Review

Practical approaches to the treatment of atrial fibrillation: focus on stroke prevention using oral anticoagulant drugs

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Practice Points

- Atrial fibrillation (AF) is associated with significant cardiovascular morbidity and mortality, mostly due to AF-related ischemic stroke, which can be particularly devastating.
- The risk for stroke strongly depends on the presence of stroke risk factors other than AF, and an individualized stroke risk assessment is mandatory. The implementation of a stroke risk factor-based approach using the CHA_2DS_2-VASc score facilitates an accurate identification of patients with truly low risk of stroke who would need no thromboprophylaxis, while all other AF patients with one or more stroke risk factors should be considered for oral anticoagulation therapy.
- The RELY, ROCKET-AF and ARISTOTLE trials on novel oral anticoagulants (NOACs) dabigatran, rivaroxaban and apixaban, respectively, demonstrated the noninferior or even superior efficacy and better safety of NOACs compared with warfarin for stroke prevention in patients with nonvalvular AF.
- Due to the pharmacological properties of NOACs and stable, predictable anticoagulant effect, there is no need for routine laboratory monitoring of anticoagulation. However, patients taking NOACs should have a standard clinical follow-up with individualized but regular assessment of renal function and bleeding risk re-evaluation.
- NOACs may have an advantage over warfarin in AF patients with increased risk of bleeding at almost any level of risk for stroke, excluding only AF patients with truly low risk of stroke and low bleeding risk.

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SUMMARY Atrial fibrillation (AF) confers a significant risk of ischemic stroke, and oral anticoagulation is the most effective therapy for thromboprophylaxis in AF. Until recently, vitamin K antagonists (VKAs) were the only available oral anticoagulants. However, numerous disadvantages of VKAs and anticipated bleeding risk with treatment have resulted in their substantial underutilization in clinical practice. Recently, the two other classes of oral anticoagulants – direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors (e.g., rivaroxaban and apixaban) – have emerged as a viable alternative to VKAs for stroke prevention in AF. In addition, efforts have been made to facilitate the optimal prevention of AF-related stroke by improvement of both stroke and bleeding risk assessment. In this review, we summarize the recent advances and discuss the contemporary practical aspects of stroke prevention in patients with nonvalvular AF.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general adult population, with prevalence of ~2% and significant cardiovascular morbidity and mortality, mostly due to AF-related ischemic stroke, which is associated with higher mortality and more long-term disability as compared with strokes from other causes [1–4]. The risk for AF-related stroke is not uniform, but strongly depends on the patient's age and presence of stroke risk factors other than AF [2].

The annual rate of stroke in untreated patients with nonvalvular AF ranges between 2 and 5% [5]. AF-related thrombi are mainly fibrin rich (so-called venous or 'red' clots), hence oral anticoagulation is superior to antiplatelet therapy for thromboprophylaxis in AF [2,5]. Until recently, vitamin K antagonists (VKAs) were the only available oral anticoagulants for stroke prevention in AF. However, numerous disadvantages of oral VKAs and anticipated bleeding risk with oral anticoagulation have resulted in substantial underutilization of these drugs for prevention of AF-related stroke, despite their clear effectiveness [2,5–7]. In addition to the fear of hemorrhagic events, the limitations of VKAs include a slow onset and offset of action, individual variations in the intensity of anticoagulant effect caused by interactions with food, other drugs and/or genetic polymorphisms, a narrow therapeutic window and the need for regular monitoring of treatment.

Recently, the two other classes of oral anticoagulants – direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors (e.g., rivaroxaban and apixaban) have emerged as a viable alternative to VKAs for stroke prevention in AF [8–11]. In addition, efforts have been made to facilitate the optimal prevention of AF-related stroke by improvement of both stroke and bleeding risk assessment using a stroke risk factor-based approach (i.e., the presence of at least one stroke risk factor) rather than stroke risk categorization [2,12–14], and attempting to identify (and correct) the modifiable bleeding risk factors rather than to waive oral anticoagulation therapy when the risk of bleeding is increased [2,14–18]. Indeed, growing evidence suggests that most AF patients would benefit from oral anticoagulation at any bleeding risk level [2,14]. A stroke risk factor-based approach should simplify the decision-making regarding oral anticoagulant treatment, given that the presence of at least one risk factor for stroke qualifies the patient for oral anticoagulation [2,14].

In this review, we summarize the recent advances and discuss the contemporary practical aspects of stroke prevention in patients with nonvalvular AF.

Stroke risk stratification & bleeding risk assessment in patients with nonvalvular AF

Patients with AF have approximately a fivefold greater risk for stroke than individuals in normal sinus rhythm [2]. Although oral anticoagulation effectively reduces the risk for stroke, it is associated with an increased risk for bleeding compared with no treatment, and both stroke and bleeding events can be devastating in the setting of AF [1–5,19]. Given that the risk for stroke is not uniform across the AF population, careful assessment of each individual patient is mandatory to tailor an appropriate antithrombotic treatment balancing the benefit from stroke reduction and potential harms from bleeding events [2].

To facilitate clinical decision-making regarding oral anticoagulant therapy, a number of stroke risk assessment scores have been proposed [20]. Essentially, these scores are combinations of more or less consistently validated stroke risk factors that were identified from the nonwarfarin arms of now historical trials on warfarin, various AF cohorts, or expert consensus statements [21]. For example, the $CHADS_2$ score (Table 1) was derived from the warfarin trials that included <10% of patients who were screened, suggesting that it was a highly selected patient population [22,23]. Nonetheless, the score became widely used in clinical practice, mostly due to its simplicity.

The $CHADS_2$ score incorporates several of the most consistently validated stroke risk factors (e.g., S for prior stroke or transient ischemic attack – 2 points; H for hypertension, A for age >75 years and D for diabetes – 1 point each) and one less consistent risk factor (C for congestive heart failure). More recent data from a number of 'real-world' cohorts provided strong evidence of the significant independent predictive value of several other stroke risk factors, namely vascular disease (including myocardial infarction, complex aortic plaque and peripheral vascular disease) [24], female gender [25], less advanced age (starting from the age of 65 years) [26] and moderate-to-severe left ventricular systolic dysfunction [27], the latter being a truly independent risk factor for stroke, in contrast to a history of heart failure, which is less consistent [2,21]. These findings have resulted in formulation of the CHA_2DS_2-VASc score (Table 1), which is more inclusive of common stroke risk factors compared with the $CHADS_2$ score [12].

Using the $CHADS_2$ score a classification into low, moderate and high stroke risk category (corresponding to the score values of 0, 1 and ≥2, respectively) has been promoted. However, AF patients with a $CHADS_2$ score of 0 still have a nearly 2% annual risk for stroke (Table 2) and too many patients are classified as having a moderate stroke risk ($CHADS_2$ score of 1) with oral anticoagulation being only optional in this subset [2]. Until now, the CHA_2DS_2-VASc score has been validated in a number of AF cohorts and has been consistently demonstrated to be much more reliable at identifying truly low-risk patients, while classifying very few patients into moderate risk category and being as accurate as the $CHADS_2$ at identifying high-risk patients [2,12–14,28]. Indeed, the 'real-world' population studies have demonstrated a negative net clinical benefit of oral anticoagulation (i.e., the difference between strokes reduced and bleedings caused by treatment) only in patients with the CHA_2DS_2-VASc score of 0, indicating that only these patients have truly low risk of stroke and do not need any thromboprophylaxis, while all other patients should be considered for an oral anticoagulant [14]. Conversely, decisions of whether to use oral anticoagulation or not based exclusively on a $CHADS_2$ score value of 0–1 may lead to many

Table 1. The $CHADS_2$ and CHA_2DS_2-VASc score schemes for stroke risk stratification in atrial fibrillation, and HAS-BLED score for bleeding risk assessment.

Scheme		Points
$CHADS_2$ score		
C	Congestive heart failure	1
H	Hypertension†	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S_2	Stroke/TIA/TE	2
Maximum score		6
CHA_2DS_2-VASc score		
C	Congestive heart failure or LVEF ≤40%	1
H	Hypertension†	1
A_2	Age ≥75 years	2
D	Diabetes mellitus	1
S_2	Stroke or TIA or TE	2
V	Vascular disease‡	1
A	Age 65–74 years	1
Sc	Sex category (female gender)	1
Maximum score		9
HAS-BLED score		
H	Hypertension§	1
A	Abnormal renal/liver function¶	1 or 2
S	Stroke	1
B	Bleeding#	1
L	Labile INRs††	1
E	Elderly (age ≥65 years)	1
D	Drug therapy/alcohol intake‡‡	1 or 2
Maximum score		9

†Blood pressure consistently >140/90 mmHg (or treated hypertension with medication).
‡Peripheral artery disease, myocardial infarction and/or aortic plaque.
§Systolic blood pressure >160 mmHg.
¶Abnormal renal function defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/l. Abnormal liver function defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2× upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3× upper limit normal).
#Major bleeding history (anemia or predisposition to bleeding).
††Unstable/high INRs or poor time in therapeutic range (e.g., <60%).
‡‡Concomitant therapy such as antiplatelet agents, NSAIDs/consuming eight or more alcoholic drinks per week.
INR: International normalized ratio; LVEF: Left ventricular ejection fraction; TE: Thromboembolism; TIA: Transient ischemic attack.

Table 2. Adjusted stroke rates using $CHADS_2$ and CHA_2DS_2-VASc score, and adjusted bleeding rates using the HAS-BLED score in patients with atrial fibrillation.

Score	Adjusted stroke rate (% per year)
$CHADS_2$ score	
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2
CHA_2DS_2-VASc score	
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2
HAS-BLED score	
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50
6	0.0
7	–
8	–
9	–

Adapted with permission from [2].

AF patients not receiving an optimal thromboprophylaxis while being at substantial risk for stroke. For example, in a pooled analysis of AF patients with a $CHADS_2$ scores of 1 from the AVERROES and ACTIVE trials who were treated with aspirin with or without clopidogrel, the CHA_2DS_2-VASc score reclassified only 26% of patients to a low annual stroke risk of ≤1%, demonstrating that as many as three-quarters of AF patients with a $CHADS_2$ score of 1 should be considered for oral anticoagulation treatment [29].

The risk for AF-related stroke is not influenced by the clinical type of AF (e.g., paroxysmal, persistent or permanent AF) [2,30] or the presence or absence of AF-related symptoms [2,31].

The HAS-BLED score (hypertension, abnormal renal and/or liver function, stroke, bleeding, labile international normalized ratio [INR], age >65, concomitant drugs and/or alcohol) has been introduced as a simple tool for bleeding risk assessment (Table 1) with better predictability as compared with other scores [2,14–18]. A HAS-BLED score of ≥3 indicates increased risk for bleeding (Table 2). However, a high HAS-BLED score *per se* should not be the reason to stop oral anticoagulation, but it should highlight the potentially reversible risk factors for bleeding (e.g., uncontrolled blood pressure, labile INRs and concomitant aspirin use), which should be corrected. Indeed, a recent trial with nearly 200,000 patients with AF demonstrated a positive clinical benefit in all AF patients with a CHA_2DS_2-VASc score ≥1, regardless of the bleeding risk level as measured by the HAS-BLED score value, and the net clinical benefit was the greatest (>6% per year) for patients with a HAS-BLED score of 4 and a CHA_2DS_2-VASc score of 6 (i.e., the patients at increased risk of both stroke and bleeding) [14]. However, a regular and careful follow-up of such patients is necessary [2].

Antiplatelet drugs & oral VKAs for stroke prevention in nonvalvular AF

Oral VKAs (i.e., warfarin, acenocoumarol and fenprocoumon) inhibit the vitamin K-dependent gamma-carboxylation of plasma coagulation factors II, VII, IX and X in the liver and are metabolized by CYP450. Oral VKAs have a prolonged action and substantial variations of the anticoagulant effect due to a number of interactions with food and alcohol, other drugs and the individual's genetic background. The narrow therapeutic window of VKAs necessitates close laboratory monitoring of anticoagulation intensity and frequent dose adjustments, given that a poor control of anticoagulation increases the risks for both thrombotic and bleeding events [32].

Warfarin was associated with an impressive 67% reduction of ischemic strokes and a 26% reduction of all-cause mortality compared with placebo; as compared with aspirin alone or the combination of aspirin plus clopidogrel, warfarin reduced the risk of ischemic stroke by 52% and 40%, respectively, but bleeding rates were similar with aspirin plus clopidogrel versus warfarin [5]. In patients unsuitable for or unwilling to take oral VKAs, the combination of aspirin

plus clopidogrel was superior to aspirin alone for stroke prevention, at the expense of a 57% increase in the risk of major bleeding with aspirin plus clopidogrel [33]. Aspirin was associated with a modest, nonsignificant 19% reduction of stroke and similar mortality rates compared with placebo [5]. In a recent trial comparing aspirin 150–200 mg daily with no therapy for stroke prevention in low-risk AF patients in a Japanese AF cohort, aspirin did not reduce thromboembolic events (the annual incidence of events was 3.1% with aspirin vs 2.4% with no therapy), and the use of aspirin was associated with a nonsignificant increase in major hemorrhage [34].

Both efficacy and safety of oral VKAs strongly depend upon the time in therapeutic range (TTR) with INR values between 2 and 3, and maximum benefits from VKAs are achieved at TTRs ≥70% [2,32,35]. Substantial efforts have been made to increase the TTR using anticoagulation management services, patient self-testing and pharmacogenetic testing, but the TTR seldom exceeds 70% in routine clinical practice [32,35–37]. However, a recent meta-analysis of warfarin treatment groups in eight contemporary randomized clinical trials on stroke prevention revealed relatively low residual annual rates of stroke with warfarin at mean TTR values of 55–68% [38]. Compared with earlier warfarin trials with lower mean TTRs, there was a significant reduction in residual stroke risk with warfarin in contemporary trials (from 2.07 to 1.66%) [5,38]. A pooled rate of intracranial hemorrhage in modern trials was 0.61% (95% CI: 0.48–0.73), and the incidence of major bleedings ranged from 1.40 to 3.40%. Unfortunately, a considerable inconsistency in definition of bleeding events prevented a direct comparison of major bleeding rates in earlier versus contemporary trials.

Despite the improvements in management of chronic oral anticoagulation with warfarin, at least 40% of AF patients who should be anticoagulated are not treated with VKAs in contemporary clinical practice, and rates of discontinuation of VKAs are high [39]. For example, in a recent report, only 45% of patients who were prescribed VKAs for secondary stroke prevention continued treatment beyond 2 years [40]. Suboptimal use of VKAs is particularly pronounced in elderly and patients with renal dysfunction, mostly due to a concern that bleeding risk could outweigh the benefits of VKAs in these populations [41,42]. In a recent large cohort study of AF patients, chronic kidney disease was associated with an increased risk of stroke and bleeding, and warfarin (but not aspirin) treatment was associated with a significant reduction of stroke risk; however, the risk of bleeding was further increased with both warfarin and aspirin treatment [43]. Conversely, a convincing body of evidence supports the efficacy and safety of warfarin treatment in elderly AF patients [44].

Novel oral anticoagulants for thromboprophylaxis in nonvalvular AF: clinical randomized trials

The limitations of VKAs and difficulties associated with a long-term treatment with these drugs prompted the search for more convenient and possibly safer treatment options for thromboprophylaxis in AF. Recently, the two classes of novel oral anticoagulants (NOACs) that act as specific direct inhibitors of a single coagulation factor – direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors (e.g., rivaroxaban, apixaban) – have successfully completed a clinical evaluation program for stroke prevention in AF [8–11]. In addition, a number of NOACs are at various stages of development (e.g., edoxaban) [45,46].

In contrast to VKAs, NOACs act rapidly and have a predictable pharmacology with a stable, dose-related anticoagulant effect, no food interaction and very few clinically relevant interactions with other drugs, which allows a fixed-dosing without regular monitoring of anticoagulation [47]. Nonetheless, there are clinically important differences in pharmacology among NOACs, and caution is needed in patients with significant renal or liver impairment, patients concomitantly using potent P-glycoprotein or CYP3A4 inhibitors or inducers and patients >80 years old **(Table 3)** [48].

The Phase III randomized trials comparing the efficacy and safety of NOACs to adjusted-dose warfarin for prevention of stroke or systemic thromboembolism in patients with nonvalvular AF, namely the RE-LY trial (dabigatran 110 mg twice daily (b.i.d.) and 150 mg b.i.d.) [8], the ROCKET-AF trial (rivaroxaban 20 mg once daily, and 15 mg once daily in patients with creatinine clearance [CrCl] 30–49 ml/min) [9] and the ARISTOTLE trial (apixaban 5 mg b.i.d. and 2.5 mg b.i.d. if ≥2 of the following criteria are present: age ≥80 years, body weight ≤60kg or serum creatinine ≥1.5 mg/dl) [10] are

Table 3. Clinical pharmacology of novel oral anticoagulants and warfarin.

Drug	Target	T_{max} (h)	Half-life (h)	Renal elimination	Recommended dosing[†]	Dosing in renal impairment	Clinically relevant drug interactions	Special clinical considerations
Dabigatran	IIa (thrombin)	2	12–14	80% renal	150 mg b.i.d.	110 mg b.i.d.	Potent P-gp inhibitors or inducers	110 mg b.i.d. when coadministered with verapamil (both drugs to be taken at the same time)
Rivaroxaban	Xa	2–4	5–9 (9–13 in elderly)	1/3 renal, 2/3 liver	20 mg once daily	15 mg once daily (CrCl: 30–49 ml/min)	Potent CYP3A4 or P-gp inhibitors or inducers	To be taken with meals (increased bioavailability)
Apixaban	Xa	1–3	8–15	25% renal, 75% fecal	5 mg b.i.d.	2.5 mg b.i.d.	Potent CYP3A4 or P-gp inhibitors or inducers	–
Warfarin	VKA (VCORC1)	Variable	35–46	0%	INR-guided; target INR: 2–3	INR-guided; target INR 2–3	CYP2C9, 3A4, 1A2 inhibitors, dietary vitamin K	A number of food and drug interactions

P-gp inhibitors: quinidine, verapamil, amiodarone, clarithromycin; P-gp inducers: rifampicin, carbamazepine, phenytoin; CYP3A4 inhibitors: antifungals (e.g. ketoconazole), chloramphenicol, clarithromycin, protease inhibitors; CYP3A4 inducers: phenytoin, carbamazepine, phenobarbital.
[†]Data taken from [48].
b.i.d.: Twice daily; CrCl: Creatinine clearance; INR: International normalized ratio; P-gp: P-glycoprotein; T_{max}: Time to maximum plasma concentration; VKA: Vitamin K antagonists.

summarized in Table 4. The ROCKET-AF study population included AF patients with at least two additional risk factors for stroke or previous stroke as a single risk factor (the mean $CHADS_2$ score was 3.5 in the trial), while the RE-LY and ARISTOTLE trials included AF patients with at least one additional stroke risk factor (the mean $CHADS_2$ score was 2.1 in both trials. However, approximately 30% of patients in the ARISTOTLE trial and 33% of patients in the RE-LY trial had a $CHADS_2$ score of >2. In addition, the mean TTR in the ROCKET-AF trial was lower (55%) compared with the mean TTR in the RE-LY and ARISTOTLE trial (64 and 62%, respectively) [8–10].

Regarding the primary efficacy end point of any stroke or systemic embolism, NOACs were at least noninferior (dabigatran 110 mg b.i.d., rivaroxaban) or even superior (dabigatran 150 mg, apixaban) to warfarin, and only dabigatran 150 mg b.i.d. was superior to warfarin in ischemic stroke risk reduction (Table 4). With respect to the primary efficacy end point of major bleeding, dabigatran 110 mg b.i.d. and apixaban were superior to warfarin (the two drugs reduced major bleedings by 20 and 31%, respectively), while dabigatran 150 mg b.i.d. and rivaroxaban were noninferior to warfarin. In addition, dabigatran 150 mg b.i.d. and rivaroxaban were associated with significantly more gastrointestinal bleeding (Table 4). However, there was a significant reduction in hemorrhagic stroke and intracranial bleeding with all three drugs compared with warfarin, and this is most probably a key benefit of these drugs [8–10]. NOACs also reduced all-cause mortality by approximately 10% across the three trials, but the difference reached statistical significance only for apixaban ($p = 0.046$). Only dabigatran 150 mg b.i.d. significantly reduced vascular mortality compared with warfarin (relative risk: 0.85; 95% CI: 0.72–0.99; $p = 0.04$) [8].

A number of prespecified or *post-hoc* subanalyses of the RE-LY trial showed that the beneficial effects of dabigatran were generally consistent across all *post-hoc* or prespecified subanalyses including the prior use of VKAs, the TTR, elective cardioversion, the $CHADS_2$, secondary stroke prevention, renal function and age [8,49–53]. Similar to dabigatran, the prespecified subanalyses of the ROCKET-AF trial [54,55] and the ARISTOTLE trial [56–59] showed a consistency in rivaroxaban and apixaban effects in all analyzed subgroups. Patients with significant renal dysfunction and CrCl <30 ml/min were excluded from

the RE-LY, ROCKET-AF and ARISTOTLE trials [8–10]. However, in patients with moderate renal dysfunction (e.g., CrCl: 30–49 ml/min) the benefits of dabigatran, rivaroxaban and apixaban in terms of stroke prevention were consistent with those in the overall study population and, importantly, were not associated with increased bleeding risk [53,54,57,58].

In the primary analysis of the RE-LY trial there was an increase of borderline statistical significance in the rate of myocardial infarction with dabigatran 150 mg compared with warfarin (relative risk: 1.38; 95% CI: 1.00–1.91; p = 0.048), and the difference became insignificant after the inclusion of silent myocardial infarctions (relative risk: 1.27; 95% CI: 0.94–1.71; p = 0.12) [8,60]. Nonetheless, treatment effects of dabigatran were consistent in patients at higher and lower risk of myocardial ischemic events, and there was no excess of new angina hospitalizations, revascularizations or vascular deaths [61].

The AVERROES trial compared apixaban to aspirin for stroke prevention in AF patients who have failed or were unsuitable for VKAs, and clearly demonstrated the superiority of apixaban over aspirin (>50% reduction in stroke or systemic embolism with apixaban) with similar rates of major bleeding (p = 0.33) and hemorrhagic stroke (0.2% per year) in both treatment arms; the risk of permanent drug discontinuation was

Table 4. Randomized clinical trials comparing novel oral anticoagulants to warfarin for stroke prevention in nonvalvular atrial fibrillation.

Characteristic	RE-LY†		ROCKET AF‡	ARISTOTLE§
Number of patients	18,113		14,264	18,201
Drug	Dabigatran		Rivaroxaban	Apixaban
Dosing	110 mg b.i.d. or 150 mg b.i.d.		20 mg once daily	5 mg b.i.d.
Study design	PROBE		Randomized, double-blinded	Randomized, double-blinded
Mean age (years)	71.5		73	70
Mean $CHADS_2$ score	2.1		3.5	2.1
TTR (%)	64		55	62.2
Primary efficacy end point	Stroke or systemic embolism		Stroke/systemic embolism	Stroke/systemic embolism
Primary safety outcome	Major hemorrhage		Composite of major and clinically relevant nonmajor bleeding	Major bleeding
Primary analysis	Noninferiority Intention to treat		Noninferiority On treatment/intention to treat	Noninferiority Intention to treat
Study results (intention to treat)	Dabigatran 110 mg vs warfarin	Dabigatran 150 mg vs warfarin	Rivaroxaban vs warfarin	Apixaban vs warfarin
Primary efficacy end point (RR; 95% CI)	0.91; 0.74–1.11; p = 0.34	0.66; 0.53–0.82; p < 0.001	0.88; 0.75–1.03; p = 0.12	0.79; 0.66–0.95; p = 0.01
Ischemic stroke (RR; 95% CI)	1.11; 0.89–1.40; p = 0.35	0.76; 0.60–0.98; p = 0.03	0.94; 0.75–1.17; p = 0.581	0.92; 0.74–1.13; p = 0.42
Hemorrhagic stroke (RR; 95% CI)	0.31; 0.17–0.56; p < 0.001	0.26; 0.14–0.49; p < 0.001	0.59; 0.37–0.93; p = 0.024	0.51; 0.35–0.75; p < 0.001
Intracranial hemorrhage (RR; 95% CI)	0.31; 0.20–0.47; p < 0.001	0.40; 0.27–0.60; p < 0.001	0.67; 0.47–0.93; p = 0.019	0.42; 0.30–0.58; p < 0.001
Major bleeding (RR; 95% CI)	0.80; 0.69–0.93; p = 0.003	0.93; 0.81–1.07; p = 0.31	Not specified; p = 0.576	0.69; 0.60–0.80; p < 0.001
Gastrointestinal bleeding (RR; 95% CI)	1.10; 0.86–1.41; p = 0.43	1.50; 1.19–1.89; p < 0.001	Not specified; p < 0.001	0.89; 0.70–1.15; p = 0.37
Death from any cause (RR; 95% CI)	0.91; 0.80–1.03; p = 0.13	0.88; 0.77–1.00; p = 0.051	0.85; 0.70–1.02; p = 0.073	0.89; 0.80–0.99; p = 0.046
Drug discontinuation at the end of follow-up (%)	14.5 vs 10.2	15.5 vs 10.5	23.7 vs 22.2	25.3 vs 27.5

†Data taken from [8].
‡Data taken from [9].
§Data taken from [10].
b.i.d.: Twice daily; PROBE: Prospective open-labeled blinded end point evaluation; RR: Relative risk; TTR: Time in therapeutic range.

12% lower in the apixaban group than in the aspirin group (hazard ratio with apixaban: 0.88; 95% CI: 0.78–0.99; p = 0.03) and apixaban was better tolerated than aspirin [11]. These findings have important clinical implications as they suggest that apixaban could be a preferable (more efficacious, safer and better tolerated) alternative to aspirin for thromboprophylaxis in AF patients who refuse or are not suitable for oral VKAs.

Overall, NOACs were well tolerated in clinical trials, with no evidence of hepatotoxicity [8–10,11]. The most clinically relevant side-effect was dabigatran-related dyspepsia with an increased dabigatran discontinuation rate (11.8% for dabigatran 110 mg and 11.3% for dabigatran 150 mg b.i.d.) compared with warfarin (5.8%; p < 0.001) [8].

Novel oral anticoagulants for thromboprophylaxis in nonvalvular AF: practical considerations

Dabigatran and rivaroxaban have been approved for the prevention of stroke or systemic embolism in nonvalvular AF in the EU, USA, Canada and many other countries, and apixaban is awaiting approval. The knowledge of the NOACs' pharmacological characteristics and performances should facilitate the optimal use of these drugs in clinical practice.

■ Dabigatran etexilate

Dabigatran etexilate is a prodrug that is converted to active dabigatran following oral intake. Absorption is enhanced by an acid microenvironment that is potentiated by the tartaric acid core of small pellets coated with dabigatran etexilate within a capsule. Hence, the absorption of dabigatran etexilate is not significantly affected by variations in intrinsic gastric pH, even in the presence of proton pump inhibitors [62]. However, the acid core might be responsible for dabigatran-related dyspepsia and, in such cases, the drug should be taken with a glass of water or meals. Of note, dabigatran absorption may be delayed but not diminished by food. Given that dabigatran does not inhibit the CYP450 enzymes, the potential for drug–drug interactions is low [48,62]. The most clinically relevant drug interactions of dabigatran are those with potent P-glycoprotein inhibitors (e.g., quinidine, verapamil, amiodarone, clarithromycin and dronedarone). P-glycoprotein is a transport protein that pumps many substances (including toxins and various drugs) out of cells. In the presence of strong P-glycoprotein inhibitors, the P-glycoprotein-mediated efflux of dabigatran etexilate from gastrointestinal cells back to the lumen may be attenuated, leading to increased systemic delivery of dabigatran (and increased plasma concentrations) at the time of drug ingestion. Hence, dabigatran is contraindicated with quinidine use and, when coadministered with verapamil, the 110 mg b.i.d. dabigatran dose is recommended (however, the patient should be instructed to take both drugs at the same time). Caution is needed with concomitant use of dabigatran and amiodarone or clarithromycin, but no dose reduction is required [48]. Coadministration with dronedarone is not recommended, mostly due to the lack of adequate clinical data. On the other hand, potent P-glycoprotein inducers such as kantarion (St John's wort) or rifampicin may significantly reduce the plasma levels of dabigatran [62].

Dabigatran is a competitive, direct, reversible thrombin inhibitor that affects both clot-bound and free thrombin. The drug is administered in two doses, either 110 mg b.i.d. or 150 mg b.i.d. It reaches peak plasma levels at 2 h following oral administration with a mean half-life of approximately 11 h (after administration of multiple doses of dabigatran, half-life is prolonged to 12–14 h). The drug is eliminated predominantly in an unchanged form by the kidneys (80%) and dabigatran plasma concentration increases with impaired renal function [62]. Hence, assessment of renal function is mandatory prior to the initiation of treatment with dabigatran, along with regular monitoring of renal function at least annually in patients with normal (CrCl ≥80 ml/min) or mild (CrCl 50–79 ml/min) renal impairment and two- to three-times per year in those with moderate (CrCl: 30–49 ml/min) renal dysfunction, or whenever a decline in renal function is anticipated. In general, the recommended dose of dabigatran is 150 mg b.i.d. [48]. No dose adjustment is necessary for patients with mild renal impairment, and patients with moderate renal dysfunction should receive dabigatran 110 mg b.i.d. only in the presence of additional risk factors for bleeding, including age of 75–80 years. Patients with more severe renal failure (CrCl <30 ml/min) were excluded from the RE-LY trial, and dabigatran should not be used in such patients [8,48]. In the USA, dabigatran 75 mg b.i.d. is allowed for patients with CrCl

≥15 ml/min, although it has not been tested in clinical trials [63]. The dose of 110 mg b.i.d. is recommended for patients aged >80 years regardless of whether the renal function is normal or mildly to moderately impaired [11,48,62–66]

Rivaroxaban

Rivaroxaban is a reversible, direct inhibitor of factor Xa, which affects both free and clot-associated prothrombinase activity. Rivaroxaban bioavailability increases with food intake, which is recommended. The drug is rapidly absorbed, reaching a maximum concentration after 2–4 h, with a half-life of up to 9–13 h **(Table 3)**. Approximately a third of rivaroxaban is eliminated via the kidneys, and the remaining two-thirds are metabolized by the liver [67]. For thromboprophylaxis in AF, rivaroxaban is administered in a single daily dose of 20 mg, and in patients with moderate renal impairment 15 mg once daily is recommended [48]. Given that the drug is metabolized predominantly by the liver and is a substrate of P-glycoprotein, rivaroxaban should not be used concomitantly with strong inhibitors of CYP450 3A4 or P-glycoprotein inhibitors **(Table 3)** [48,67]. Rivaroxaban is not recommended in patients with a severe renal impairment (CrCl <15 ml/min), and clinical data on patients with CrCl of 15–29 ml/min are limited [48].

Apixaban

Apixaban is a reversible, direct factor Xa inhibitor with a high oral bioavailability. The maximum plasma concentrations of apixabane are reached 1–4 h following ingestion, and absorption is not affected by food intake. Apixaban is administered in a dose of 5 mg b.i.d. The drug has a half-life of 8–15 h and is predominantly eliminated via hepatic metabolism (75%), including CYP3A4-dependent and other pathways. Apixaban should not be coadministered with strong inhibitors of CYP3A4 and caution is required with concomitant use of P-glycoprotein inhibitors or inducers, or potent CYP3A4 inducers **(Table 3)** [63]. Patients with severe renal impairment (CrCl <25 ml/min) were excluded from the ARISTOTLE trial [10]. Hence, apixaban should not be used in patients with CrCl <30 ml/min, and the dose should be reduced to 2.5 mg b.i.d. in patients with more than two of the following criteria: age ≥80 years, body weight <60kg or a serum creatinine of ≥1.5 mg/dl (133 µmol/l) [10,63].

Evaluation of anticoagulant activity of novel oral anticoagulants

In contrast to VKAs, NOACs have a predictable and stable pharmacokinetic profile that avoids the need for routine anticoagulation monitoring and dose adjustments based on a specific coagulation test. Although a fixed-dosing regimen without anticoagulation monitoring is an advantage of NOACs over VKAs in routine clinical practice, assessment of anticoagulation intensity might be needed in certain clinical situations such as suspected overdosing, development of thrombosis or uncontrolled bleeding during treatment, emergency procedures or elderly patients with impaired renal function. To date, only nonspecific coagulation tests indicating the presence rather than the intensity of anticoagulation effect are available, and interpretation of coagulation assays should be done in relation to the time of blood sampling with respect to administration of the last dose of NOAC [2,15,48,62–64,68].

Dabigatran affects the thrombin-mediated conversion of fibrinogen to fibrin, which causes the prolongation of all routine coagulation assays, and the maximal effect on clotting parameters closely reflects the peak plasma concentrations of the drug [68]. However, the effect of increasing plasma concentrations of dabigatran on various coagulation tests is dissimilar. For example, the activated partial thromboplastin time (aPTT) is not a particularly sensitive measure for quantification of anticoagulant intensity as the aPTT values flatten at higher dabigatran concentrations. Nonetheless, aPTT is a useful qualitative measure of anticoagulant activity (to detect the presence of dabigatran, but not to evaluate its concentration). If the blood is taken immediately prior the next dabigatran dose, a two- to three-fold prolongation of aPTT (aPTT >80 s) indicates a higher risk of bleeding, while a 1.5-fold increase of aPTT is expected in patients taking dabigatran 150 mg b.i.d. Normal aPTT values exclude any clinically relevant anticoagulant activity in the blood sample [64,68]. The activated clotting time assay is based on a principle similar to the aPTT test, but data for activated clotting time with dabigatran are limited (the test is commonly used at the bedside, to measure the effect of unfractionated heparin in patients undergoing various invasive procedures). The thrombin clotting time assay directly reflects the thrombin activity and

is more sensitive than aPTT for assessment of dabigatran anticoagulation activity. Since the thrombin clotting time assay results strongly depend on the coagulometer and used thrombin lot, the commercially available Hemoclot® Thrombin Inhibitor Assay (Hyphen BioMed, France) with direct calibration using lyophilized dabigatran standards is advised [64,68]. The ecarin clotting time is a specific assay for thrombin generation, but data on the test utility with dabigatran in clinical practice are limited [64]. At clinically relevant plasma concentrations, dabigatran has a small effect on prothrombin time (PT) and INR measurement should not be used for the assessment of dabigatran anticoagulation activity [48,64,68].

Rivaroxaban prolongs PT and aPTT in a concentration-dependent manner, with a greater sensitivity for PT. Although a PT value may serve for a rough nonspecific estimate of rivaroxaban activity, a conversion of PT values to INR is not advised as the INR was calibrated and validated only for VKAs. A more sensitive estimate of anticoagulation activity of oral Factor Xa inhibitors is an anti-Factor Xa assay. Recently, an assay that uses rivaroxaban-containing plasma calibrators has been developed, which may provide the optimal method for evaluation plasma concentrations of rivaroxaban [48,68].

The periprocedural management of AF patients taking a novel oral anticoagulant

The periprocedural management of patients taking an oral VKA is a common clinical task. A temporary discontinuation of VKAs (to reduce the risk of bleeding) plus bridging anticoagulation with unfractionated heparin or low-molecular-weight heparin (to reduce the risk of thromboembolic events) was a common clinical practice for an elective procedure or surgery. However, growing evidence suggests that many invasive procedures could be safely performed on uninterrupted warfarin [2,48,69] and a bridging strategy might not necessarily reduce the rate of perioperative thromboembolism [70]. The two ongoing randomized clinical trials, the PERIOP-2 [101] and BRIDGE [102] trials, will compare bridging with no bridging strategies in warfarin-treated patients who require elective surgery, but the results will not be available for several years. Meanwhile, bridging is recommended in AF patients on VKAs undergoing elective surgery who are at increased risk for thromboembolic events; the decision to use a bridging strategy in AF patients at low-to-moderate thromboembolic risk should be based on individualized risk factors for bleeding and thromboembolism [2]. Nonetheless, VKAs should be discontinued approximately 5 days (warfarin) to 10 days (phenprocoumon) before surgery, to allow the INR to reach the subtherapeutic levels; assuming the hemostasis is adequate, VKA treatment should be reinstituted at usual maintenance doses in the evening of surgery or the next morning [2].

For patients taking a NOAC, temporary cessation of anticoagulant treatment before elective surgery should be considered. In patients with normal renal function, dabigatran should be stopped at least 24 h prior to surgery with standard risk of procedure-related bleeding as the plasma concentrations of dabigatran will fall to 25% of the steady-state minimal concentrations during that period. However, in patients undergoing major surgery with a high risk of procedure-related bleeding (such as neurosurgery, cardiothoracic or abdominal surgery, or surgery of any major organ) dabigatran should be interrupted at least 48 h before the procedure (to allow the plasma concentrations of dabigatran to fall to 5–10% of regular minimal concentrations). In patients with mild or moderate renal impairment, dabigatran should be discontinued at least 3 or 4 days (respectively) before surgery [64,68]. Based on half-life studies, a 24-h gap would seem appropriate in patients taking an oral Factor Xa inhibitor [68]. Due to a rapid onset and offset of NOACs action, no bridging is needed for the majority of interventions, and NOACs can be restarted as soon as effective hemostasis has been achieved [48].

Regarding elective cardioversion, available data suggest that it can be safely performed in AF patients taking dabigatran [51] with a requirement of at least 3 weeks of anticoagulation treatment before cardioversion and at least 4 weeks of oral anticoagulation following cardioversion (or life-long, for most of AF patients) [2,48]. There are insufficient data on the safety of AF catheter ablation with uniterrupted NOAC, while AF catheter ablation on uninterrupted VKA is recommended with a target INR of 2.0–2.5 [48].

The growing population of AF patients presenting with acute coronary syndromes or undergoing elective percutaneous coronary intervention/stenting is a challenge, given that

most of these patients will need a dual antiplatelet therapy plus an oral anticoagulant (i.e., triple treatment) for a variable length of time [2,15,48,63,71]. Triple therapy containing VKA improves prognosis (in terms of reduced mortality and major adverse cardiac effects) even in AF patients at increased risk for bleeding (HAS-BLED score ≥3) [72]. However, triple therapy substantially increases the risk of major bleeding compared with monotherapy, and every effort should be made to minimize the risk for bleeding, which includes maintenance of INR at the lower end of therapeutic range (2.0–2.5) and use of bare metal stents whenever possible to limit the duration of triple therapy [2,15,48,71,73]. Given that concomitant use of clopidogrel was only allowed in the RE-LY trial [8], there are limited data on triple therapy with NOACs in AF patients. Of note, randomized data on NOACs in patients with recent acute coronary syndrome should not be mechanically transferred to AF patients since rivaroxaban was tested in lower doses (2.5 mg b.i.d. and 5 mg b.i.d.) compared with the dose used for stroke prevention in AF patients (20 mg once daily), and apixaban 5 mg b.i.d. was associated with increased rates of major bleeding and no reduction in cardiovascular events [63].

The occurrence of a thromboembolic event in an adequately anticoagulated patient represents a treatment failure, and switching to an alternative anticoagulant may be considered. Nonetheless, if an acute ischemic stroke occurs at prolonged aPTT in a patient taking dabigatran (or at prolonged PT in a patient on rivaroxaban) thrombolysis should not be administered because the patient is most likely already adequately anticoagulated [48].

■ Management of bleeding complications during treatment with novel oral anticoagulants

There is no specific antidote for NOACs or a well-established procedure for reversal of anticoagulation in emergency situations, although specific factors are under investigation [74]. Nonetheless, management of bleeding events in patients taking NOAC is largely supportive, given that these drugs have a relatively short half-life. In the case of minor bleeding, delaying the next dose or temporary drug discontinuation will usually suffice. Moderate-to-severe bleeding should prompt symptomatic treatment, maintenance of adequate diuresis, identification of bleeding site, mechanical compression at the bleeding site (or surgical hemostasis where required), fluid replacement and blood transfusion (if needed). Oral charcoal may be administered if dabigatran has been recently ingested. Severe or life-threatening bleeding would require consideration of activated recombinant factor VII (rFVIIa) or prothrombin complex concentrate (PCC) administration, or hemodialysis or charcoal filtration (for dabigatran) [48,68].

Thromboprophylaxis in nonvalvular AF using oral anticoagulation: VKAs or NOACs?

A recent large cohort study with nearly 200,000 AF patients convincingly demonstrated that, in almost all AF patients (excluding those with truly low risk of stroke, i.e., those with a CHA_2DS_2-VASc score of 0), the risk of ischemic stroke without oral anticoagulant treatment exceeds the risk of intracranial bleeding with oral anticoagulation, and the net clinical benefit of warfarin was even greater at higher values of HAS-BLED score [14]. Indeed, the recent European Society Association guidelines for the management of AF update recommended no antithrombotic therapy only in AF patients with truly low risk of stroke (i.e., with the CHA_2DS_2-VASc score of 0) [48]. In addition, in female patients aged <65 years with lone AF (and a CHA_2DS_2-VASc score of 1 due to their gender) no antithrombotic therapy should be considered, as female gender does not independently increase the risk of stroke in this subset of AF patients [48].

Another recent 'real world' modeling analysis found that the three NOACs (dabigatran, rivaroxaban and apixaban) had a greater net clinical benefit than warfarin in AF patients at high risk of stroke (as measured with $CHADS_2$ score ≥1 or CHA_2DS_2-VASc ≥2) regardless of the bleeding risk, which could be expected. However, a positive net clinical benefit with apixaban and dabigatran 110 mg b.i.d. was also documented in patients with a $CHADS_2$ score of 0 but at high risk of bleeding, and these patients would be less likely to receive oral anticoagulation with warfarin [75].

Overall, the available evidence strongly suggests that any oral anticoagulant is better than nothing for the majority of AF patients, while NOACs may have advantage over VKAs in

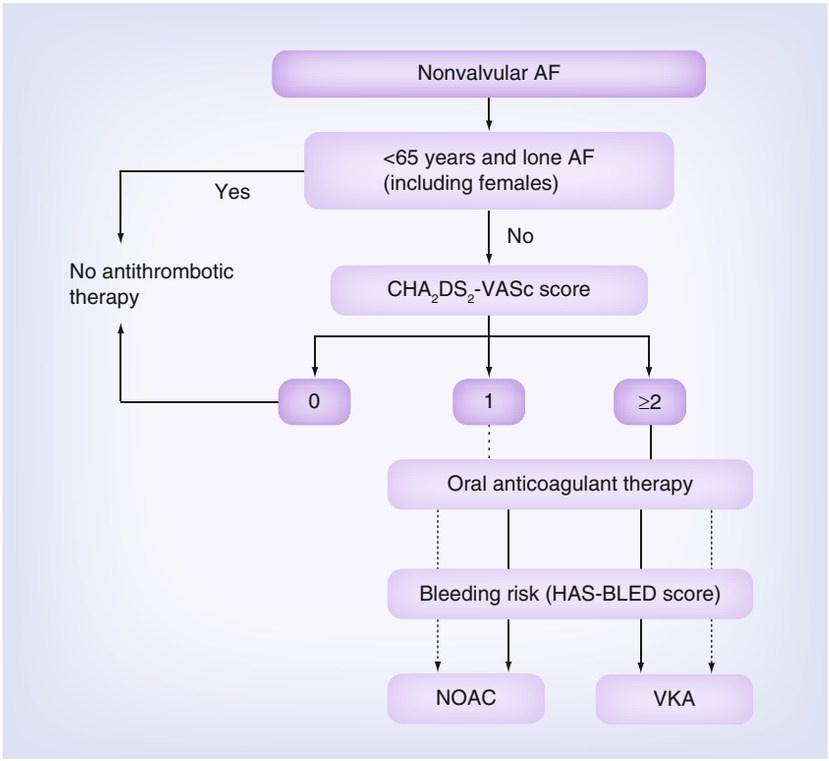

Figure 1. Thromboprophylaxis in nonvalvular atrial fibrillation.
AF: Atrial fibrillation; NOAC: Novel oral anticoagulant; VKA: Vitamin K antagonist. Adapted with permission from [48].

patients with increased risk of bleeding at almost any level of risk for stroke, excluding only AF patients with truly low risk of stroke and low bleeding risk (Figure 1). Indeed, NOACs have been acknowledged as a viable or even preferable alternative to VKAs in the most recent guidelines or focused updates on AF management [2,48,76,77]. Therefore, most of the first-diagnosed AF patients who need oral anticoagulation and those unsuitable or unwilling to take warfarin should be considered for NOACs. Of note, the risk of both ischemic stroke and bleeding is highest at the initial period of treatment with warfarin [78]. Patients already taking warfarin with unstable INRs should also be considered for switching to one of the NOACs, provided that the labile INR was not caused by a poor compliance to treatment (relatively short half-life of NOACs necessitates a strict compliance as missing just one dose may cause an insufficient anticoagulation).

The rationale for switching to NOACs is less convincing in patients taking VKA with well-controlled INR values (i.e., the TTR >70%) who accept regular laboratory monitoring; the relative benefits of NOACs are less pronounced in these patients. Cost issues could also affect the choice of oral anticoagulant, and estimates of cost–effectiveness of dabigatran, rivaroxaban and apixaban favor these drugs [79–82]. For example, dabigatran 150 mg b.i.d. was only not cost effective at the TTR values of >72.6%, which is difficult to achieve in clinical practice [79].

Once the decision has been made to initiate treatment using NOACs, the knowledge of pharmacological characteristics and performances of the novel drugs along with the patient's characteristics and preferences should facilitate the choice of a specific drug. Given that direct comparison of the novel oral anticoagulants in head-to-head trials is not likely to be attempted in the near future, an indirect comparison (with certain limitations due to the trial heterogeneity) may offer some insights. For example, such an analysis revealed a significantly lower risk of stroke and systemic embolism, hemorrhagic stroke and nondisabling stroke with dabigatran 150 mg b.i.d. compared with rivaroxaban. For ischemic stroke, there were no significant differences between the NOACs. However, major bleeding was significantly lower with apixaban compared with dabigatran 150 mg b.i.d. or rivaroxaban, but not significantly different from dabigatran 110 mg b.i.d; dabigatran 110 mg b.i.d. was associated with less major bleeding and intracranial bleeding compared with rivaroxaban [83].

Current data indicate that NOACs are not only a more convenient alternative to VKAs for stroke prevention in nonvalvular AF – these drugs are better than warfarin regarding safety and efficacy in stroke prevention and growing clinical experience with NOACs in a 'real-world' setting will yield more information on many aspects of a long-term anticoagulation with these agents. The recently reported results of the RELY-ABLE trial, which included patients from the dabigatran arm of the RE-LY trial who were still receiving the drug at the end of the randomized study period, demonstrated consistently low rates of stroke and major bleeding with long-term dabigatran as compared with those seen during the main RE-LY study period [103].

Conclusion

Nonvalvular AF confers a substantial risk of stroke or systemic embolism, and careful assessment of the absolute risks of stroke and

bleeding complications should guide appropriate thromboprophylaxis in each individual AF patient. Novel oral anticoagulants are expected to change the scope of anticoagulation dramatically, facilitating the clinical uptake of the concept that stroke risk is a continuum rather than a category and that only patients without any stroke risk factor would not need any thromboprophylaxis, while all other AF patients with one or more stroke risk factors should be considered for oral anticoagulation. However, only the long-term use of the novel oral anticoagulants in a real-world setting will demonstrate how these new drugs compare with more established treatment options regarding efficacy, safety and cost–effectiveness.

Future perspective

Increasing availability of the novel, safer and more convenient oral anticoagulant drugs should substantially lower the threshold for oral anticoagulation therapy in patients with nonvalvular AF and the proportion of patients receiving oral anticoagulant therapy will be increasing in the near future. In addition, growing number of various novel oral anticoagulants, with different pharmacological profiles, as well as the identification of other potential targets in the coagulation process, should facilitate a more personalized (and hopefully more effective and safer) thromboprophylaxis, tailored according to the patients' individual characteristics or even preferences. Finally, growing knowledge on the pathophysiology and clinical implications of both manifested and clinically silent AF-related cerebral thromboembolism with increasing identification of additional stroke risk factors (including the biomarkers), combined with the availability of more convenient and safer oral anticoagulant drugs could eventually expand the indication for oral anticoagulant therapy to all patients with AF, regardless of the presence or absence of clinically evident comorbidities.

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