 60 kg, age ≥ 80 years, serum creatinine ≥ 133 mmol/L (1.5 mg/dL) (or single criterion, ie if creatinine clearance 15–29 mL/min)
Dabigatran[23]	150 mg (2x/day)/ 110 mg (2x/day)	There are no predefined dose reduction criteria in the phase III[a] trial
Edoxaban[74]	60 mg (1x/day)	30 mg (1x/day) if weight ≤ 60 kg or creatinine clearance 15–49 mL/min or concomitant therapy with strong P-glycoprotein (P-Gp) inhibitors
Rivaroxaban[75]	20 mg (1x/day)	151515g (1x/day) if creatinine clearance ≤ 15–49 mL/min

on a once-daily dosing regimen, the allowable time span for the missed full dose can be administered up to 12 h after the scheduled intake of the drug. After the time allowed for the intake of the drug has passed, the patient's schedule of drug intake must be skipped, and the drug is given according to the next schedule [76].

6.2 Accidental Intake of Drugs with Double Doses

If the patient is inadvertently taking a double dose of the drug, for NOAC on a twice daily dosing regimen and the patient is on a double intake, then the next planned dose intake (i.e. after 12 h) can be skipped, and the regular twice daily dosing regimen can be started. Returned 24 h after the intake of the double dose of the drug. As for NOAC with a once-daily dosing regimen and the patient accidentally takes a double dose, the patient should continue the normal dosing regimen, without having to miss the next daily dose [76].

6.3 Doubts About Dosage Intake

Patients often forget or have doubts about the intake of doses of the drugs they should be taking, for NOAC with a twice-daily dosing regimen and the patient has doubts about the intake of these drugs, it is recommended not to use other drugs, but continue with the regular dosing regimen, i.e. start with subsequent doses at 12 h intervals. As for NOAC with a once-daily dosing regimen and the patient has doubts about the intake of the dose, if the risk of thromboembolism is high, i.e. with a CHA2DS2-VASc score of more than 3, it is recommended to take another drug 6–8 h after the proper intake (when the patient is in doubt). -undecided) and then continue the planned dosing regimen. In cases of low thromboembolic risk, i.e. CHA2DS2-VASc score less than 2, the patient is advised to wait until the next scheduled dose [76].

7 Indications for Anticoagulant Therapy and Choice Between VKA and NOAC

After the indications for therapy with oral anticoagulants were established, based on several studies NOAC was found to be preferred over VKA in all atrial fibrillation patients who were eligible for NOAC administration [9, 10]. When starting therapy with NOAC, clinicians must understand the renal and hepatic function of these patients, because all NOACs are eliminated to some extent by the kidneys, and renal function can affect NOAC dosage. Kidney function in the form of Creatinine Clearance (CrCl) can be assessed using the Cockcroft-Gault formula as has been used in four phase III trials, namely;

$$\text{CrCl (mg/dL)} = \frac{(140 - \text{age}) \times \text{BW (kg)} \times (0,85 \text{ if female})}{72 \times \text{serum Creatinine (mg/dL)}}$$

Indeed, the use of other formulas including the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) can overestimate kidney function especially in older patients and in patients who are of low body weight [77].

8 Bleeding Profile Should Be Checked During Follow Up

The bleeding risk, which can be estimated using the HAS-BLED score, is not in itself a reason not to give oral anticoagulants to patients with atrial fibrillation who are at risk for stroke or reduce the dose of NOAC. On the other hand, especially in patients with a high bleeding risk, such as patients with a HAS-BLED score of more than 3, these patients should be tested to identify modifiable bleeding risk factors [10, 78], and should be followed up early and more frequently for a thorough examination [79]. Likewise, the presence of weakness, decreased cognitive function and the risk of falling, then this should not be a reason not to give anticoagulants to patients. Comprehensive treatment needs to be provided to minimize the risk of falling and to ensure optimal compliance [76].

9 Choose the Type and Dosage of NOAC

Currently there are four types of NOAC available in different doses for different indications and with different dosage reduction criteria, so the identification of the right dose is more complicated, and is one of the main challenges in daily use and this leads to individualization. in the treatment. There are also policy-related factors, such as consent regulations, formulary restrictions, and treatment costs, all of which can affect the availability of NOACs in the community [76].

All types of NOAC have been carried out in randomized prospective trials with large samples, and it has been reported that there is efficacy and safety of each type of NOAC. A clinical trial with a different dose, of course, will be done in a different way. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

(ARISTOTLE) clinical trial using apixaban and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) using rivaroxaban, patients receive a reduced standard dose in the presence of predetermined patient characteristics [24, 75].

In contrast, in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) clinical trial using dabigatran and also the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) clinical trial using edoxaban, both at a lower dose and at a higher dose, were then tested in a full cohort of patients (without further dose reductions for dabigatran, and with further dose reductions for edoxaban in selected patients) [74, 80].

NOAC dose reduction is recommended according to the dose reduction criteria in the guidelines [10]. The dose of NOAC that has been clinically tested and approved, then NOAC therapy should be used to provide optimal benefit to the patient. There are many publications confirming that NOAC is at least as safe and efficacy as warfarin [81–86]. However, there are several studies reporting on the use of higher doses in anticipation of off-label dosing of NOAC [82, 87–99]. This is related to the fact that most Healthcare providers are concerned about the risk of bleeding, while the risk of stroke is seen as a natural course of the disease. However, various clinical trials with large sample sizes and based on serial observational reports that high-risk patients will benefit more from anticoagulant therapy [24, 74, 84, 100–102]. Involvement of the patient in the decision-making process and discussing together the choice of anticoagulant is the key to adequately assessing the patient's needs, because the risk of stroke is greater than the risk of bleeding [103–105].

In addition, it is important to consider concomitant medications (co-medications), as some of them may have contraindications or result in unfavorable drug-drug interactions. Consideration should also be given to the patient's age and susceptibility, body weight, renal function and other comorbidities that may influence the choice. Proton pump inhibitors (PPIs) may be considered to reduce the risk of gastrointestinal bleeding, especially in patients with a history of bleeding or gastrointestinal ulcers, and patients requiring co-medication of double antiplatelet therapy [106–111].

There are also studies that focus on gastroprotective effects, particularly shown in patients receiving antiplatelet therapy or VKA [112–114], while data on the preventive effect in patients treated with NOAC are still very limited [106]. There are several decision-making tools available to guide clinicians on the most suitable use of NOAC for specific target groups [115–118].

10 Management of Atrial Fibrillation Patients Treated with NOAC in the Acute Phase of Stroke

Management of atrial fibrillation patients with NOAC therapy in acute phase ischemic stroke can be seen in Fig. 1.

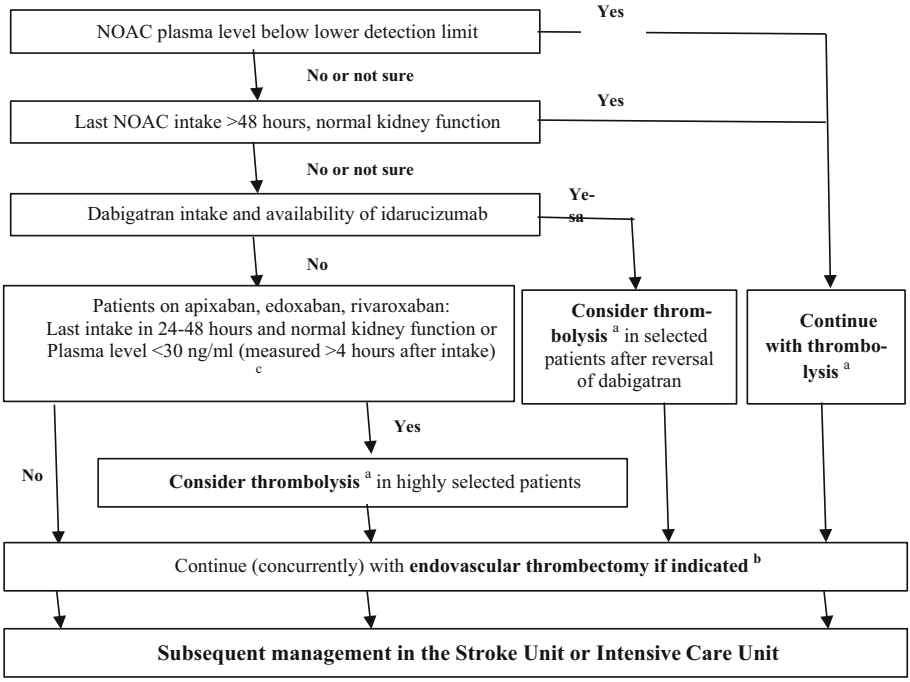

Fig. 1. Immediate management of acute ischemic stroke patients with relevant neurologic deficits in patients receiving NOAC therapy. aSystemic thrombolysis is indicated only if there are no contraindications to labelling intravenous rt-PA. bEndovascular thrombe

11 NOAC Plasma Level Measurement Indications

There are no studies reporting on drug level measurement and dose adjustment based on laboratory coagulation parameters, ideally a dose reduction if a higher plasma level is found, or an increase in the dose if a lower plasma level is found, and this would increase the benefit of NOAC in long-term therapy. Long. However, routine monitoring of plasma levels and subsequent dose adjustments are generally rarely carried out [76].

Laboratory studies of drug exposure and anticoagulant effects can assist physicians in emergencies such as bleeding, urgent elective procedures suspected of overdose, and acute stroke. Also in special situations, such as possible drug interactions, extreme weight gain, or impaired kidney function, plasma levels can help in clinical decision making [120, 121].

12 Management of Post-acute Stroke Patients with Risk Factors for Atrial Fibrillation

12.1 Patients with Atrial Fibrillation After Ischemic Stroke or Transient Ischemic Attack

Physicians should always think long term when treating patients with atrial fibrillation, because it can be a cause of stroke and the condition can be prevented [20, 122]. To date there is no evidence in Randomized Control Trials to support that one NOAC is better than another, or to switch one NOAC. to another in patients with transient ischemic attack (TIA) or ischemic stroke on NOAC therapy. NOAC therapy can be individualized and must take into account the presence of comorbidities and the medications being co-medicated. In acute ischemic patients with a history of NOAC therapy, measurement of plasma NOAC levels at the time of hospital admission can help assess patient compliance in taking these drugs [76].

Since the disruption of the blood-brain barrier associated with stroke may increase the risk of secondary hemorrhagic transformation, (re-)starting oral anticoagulants must balance the risk of recurrent ischemic stroke with the risk of bleeding. Data from RCTs with large samples were missing, because the NOAC phase III study excluded patients within 7 to 30 days after stroke and within 3 to 6 months after a severe stroke [21]. As this RCT is still ongoing, the current recommendations are based on mutual consensus [43, 123], observational studies [124–126], and analyzes of individual patient data from prospective cohort studies [127].

The 2020 European Society of Cardiology (ESC) Guidelines on the management of atrial fibrillation state that oral anticoagulation should be (re)started as soon as possible from a neurological perspective, which in most cases is in the first 2 weeks [10]. The 2019 AHA/ASA guidelines conclude that for the majority of patients with acute ischemic stroke associated with atrial fibrillation, it is reasonable to initiate oral anticoagulant therapy between 4 and 14 days after the onset of neurologic symptoms [123]. However, there are different opinions, namely the consensus of experts from the European Stroke Organization (ESO) concluded that recommendations about the optimal time to start anticoagulant therapy in patients with acute ischemic stroke cannot be made [21].

There are currently several randomized trials, such as ELAN, OPTIMAS, TIMING, START, and AREST in which the initial focus of NOAC therapy is compared with delayed (return) after acute ischemic stroke, and these studies are ongoing and report expected outcomes in the year 2021/2022 [127]. Practical guidance is needed for common clinical dilemmas, as first defined in the 2015 EHRA Practical Guide, namely oral anticoagulation followed by prescription and label use of NOAC, or starting the next day in patients with Transient Ischemic Attack (TIA) after exclusion. Intracerebral hemorrhage/secondary hemorrhagic transformation with imaging studies, and taking into account the size of the acute ischemic brain lesion based on these examinations [15, 43].

If the infarct size in a patient would substantially increase the risk of hemorrhagic transformation in a minor stroke patient, then therapy with oral anticoagulants may be initiated 3 days after the acute ischemic stroke (Fig. 2). Furthermore, in patients with moderate stroke, anticoagulation can be started after 6 to 8 days, then in patients with severe stroke it can be given after 12 to 14 days, after excluding secondary hemorrhagic

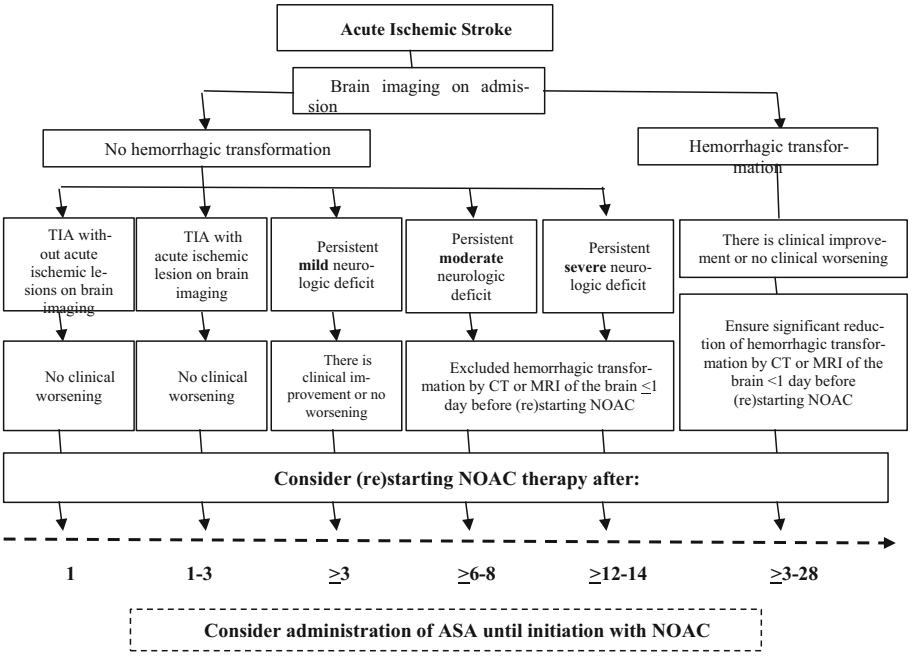

Fig. 2. (Re-) initiation of anticoagulation after TIA/stroke. Without RCT evidence, based on expert opinion, inclusion of patients in the ongoing study could be considered. (Re-)initiation can be given only if there are no contraindications and if stroke size. CT: *computed tomography*; LA: *left atrium*; LAA: *left atrial appendage*; MRI: *magnetic resonance imaging*; NOAC: *non-vitamin K antagonist oral anticoagulant*; RCT: *randomized clinical trial*; TIA: *transient ischaemic attack.*

transformation by re-examination of brain imaging, with computed tomography (CT) or magnetic resonance imaging (MRI). As explained earlier, time considerations and actions taken based on expert suggestions can be considered until evidence becomes available, so a multidisciplinary team approach is mandatory in these situations [76].

When to (re-)start oral anticoagulants is the patient's decision, but should consider if there is a thrombus in the left atrium or if there is evidence of cerebral amyloid angiopathy. Although micro cerebellar hemorrhage detected on MRI is independently associated with an increased risk of symptomatic intracerebral hemorrhage, it is also associated with a risk of recurrent acute ischemic stroke, further the burden of cerebral microblading associated with intracranial hemorrhage remains to be determined [21, 127–129]. If there is cerebral microblading alone, it cannot determine the decision to give anticoagulants.

Because of the rapid onset of action of NOAC and the associated risk of bleeding, administration of heparin before (re-)starting therapy with NOAC or treatment with LMWH as an anticoagulant is not recommended [21]. If initiation of therapy with oral anticoagulants is delayed in acute ischemic stroke patients, aspirin should be given before initiation [21].

In the case of oral anticoagulants given in peri-onset stroke, aspirin administration should be delayed according to the NOAC half-life and renal function or should be based on the results of specific coagulation tests. Antiplatelet administration for secondary stroke prevention in patients with atrial fibrillation after acute ischemic stroke should be discontinued when (re-) starting NOAC therapy, unless there is a clear indication for the use of co-medication, for example in patients with new coronary or carotid stenting [21].

Use of NOAC on discharge from hospital in stroke patients due to atrial fibrillation was associated with more days spent at home and lower rates of cardiovascular events compared with VKA based on a large multicenter cohort study including stroke patients [130]. Of note, higher doses of NOAC Appropriate care and patient compliance are critical to ensure optimal secondary stroke prevention [19, 90, 130].

12.2 Atrial Fibrillation Patients with Ischemic Stroke and Atherosclerosis

The addition of antiplatelets to NOAC therapy for a period of time may be necessary or considered in acute ischemic stroke patients with atrial fibrillation, if the stroke is most likely due to large-vessel disease, symptomatic (intracranial) stenosis, or the patient has recently undergone a stenting procedure, and is at risk for bleeding. Considered low. However, evidence for this therapeutic approach is lacking and further research is needed [131]. Atrial fibrillation patients with acute ischemic stroke due to symptomatic high-grade carotid stenosis should undergo carotid endarterectomy, because carotid stenting requires double antiplatelet therapy in addition to oral anticoagulant therapy with a higher risk of bleeding [131].

In atrial fibrillation patients undergoing carotid endarterectomy, aspirin is recommended before and for several days after surgery, but should be discontinued while continuing NOAC therapy. Atrial fibrillation patients with asymptomatic atherosclerosis or internal carotid artery and/or intracranial artery stenosis should be treated with statins and oral anticoagulants, without the need for additional antiplatelet therapy, and the condition is similar to stable coronary artery disease [131].

References

1. Krishnamurthi RV, Feigin VL, Forouzanfar MH, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013;1:e259–281.
2. Kamel H, Healey, JS. Cardioembolic Stroke. Circulation Research, 2017; 120(3): 514-526.
3. Yiin GSC, Howard DPJ, Paul NLM, Li L, Luengo-Fernandez R, Bull LM, Welch SJV, Gutnikov SA, Mehta Z, Rothwell PM. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation–related embolic vascular events: a population-based study. Circulation. 2014;130:1236-1244.
4. Prystowsky EN, Katz AM. Atrial fibrillation. In: Textbook of Cardiovascular Medicine. Philadelphia: Lippincott-Raven, 1998:1661.
5. Gutierrez C, Blanchard DG. Diagnosis and Treatment of Atrial Fibrillation. Am Fam Physician, 2016;94(6):442-452.

6. DuBose-Briski V, Yao X, Dunlay SM, Dhruva SS, Ross JS, Shah ND, Noseworthy PA. Evolution of the American College of Cardiology and American Heart Association Cardiology Clinical Practice Guidelines: A 10-Year Assessment. J Am Heart Assoc., 2019;8(19):e012065.
7. Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T., et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythm, 2017;33: 345-367.
8. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C., et al. Focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol, 2018;34:1371-1392.
9. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr., et al.; AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. Circulation, 2019;140: e125-151.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J., 2021;42:373-498.
11. Barnes GD, Ageno W, Ansell J, Kaatz S; Subcommittee on the Control of Anticoagulation of the International Society on Thrombosis and Haemostasis. Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH. J Thromb Haemost, 2015;13: 1154–1156.
12. Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism. Eur Heart J, 2011;32: 1968-1976.
13. 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. Lancet, 2014;383: 955-962.
14. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J., et al.; European Heart Rhythm Association. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace, 2013;15:625–651.
15. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, 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;17:1467-1507.
16. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L., et al.; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J, 2018;39: 1330–1393.
17. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L., et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. Europace, 2018;20: 1231-1242.
18. Macha K, Marsch A, Siedler G, Breuer L, Strasser EF, Engelhorn T., et al. Cerebral ischemia in patients on direct oral anticoagulants. Stroke, 2019;50: 873-9.
19. Hellwig S, Grittner U, Audebert H, Endres M, Haeusler KG. Non-vitamin K-dependent oral anticoagulants have a positive impact on ischaemic stroke severity in patients with atrial fibrillation. Europace, 2018;20: 569-574.

20. Meinel TR, Frey S, Arnold M, Kendroud S, Fischer U, Kaesmacher J., et al. Clinical presentation, diagnostic findings and management of cerebral ischemic events in patients on treatment with non-vitamin K antagonist oral anticoagulants – a systematic review. PloS One, 2019;14:e0213379.
21. Klijn CJ, Paciaroni M, Berge E, Korompoki E, Korv J, Lal A., et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. Eur Stroke J, 2019;4: 198-223.
22. Nguyen NY, Frishman WH. Restarting oral anticoagulation in patients with atrial fibrillation after an intracranial hemorrhage. Cardiol Rev, 2020;28: 190-196.
23. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S., et al. Apixaban in patients with atrial fibrillation. N Engl J Med, 2011;364: 806-817.
24. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M., et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med, 2011; 365:981-992.
25. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J., et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation, 2011;123: 2363-2372.
26. Giugliano RP, Ruff CT, Rost NS, Silverman S, Wiviott SD, Lowe C., et al. Cerebrovascular events in 21105 patients with atrial fibrillation randomized to edoxaban versus warfarin: effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48. Stroke, 2014;45: 2372-2378.
27. Lopes RD, Guimaraes PO, Kolls BJ, Wojdyla DM, Bushnell CD, Hanna M., et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. Blood, 2017;129: 2980-2987.
28. Inohara T, Xian Y, Liang L, Matsouaka RA, Saver JL, Smith EE., et al. Association of intracerebral hemorrhage among patients taking non-vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. JAMA, 2018; 319: 463-473.
29. Kurogi R, Nishimura K, Nakai M, Kada A, Kamitani S, Nakagawara J., et al.; JASPECT Study Collaborators. Comparing intracerebral hemorrhages associated with direct oral anticoagulants or warfarin. Neurology, 2018;90: e1143-e1149.
30. Karthikeyan G, Eikelboom JW. The CHADS2 score for stroke risk stratification in atrial fibrillation: friend or foe? Thromb Haemost., 2010; 104: 45-48.
31. Keogh C, Wallace E, Dillon C, Dimitrov BD, Fahey T. Validation of the CHADS2 clinical prediction rule to predict ischaemic stroke: a systematic review and meta-analysis. Thromb Haemost. 2011; 106: 528-538.
32. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA, 2001; 285: 2864-2870.
33. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0–1: a nationwide cohort study. Thromb Haemost., 2012; 107: 1172-1179.
34. Friberg L, Rosenqvist M, Lip GY. 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;33:1500–1510.
35. Lane DA, Lip GY. Use of the CHA2DS2-VASc and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation. Circulation, 2012;126:860-865.
36. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. Chest. 2010;137:263-272.

37. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel userfriendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. Chest, 2010;138:1093-1100.
38. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S., et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J., 2010;31:2369-2429.
39. Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patient's implications for thromboprophylaxis: Implications for thromboprophylaxis. J Am Coll Cardiol. 2010;56:827-837.
40. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J., 2006;151:713-719.
41. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane DA, Levi M, Marin F, Palareti G, Kirchhof P. Bleeding risk assessment and management in atrial fibrillation patients: executive summary of a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. Thromb Haemost., 2011;106:997-1011.
42. Roldan V, Marin Ortuno F, Manzaro-Fernandez S, Gallego P, Valdes M, Vincente V, Lip GY. Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a 'real world' anticoagulated atrial fibrillation population. June 21, 2012. Chest. DOI https://doi.org/10.1378/chest.12-0608. 2012.
43. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B., et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace, 2016;18:1609–1678.
44. Lip GY, Collet JP, Caterina R, Fauchier L, Lane DA, Larsen TB., et al.; ESC Scientific Document Group. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Europace, 2017;19:1757–1758.
45. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ., et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J, 2017;38: 2739–2791.
46. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ., et al.; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med, 2013;369:1206–1214.
47. Duraes AR, de Souza Lima Bitar Y, Schonhofen IS, Travassos KSO, Pereira LV, Filho JAL., et al. Rivaroxaban versus warfarin in patients with mechanical heart valves: open-label, proof-of-concept trial - the RIWA study. Am J Cardiovasc Drugs., 2020 Nov 5.
48. Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M., et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and valvular heart disease: findings from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation, 2015;132:624-632.
49. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M., et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease: the RE-LY Trial (Randomized Evaluation of LongTerm Anticoagulant Therapy). Circulation, 2016;134:589-598.

50. Breithardt G, Baumgartner H, Berkowitz SD, Hellkamp AS, Piccini JP, Stevens SR., et al.; ROCKET AF Steering Committee & Investigators. Clinical characteristics and outcomes with rivaroxaban vs. warfarin in patients with non-valvular atrial fibrillation but underlying native mitral and aortic valve disease participating in the ROCKET AF trial. Eur Heart J., 2014;35:3377–3385.
51. De Caterina R, Renda G, Carnicelli AP, Nordio F, Trevisan M, Mercuri MF., et al. Valvular heart disease patients on edoxaban or warfarin in the ENGAGE AFTIMI 48 trial. J Am Coll Cardiol., 2017;69:1372-1382.
52. Pan KL, Singer DE, Ovbiagele B, Wu YL, Ahmed MA, Lee M. Effects of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease: a systematic review and meta-analysis. 2017;6:e005835.
53. 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;69:1363-1371.
54. Guimaraes HP, Lopes RD, de Barros E, Liporace IL, Sampaio RO, Tarasoutchi F., et al. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. N Engl J Med., 2020;383:2117-2126.
55. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF., et al. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. N Engl J Med., 2020;382:1696–1707.
56. Seeger J, Gonska B, Rodewald C, Rottbauer W, Wohrle J. Apixaban in patients with atrial fibrillation after transfemoral aortic valve replacement. JACC Cardiovasc Interv., 2017;10:66-74.
57. Noseworthy PA, Yao X, Shah ND, Gersh BJ. Stroke and bleeding risks in NOAC- and warfarin-treated patients with hypertrophic cardiomyopathy and atrial fibrillation. J Am Coll Cardiol., 2016;67:3020-3021.
58. Dominguez F, Climent V, Zorio E, Ripoll-Vera T, Salazar-Mendiguchia J, Garcia-Pinilla JM., et al. Direct oral anticoagulants in patients with hypertrophic cardiomyopathy and atrial fibrillation. Int J Cardiol., 2017;248:232-238.
59. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS., et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. Chest, 2019;155:354-363.
60. Lee HJ, Kim HK, Jung JH, Han KD, Lee H, Park JB., et al. Novel oral anticoagulants for primary stroke prevention in hypertrophic cardiomyopathy patients with atrial fibrillation. Stroke, 2019;50:2582-2586.
61. De Caterina R, Camm AJ. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial. Europace, 2016;18:6-11.
62. Kawashima H, Watanabe Y, Hioki H, Kozuma K, Kataoka A, Nakashima M., et al.; OCEAN-TAVI Investigator. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation after TAVR. JACC Cardiovasc Interv, 2020; 13:2587–2597.
63. Collet JP, Berti S, Cequier A, Van Belle E, Lefevre T, Leprince P., et al. Oral antiXa anticoagulation after trans-aortic valve implantation for aortic stenosis: the randomized ATLANTIS trial. Am Heart J., 2018;200:44-50.
64. van Mieghem NM, Unverdorben M, Valgimigli M, Mehran R, Boersma E, Baber U., et al. Edoxaban Versus standard of care and their effects on clinical outcomes in patients having undergone Transcatheter Aortic Valve Implantation in Atrial Fibrillation-Rationale and design of the ENVISAGE-TAVI AF trial. Am Heart J, 2018;205:63-69.
65. Dangas GD, Tijssen JGP, Wohrle J, Sondergaard L, Gilard M, Mollmann H., et al.; GALILEO Investigators. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. N Engl J Med., 2020;382:120–129.

66. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W., et al. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. Circulation, 2017;136:2420-2436.
67. Nasser MF, Gandhi S, Siegel RJ, Rader F. Anticoagulation for stroke prevention in patients with hypertrophic cardiomyopathy and atrial fibrillation: a review. Heart Rhythm, 2021;18:297-302.
68. van Diepen S, Hellkamp AS, Patel MR, Becker RC, Breithardt G, Hacke W., et al. Efficacy and safety of rivaroxaban in patients with heart failure and nonvalvular atrial fibrillation: insights from ROCKET AF. Circ Heart Fail., 2013;6:740-747.
69. McMurray JJ, Ezekowitz JA, Lewis BS, Gersh BJ, van Diepen S, Amerena J., et al.; for the ARISTOTLE Committees and Investigators. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. Circ Heart Fail, 2013;6: 451–460.
70. Magnani G, Giugliano RP, Ruff CT, Murphy SA, Nordio F, Metra M., et al. Efficacy and safety of edoxaban compared with warfarin in patients with atrial fibrillation and heart failure: insights from ENGAGE AF-TIMI 48. Eur J Heart Fail, 2016;18: 1153-1161.
71. Male C, Lensing AWA, Palumbo JS, Kumar R, Nurmeev I, Hege K., et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol, 2020;7:e18-27.
72. Brandao LR, Albisetti M, Halton J, Bomgaars L, Chalmers E, Mitchell LG., et al. Safety of dabigatran etexilate for the secondary prevention of venous thromboembolism in children. Blood, 2020;135:491-504.
73. Pengo V, Denas G, Zoppellaro G, Jose SP, Hoxha A, Ruffatti A., et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. Blood, 2018;132:1365-1371.
74. 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; 369:2093-2104.
75. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W., et al.; the ROCKET AF Steering Committee. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med., 2011;365:883–891.
76. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace, 2021 Apr 25:euab065.
77. Chan YH, Chao TF, Lee HF, Yeh YH, Yeh CH, Huang YC et al. Impacts of different renal function estimation formulas on dosing of DOACs and clinical outcomes. J Am Coll Cardiol., 2020;76:1808-1810.
78. Kirchhof P, Haas S, Amarenco P, Hess S, Lambelet M, van Eickels M et al.; XANTUS Investigators. Impact of modifiable bleeding risk factors on major bleeding in patients with atrial fibrillation anticoagulated with rivaroxaban. J Am Heart Assoc., 2020;9:e009530.
79. Guo Y, Lane DA, Chen Y, Lip GYH; mAF-App II Trial investigators. Regular bleeding risk assessment associated with reduction in bleeding outcomes: the mAFA-II randomized trial. Am J Med 2020; 133: 1195–1202.e2.
80. 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; 361:1139-1151.
81. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, Shah ND., et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc., 2016;5(6):e003725.
82. Steinberg BA, Gao H, Shrader P, Pieper K, Thomas L, Camm AJ et al.; ORBITAF Investigators. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. Am Heart J., 2017;194:132–140.

83. Cowan JC, Wu J, Hall M, Orlowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. Eur Heart J., 2018;39:2975-2983.
84. Forslund T, Komen JJ, Andersen M, Wettermark B, von Euler M, MantelTeeuwisse AK et al. Improved stroke prevention in atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants. Stroke, 2018;49:2122-2128.
85. Lee SR, Choi EK, Kwon S, Han KD, Jung JH, Cha MJ et al. Effectiveness and safety of contemporary oral anticoagulants among Asians with non-valvular atrial fibrillation. Stroke, 2019;50:2245-2249.
86. Lee SR, Choi EK, Kwon S, Jung JH, Han KD, Cha MJ et al. Effectiveness and safety of direct oral anticoagulants in relation to temporal changes in their use. Circ Cardiovasc Qual Outcomes, 2020;13:e005894.
87. 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: the ORBIT-AF II Registry. J Am Coll Cardiol., 2016;68:2597-2604.
88. Hess PL, Kim S, Fonarow GC, Thomas L, Singer DE, Freeman JV et al.; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Patients and Investigators. Absence of oral anticoagulation and subsequent outcomes among outpatients with atrial fibrillation. Am J Med., 2017;130:449–456.
89. Lip GY, Keshishian A, Li X, Hamilton M, Masseria C, Gupta K., et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients. Stroke, 2018;49:2933-2944.
90. Steinberg BA, Shrader P, Pieper K, Thomas L, Allen LA, Ansell J et al.; the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) II Investigators. Frequency and outcomes of reduced dose non-vitamin K antagonist anticoagulants: results from ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J Am Heart Assoc., 2018;7:e007633.
91. Haas S, Camm AJ, Bassand JP, Angchaisuksiri P, Cools F, Corbalan R et al.; GARFIELD-AF Investigators. Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. Am Heart J., 2019;213:35–46.
92. Lee SR, Lee YS, Park JS, Cha MJ, Kim TH, Park J et al. Label adherence for non-vitamin K antagonist oral anticoagulants in a prospective cohort of Asian patients with atrial fibrillation. Yonsei Med J., 2019;60:277-284.
93. Maura G, Billionnet C, Drouin J, Weill A, Neumann A, Pariente A. Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011-2016. BMJ Open, 2019;9:e026645.
94. Mazurek M, Halperin JL, Huisman MV, Diener H-C, Dubner SJ, Ma CS., et al. Antithrombotic treatment for newly diagnosed atrial fibrillation in relation to patient age: the GLORIA-AF registry programme. Europace, 2019;22:47-57.
95. Xing LY, Barcella CA, Sindet-Pedersen C, Bonde AN, Gislason GH, Olesen JB. Dose reduction of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a Danish nationwide cohort study. Thromb Res., 2019;178:101-109.
96. Amarenco P, Haas S, Hess S, Kirchhof P, Lambelet M, Bach M., et al. Outcomes associated with non-recommended dosing of rivaroxaban: results from the XANTUS study. Eur Heart J Cardiovasc Pharmacother, 2019;5:70-79.
97. Garcıa-Rodrıguez LA, Martın-Perez M, Vora P, Roberts L, Balabanova Y, Brobert G et al. Appropriateness of initial dose of non-vitamin K antagonist oral anticoagulants in patients with non-valvular atrial fibrillation in the UK. BMJ Open, 2019;9:e031341.

98. Chan YH, Chao TF, Chen SW, Lee HF, Yeh YH, Huang YC et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and clinical outcomes in Asian patients with atrial fibrillation. Heart Rhythm, 2020;17:2102-2110.
99. Yu HT, Yang PS, Jang E, Kim TH, Uhm JS, Kim JY., et al. Label adherence of direct oral anticoagulants dosing and clinical outcomes in patients with atrial fibrillation. J Am Heart Assoc., 2020;9:e014177.
100. Kato ET, Giugliano RP, Ruff CT, Koretsune Y, Yamashita T, Kiss RG, et al. Efficacy and Safety of Edoxaban in Elderly Patients with Atrial Fibrillation in the ENGAGE AF-TIMI 48 Trial. J Am Heart Assoc., 2016;5(5):e003432.
101. Steffel J, Giugliano RP, Braunwald E, Murphy SA, Mercuri M, Choi Y et al. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF-TIMI 48 analysis. J Am Coll Cardiol., 2016;68:1169-1178.
102. Chao TF, Chiang CE, Lin YJ, Chang SL, Lo LW, Hu YF et al. Evolving changes of the use of oral anticoagulants and outcomes in patients with newly diagnosed atrial fibrillation in Taiwan. Circulation, 2018;138:1485-1487.
103. Lane DA, Meyerhoff J, Rohner U, Lip GYH. Atrial fibrillation patient preferences for oral anticoagulation and stroke knowledge: Results of a conjoint analysis. Clin Cardiol., 2018;41:855-861.
104. Rush KL, Burton L, Schaab K, Lukey A. The impact of nurse-led atrial fibrillation clinics on patient and healthcare outcomes: a systematic mixed studies review. Eur J Cardiovasc Nurs., 2019;18:526-533.
105. Moudallel S, van den Bemt BJF, Zwikker H, de Veer A, Rydant S, Dijk LV., et al. Association of conflicting information from healthcare providers and poor shared decision making with suboptimal adherence in direct oral anticoagulant treatment: a cross-sectional study in patients with atrial fibrillation. Patient Educ Couns., 2021;104:155-162.
106. Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, et al. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. Gastroenterology, 2015; 149: 586-595.e3.
107. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al.; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J., 2018;39:119–177.
108. Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD., et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. JAMA, 2018;320:2221-2230.
109. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A., et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J., 2018;39:123-260.
110. Moayyedi P, Eikelboom JW, Bosch J, Connolly SJ, Dyal L, Shestakovska O., et al. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. Gastroenterology, 2019;157:403-412.e5.
111. Undas A, Drabik L, Potpara T. Bleeding in anticoagulated patients with atrial fibrillation: practical considerations. Pol Arch Intern Med., 2020;130:47-58.
112. Di Minno A, Spadarella G, Spadarella E, Tremoli E, Di Minno G. Gastrointestinal bleeding in patients receiving oral anticoagulation: current treatment and pharmacological perspectives. Thromb Res., 2015;136:1074-1081.

113. Scarpignato C, Gatta L, Zullo A, Blandizzi C; for the SIF-AIGO-FIMMG Group. Effective and safe proton pump inhibitor therapy in acid-related diseases - a position paper addressing benefits and potential harms of acid suppression. BMC Med., 2016;14:179.
114. Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD., et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. Gastroenterology 2016; 151: 1105-1112.e10.
115. Shields AM, Lip GY. Choosing the right drug to fit the patient when selecting oral anticoagulation for stroke prevention in atrial fibrillation. J Intern Med., 2015;278:1-18.
116. Okumura K, Hori M, Tanahashi N, John Camm A. Special considerations for therapeutic choice of non-vitamin K antagonist oral anticoagulants for Japanese patients with nonvalvular atrial fibrillation. Clin Cardiol., 2017;40:126-131.
117. Diener HC, 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; 38:852-859.
118. Diener HC, 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; 38:860-868.
119. Drouet L, Bal Dit Sollier C, Steiner T, Purrucker J. Measuring non-vitamin K antagonist oral anticoagulant levels: when is it appropriate and which methods should be used? Int J Stroke, 2016;11: 748–758.
120. Godier A, Dincq AS, Martin AC, Radu A, Leblanc I, Antona M., et al. Predictors of preprocedural concentrations of direct oral anticoagulants: a prospective multicentre study. Eur Heart J., 2017;38:2431-2439.
121. Rottenstreich A, Zacks N, Kleinstern G, Raccah BH, Roth B, Da'as N., et al. Direct-acting oral anticoagulant drug level monitoring in clinical patient management. J Thromb Thrombolysis, 2018;45:543–549.
122. Katsi V, Georgiopoulos G, Skafida A, Oikonomou D, Klettas D, Vemmos K., et al. Noncardioembolic stroke in patients with atrial fibrillation. Angiology, 2019; 70: 299-304.
123. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K., et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 Guidelines for the early management of acute ischemic stroke: a guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke, 2019;50: e344-e418.
124. Seiffge DJ, Paciaroni M, Wilson D, Koga M, Macha K, Cappellari M., et al.; on behalf of the CROMIS-2, RAF, RAF-DOAC, SAMURAI, NOACISP LONGTERM, Erlangen and Verona registry orators. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. Ann Neurol, 2019;85: 823–834.
125. Escudero-Martinez I, Mazya M, Teutsch C, Lesko N, Gdovinova Z, Barbarini L., et al.; SITS Investigators. Dabigatran initiation in patients with non-valvular AF and first acute ischaemic stroke: a retrospective observational study from the SITS registry. BMJ Open, 2020;10:e037234.
126. Mizoguchi T, Tanaka K, Toyoda K, Yoshimura S, Itabashi R, Takagi M., et al.; SAMURAI Study Investigators. Early initiation of direct oral anticoagulants after onset of stroke and short- and long-term outcomes of patients with nonvalvular atrial fibrillation. Stroke, 2020;51: 883–891.
127. Seiffge DJ, Werring DJ, Paciaroni M, Dawson J, Warach S, Milling TJ., et al. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. Lancet Neurol, 2019;18: 117-126.

128. Wilson D, Ambler G, Shakeshaft C, Brown MM, Charidimou A, Al-Shahi Salman R., et al. Cerebral microbleeds and intracranial hemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. Lancet Neurol, 2018;17: 539-547.
129. Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S., et al. Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11-13 November 2018. Eur Stroke, J 2019;4: 307-317.
130. Xian Y, Xu H, O'Brien EC, Shah S, Thomas L, Pencina MJ., et al. Clinical effectiveness of direct oral anticoagulants vs warfarin in older patients with atrial fibrillation and ischemic stroke: findings from the Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research (PROSPER) study. JAMA Neurol, 2019;76: 1192-1202.
131. Wang Z, Korantzopoulos P, Liu T. Carotid atherosclerosis in patients with atrial fibrillation. Curr Atheroscler Rep, 2019;21: 55.