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REVIEWS

New Oral Anticoagulants in Nonvalvular Atrial Fibrillation

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The choice of an oral anticoagulant (OAC) for patients with nonvalvular atrial fibrillation (NVAF) is a major and complex clinical decision taking into account the individual risk-benefit ratio and bearing in mind the chronicity of therapy. This review focuses on the safety and efficacy of new oral anticoagulants (NOACs) compared with conventional vitamin K antagonists (VKA) in patients with NVAF. Current data suggest that NOACs are at least as effective and safe as VKAs for most NVAF subjects. The NOACs do not mandate dietary restrictions and regular pharmacodynamic monitoring, and they seem to have lesser incidence of intracranial or fatal bleeding when compared with VKAs. However, both dabigatran 150 twice daily and rivaroxaban have a slightly higher incidence of gastrointestinal bleeding when compared with VKAs. The article will delineate the current knowledge as well as scientific gaps related to the choice and dosage of anticoagulation regimens for various NVAF subsets and will address certain common clinical scenarios requiring special considerations. The article also addresses the shortcomings of NOACs: lack of therapeutic pharmacokinetic and pharmacodynamic targets, absence of tools to assess compliance and efficacy, rigid and limited dosage options, and absence of effective and inexpensive reversal agents.

KEYWORDS

Stroke prevention, Arrhythmia/all, General clinical cardiology/adult, Clinical trials

1 | PREVALENCE OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is associated with 5-fold increased risk of stroke[1–3] and is the most common preventable cause of stroke. Strokes related to AF tend to be more disabling and have higher recurrence and case fatality rates. Nonvalvular AF (NVAF) affects approximately 5 million US residents, and that number is expected to at least double by 2050.[4] Prevalence of AF increases with age, affecting approximately 5% of persons age >65 years and 10% of persons age >80 years.[5,6]

Whether AF is paroxysmal, persistent, or permanent, and regardless of symptom severity, most patients with NVAF should receive OACs to prevent thromboembolic events. Sadly, a significant proportion of NVAF patients does not receive OACs at all or suffers from suboptimal oral anticoagulation.

2 | RISK STRATIFICATION FOR STROKE IN NONVALVULAR ATRIAL FIBRILLATION

2.1 | $CHADS_2$ or CHA_2DS_2-VASc Scores

Risk stratification for patients with NVAF is based on scoring systems, such as the $CHADS_2$ or CHA_2DS_2-VASc scores, and on the AF burden. A score of 0 or 1 is defined as low risk, and a score ≥2 is considered moderate to high risk. When compared with the $CHADS_2$ score, the CHA_2DS_2-VASc score has better discriminating power in identifying the low-risk NVAF patients who may still benefit from anticoagulation.[7] The clinical risk scores provide good sensitivity and negative predictive value for stroke; however, they are limited by poor specificity, positive predictive value, and overall accuracy.[8] Therefore, in patients with intermediate and high scores, these scoring systems might not provide sufficient discrimination of the stroke risk.[9]

The greatest virtue of the stroke risk scores in NVAF is their simplicity and ease of use. However, this is also the drawback of this method, because:

1. There is no accounting for severity or duration of the conditions (for instance, newly diagnosed borderline diabetes mellitus [DM] and insulin-dependent DM of 20 years duration with considerable target-organ damage will both receive a single point; similarly, the ages of 74 and 65 years will both qualify for 1 point).
2. Certain parameters impose more risk than others (DM > heart failure).

3. There is no accounting for other items associated with stroke risk (renal insufficiency, spontaneous echocardiographic contrast, hyperthyroidism, elevated D-dimers, left atrial enlargement).
4. The atrial fibrillation burden is not taken into account. The overall annual stroke risk associated with NVAF varies between 0% and 15.2% and correlates with the CHA_2DS_2-VASc score.

Females with CHA_2DS_2-VASc score of 1 or males with CHA_2DS_2-VASc score of 0 are at low risk and mostly should not be treated, OAC. Among subjects with single risk factor, the reported annual thromboembolic event rates are variable, ranging from 0.5% to 3%. A recent retrospective analysis concluded that risk associated with score of 1 is much lower than initially thought; hence, these patients might not require anticoagulation.[10] In this cohort, the single risk-factor severity, other patient characteristics, and patient preference and means should be taken into account. There are no randomized phase 3 trials assessing the efficacy and safety of any NOAC in patients with a single risk factor; however, real-world observational data are emerging.

2.1.1 | AF Burden

The burden of NVAF seems to have some impact on both thromboembolism and cardiovascular mortality. Based on the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[11] and 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) trials, the risk of systemic embolism and mortality, respectively, is somewhat higher in patients with permanent or persistent NVAF than with paroxysmal NVAF; however, this has been conflicted by other reports.

A current European consensus document suggests that first unprovoked episode of NVAF should be treated in the same way we treat repeated episodes of NVAF. The use of anticoagulant or the dosage should not be influenced by the pattern, frequency, or number of AF episodes.

2.1.2 | Bleeding Risk on Anticoagulation

All NVAF should be assessed for bleeding propensity prior to the initiation of OAC. Scoring systems to identify the inherent risk of bleeding during OAC have been developed and subsequently validated. Some of the commonly used scoring systems are $HEMORR_2HAGES$ (hepatic or renal disease, ethanol abuse, malignancy, older age [>75 years], reduced platelet count or function, rebleeding risk, hypertension [uncontrolled], anemia, genetic factors [CYP2C9 variant], excessive fall risk, stroke), HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly age >65 years), Registro Informatizado de la Enfermedad TromboEmbólica (RIETE), and Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA).

A HAS-BLED score ≥3 indicates high risk of bleeding[12]; HAS-BLED is currently endorsed by most guidelines.[13,14]

2.1.3 | Device-Detected Atrial Fibrillation

The medical community is challenged to identify patients with asymptomatic AF to initiate primary stroke prevention. Long-term Holter monitors, event monitors, and implanted devices enhance the detection of asymptomatic AF.

Certain trials provided data regarding device-detected atrial high-rate episodes (AHRE; >190–220 bpm), which could be AF, atrial flutter, or atrial or supraventricular tachycardia, and the risk of stroke.[15] Most of these studies suggested that AHREs were associated with increased risk of thromboembolism,[16,17] stroke, AF,[18] and even death.[19,20] A temporal relationship between AHREs and stroke could not be established. Additional studies are needed to further clarify the correlation between device-detected AHREs and stroke and when OAC should be considered. The guidelines do not relate to device-detected NVAF as a separate entity; hence, it should be treated similar to clinically detected NVAF.[21]

3 | NEW ORAL ANTICOAGULANTS FOR NONVALVULAR ATRIAL FIBRILLATION

The commercially available NOACs in the United States are apixaban, dabigatran, rivaroxaban, and edoxaban. When compared with VKAs, some of their distinguishing features are rapid onset of action (1–3 hours), plasma half-life of 7 to 15 hours, and most of them being partially excreted by the kidneys.[22–27] The characteristics of these agents are summarized in Table 1.

3.1 | Rate and Rhythm Control With New Oral Anticoagulants

Special attention should be given to considerations of coexisting rhythm- and rate-control agents because some of these agents interact with NOACs. The interactions among these agents are summarized in Table 2.

4 | THE EFFICACY AND SAFETY OF NEW ORAL ANTICOAGULANTS IN NONVALVULAR ATRIAL FIBRILLATION

Four major NVAF trials have compared the efficacy and safety of NOACs with VKAs (target INR, 2–3): Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) for dabigatran,[28] ROCKET-AF for rivaroxaban,[29] ARISTOTLE for apixaban,[30,31] and the Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (ENGAGE-AF) for edoxaban.[32] These phase 3 trials resulted in the approval of these agents for commercial use for NVAF. Table 3 summarizes the differences in design, study population, and outcomes of these trials. When compared with VKAs, all NOACs reduced the risk of intracerebral, life-threatening, and fatal bleeds. Certain NOAC regimens demonstrated superiority in safety (dabigatran 110 mg twice daily), efficacy (dabigatran mg 150 twice daily), or both (apixaban).

TABLE 1 Commercially Available NOACs[23–27]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Thrombin (Factor II) inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability	7%	>80%	50%	62%
Peak level, h	2–3	3	3–4	1–2
Half-life, h	12–17	5–13	10–14	10–14
Dosing	150 mg b.i.d.; 110 mg b.i.d.[a] (75 mg b.i.d. for CrCl 15–30 mL/m)	20 mg daily with food (15 mg for CrCl 15–50 mL/m)	5 mg b.i.d. (2.5 mg b.i.d. if 2 of: Cr >1.5 mg/dL, age >80 years, wt <60 kg)	60 mg daily; CrCl 50–95 mL/m (30 mg for CrCl 15–50 mL/m)
Renal cleared, %	80	36	25	50
Drug interactions	P-gp inhibitors	CYP3A4 inhibitors and inducers	P-gp and CYP3A4 inhibitors and inducers	P-gp inhibitors
Pharmacodynamic monitoring	Ecarin clotting time > thrombin time > aPTT and ACT	Direct Xa activity, PTT mildly prolonged	Direct Xa activity, PTT mildly prolonged	Direct Xa activity, PTT mildly prolonged
When to stop presurgery	≥24 h	≥24 h	≥24 h	≥24 h
Reversal agent	Idarucizumab	Andexanet alfa[a]	Andexanet alfa[a]	Andexanet alfa[a]

Abbreviations: ACT, activated clotting time; aPTT, activated partial prothrombin time; b.i.d., twice daily; Cr, creatinine; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4; NOAC, new oral anticoagulant; P-gp, P-glycoprotein; PTT, partial prothromboplastin time; wt, weight.

[a]Not commercially available in the United States.

TABLE 2 Interactions of Rate- and Rhythm-Control Agents With NOACs

Drug	NOAC Adjustment
Verapamil	Dabigatran and edoxaban dose should be reduced, but no dose reduction is required for apixaban or rivaroxaban.
Diltiazem	Dose adjustment required only for rivaroxaban in subjects with renal dysfunction.
Dronedarone	Dabigatran is contraindicated, and edoxaban and rivaroxaban dose should be reduced.
Amiodarone	Patients should receive a reduced rivaroxaban dose in the presence of renal dysfunction.

Abbreviations: NOAC, new oral anticoagulant.

TABLE 3 Clinical Trials of NVAF for Commercially Available NOACs[28–32]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Population/duration	18,113/24 mo	14,264/290 d	18,201/1.8 y	21,105/2.8 y
Study name	RE-LY[28]	ROCKET-AF[29]	ARISTOTLE[30,31]	ENGAGE-AF[32]
Doses	110 mg/150 mg[a] b.i.d.	20 mg/d	5 mg b.i.d.	60 mg[b]/30 mg/d
CrCl for ↓dose	None	30–50 mL/m, 15 mg	Cr >1.5 mg/dL, age >80 y, wt <60 kg, 2.5 mg b.i.d.	30–50 mL/m
Means $CHADS_2$ score	2.1	3.5	2.1	2.8
Prior stroke/emboli, %	20	55	19	28
Blinding	Open	Double	Double	Double
TTR, %	64	57.8	65.7	65
Noninferiority trial	Yes	Yes	Yes	Yes
Stroke/SE ↓ARR, %	0.58, $P = 0.01$[a]	0.3, $P = 0.26$	0.33, $P = 0.011$	0.3, $P = 0.017$[b]
Major bleed ↓ARR, %	0.3, $P = 0.31$[a]	−0.15, $P = 0.5$	0.96, $P = 0.001$	0.68, $P = 0.017$[b]
ICH bleed ↓ARR, %	0.4[a]	0.2	0.5	0.2[b]
Fatal bleed ↓ARR, %	N/A[c]	0.3	0.3	0.2[b]
All death ↓ARR, %	0.5[a]	0.4	0.4	0.36[b]

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ARR, absolute risk reduction; b.i.d., twice daily; $CHADS_2$, congestive heart failure, HTN, age ≥75 y, DM, prior stroke/TIA/TE; Cr, creatinine; CrCl, creatinine clearance; DM, diabetes mellitus; ENGAGE-AF, Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation; HTN, hypertension; ICH, intracerebral hemorrhage; N/A, not applicable; NOAC, new oral anticoagulant; NVAF, nonvalvular atrial fibrillation; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SE, systemic embolism; TE, thromboembolism; TIA, transient ischemic attack; TTR, time in therapeutic range; wt, weight.

[a]Dose of 150 mg b.i.d. (n = 6076) compared with warfarin (n = 6022). [b] Analysis of only 60-mg dose (n = 7012) vs warfarin (n = 7012). [c] Life-threatening bleeding reduced by 0.35%.

The Safety, Tolerability, and Pilot Efficacy of Oral Factor Xa Inhibitor Betrixaban Compared to Warfarin (EXPLORE-Xa) was a phase 2 study that compared different doses of betrixaban (40, 60, and 80 mg daily) with warfarin. The study concluded that betrixaban is well tolerated, with similar or lower rates of bleeding compared with warfarin.[27] The efficacy of the 60-mg and 80-mg doses was similar to warfarin.

When compared with VKAs, all NOACs are associated with reduced intracranial hemorrhage and fatal bleeding.[33] Patients with well-controlled INR on VKAs with time in therapeutic range >70% and no extreme outlying INR measurements (>4 or <1.8) could be still maintained on VKAs.

5 | REVERSAL OF NEW ORAL ANTICOAGULANTS

In case of massive bleeding or emergent surgical procedure after standard resuscitation protocol, gastric lavage with activated charcoal can be used if ingestion occurred within ≤3 hours. Hemodialysis can be considered for dabigatran (due to low protein binding),[34] but not for factor Xa inhibitors.

Trials demonstrated benefit from using prothrombin complex concentrates (PCCs) in the treatment of bleeding associated with rivaroxaban[35]; however, the role of PCCs in dabigatran reversal is less conclusive.[36] Four-factor PCC (50 IU/kg) was effective for treating bleeding caused by edoxaban.[37]

Recently, idarucizumab (humanized monoclonal antibody fragment targeting specifically to dabigatran) was approved by the US Food and Drug Administration for reversing dabigatran-related anticoagulation in emergencies.[38] Andexanet is a recombinant factor Xa protein that has been shown to be effective for neutralizing the anticoagulant effect of factor Xa inhibitors in healthy volunteers; however, its clinical efficacy and safety during Xa inhibitor–related bleeding remain to be proven.[39]

6 | CARDIOVERSION, ABLATION, AND SURGERY ON NEW ORAL ANTICOAGULANTS

6.0.1 | Cardioversion

Thirty-day post-cardioversion stroke rates are approximately 1% with VKAs and 5% to 7% without VKAs. Comparative data regarding the safety of cardioversion with NOACs and VKAs emerges from RE-LY (1983 cardioversions in 1270 patients), ROCKET-AF (181 electrical cardioversions and 194 pharmacologic cardioversions), and ARISTOTLE (743 cardioversions in 540 patients), suggesting that dabigatran, rivaroxaban, and apixaban have similar safety as VKAs.[40] The X-VeRT study (Explore the Efficacy and Safety of Once-daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion) investigated the use of rivaroxaban in 1504 patients. The composite primary endpoint (stroke, transient ischemic attack, myocardial infarction, and cardiovascular death) occurred in 0.51% of the rivaroxaban arm and in 1.05% of the warfarin arm, whereas major bleeding occurred in 0.6% of the rivaroxaban arm and in 0.8% of the warfarin arm. Rivaroxaban was associated with shorter mean time to cardioversion (25 days vs 34 days; $P < 0.001$). These results added additional support for the safety of rivaroxaban-based cardioversion. Both EMANATE (http://www.clinicaltrials.gov NCT02100228; phase 4 clinical trial) and ENSURE-AF (http://www.clinicaltrials.gov NCT02072434; phase 3 clinical trial) are currently ongoing to assess the safety of cardioversion with apixaban and edoxaban, respectively, when compared with usual care.

6.0.2 | Atrial Fibrillation Ablation Procedures

Atrial fibrillation ablation procedures mandate anticoagulation during the procedure and for ≥3 months post-ablation. Periprocedural embolization still occurs in 1% to 5% of AF ablation patients, whereas asymptomatic silent new magnetic resonance imaging lesions occur in 10% to 15%. The mainstay of anticoagulation therapy has been uninterrupted warfarin or unfractionated heparin (with target activated clotting time of 300 seconds). The Study Exploring Two Treatment Strategies in Patients With Atrial Fibrillation Who Undergo Catheter Ablation Therapy (VENTURE-AF) trial prospectively compared the safety of uninterrupted rivaroxaban 20 mg to that of uninterrupted warfarin in 250 subjects and found these 2 regimens to provide similar safety.[41] Ongoing randomized clinical trials Apixaban During Atrial Fibrillation Catheter Ablation: Comparison to Vitamin K Antagonist Therapy (AFAXA) using apixaban (http://www.clinicaltrials.gov NCT02227550) and Uninterrupted Dabigatran Etexilate in Comparison to Uninterrupted Warfarin in Pulmonary Vein Ablation (RE-CIRCUIT) for dabigatran (http://www.clinicaltrials.gov NCT02348723) may provide additional information regarding the safety of these agents during AF ablation. The most validated protocol for AF ablation is uninterrupted warfarin, which, according to the European Society of Cardiology guidelines and recent consensus paper, should be preferred over NOACs.

6.0.3 | Surgical Interventions

In case of surgical interventions, preprocedural discontinuation of these agents should be based on procedural bleeding risks and the predicted pharmacokinetics of the drug in the specific patient. For procedures with low risk of bleeding, it is not necessary to hold NOACs and procedure can ideally be planned within 24 hours of drug discontinuation.[42] For procedures that carry substantial bleeding risk, holding NOACs for ≥48 hours and resumption should be based on the surgical procedure and surgeon preference (bearing in mind that therapeutic anticoagulation occurs within hours of the initial dose).

7 | ANTIPLATELET THERAPY AND NEW ORAL ANTICOAGULANTS

7.1 | Stable Coronary Artery Disease and Stable Peripheral Arterial Occlusive Disease

In the RE-LY trial, triple antithrombotic therapy (the addition of aspirin and clopidogrel to either dabigatran [150 mg twice daily or 110 mg twice daily] or warfarin) resulted in doubling of major

bleeding events. Even the addition of either aspirin or clopidogrel to dabigatran or other NOACs resulted in excessive major bleeding.

For stable coronary artery disease (CAD), the meta-analysis from the 4 NOAC clinical trials suggests that the event rates for patients treated only with NOAC or warfarin is <1.5% per year. A Joint European consensus document[43] and FDA Medicare analysis refute the notion that excessive incidence of myocardial infarction occurs when using dabigatran as a single antithrombotic agent.

A recent European consensus paper[44] suggests that for both stable CAD and peripheral artery disease, the preferred therapy is monotherapy with a NOAC (with no clear preference of a particular agent) with an addition of aspirin in rare cases in which individual risk assessment predicts exceedingly high atherothrombotic risk.

7.2 | Acute Coronary Syndrome and Recent Coronary Intervention and Stenting

The role of anticoagulation in addition to standard dual antiplatelet therapy (triple therapy) with recent coronary stenting remains controversial. The results of the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial support the notion that the addition of clopidogrel alone to warfarin is as effective and safer (significantly fewer bleeding events) than the addition of dual antiplatelet therapy (clopidogrel and aspirin; triple therapy). However, the study was not blinded and had an unusually high rate of bleeding events in the triple-therapy arm. Contemporary guideline documents do not fully address this issue. Recently published European Society of Cardiology consensus documents have made recommendations in this and other specific challenging clinical scenarios.[44–46]

According to the current American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines, for patients undergoing percutaneous coronary intervention, OACs can be interrupted prior to the procedure to decrease risk of bleeding.[47]

The recent European consensus paper[44] suggests that NVAF patients after coronary stenting can be treated by either warfarin (target INR, 2–2.5) or a lower-dose NOAC (with no preference). The suggested dosage is apixaban 2.5 mg twice daily, rivaroxaban 15 mg daily, dabigatran 110 mg daily, and edoxaban 30 mg daily. These recommendations are not substantiated by any clinical trial and may not suit patients with excessively high stroke risk based on $CHADS_2$ or CHA_2DS_2-VASc score, especially those with a previous embolic event or stroke.

8 | MECHANICAL AND BIOLOGIC PROSTHETIC VALVES

8.1 | Mechanical Prosthetic Valves

The Dabigatran Etexilate in Patients With Mechanical Heart Valves (RE-ALIGN) trial[45] compared the safety and efficacy of high-dose dabigatran (trough level, ≥50 ng/mL) with VKAs in 252 subjects with mechanical valves. The dabigatran arm suffered an excessive stroke rate (9 patients vs 0) and more incidents of major bleeding (7 patients vs 2) and a higher rate of valve thrombosis, resulting in study discontinuation. The only choice at this time for mechanical prosthetic valves is a VKA (with target INR based on valve location, type, and associated clinical conditions) and low-dose aspirin. The use of NOACs is prohibited in these patients.

8.2 | Biologic Valves or Post–Transcatheter Aortic Valve Replacement

Current trials show conflicting data regarding the safety and efficacy of prescribing warfarin during the initial 3 to 6 months after surgical biologic aortic valve replacement to reduce thromboembolic complications or cardiovascular mortality.

Biologic aortic or mitral valves do not mandate anticoagulation; so although VKAs are optional for the initial 3 months for both aortic and mitral valve replacement (class IIa recommendation), based on the Society of Thoracic Surgeons registry, VKAs are not routinely prescribed. Usually patients are given aspirin 75 to 100 mg daily for life after any surgical biologic valve replacement.

After transcatheter aortic valve replacement (TAVR), patients receive aspirin ≤100 mg/d for life and clopidogrel 75 mg/d for the initial 30 days. Patients with biologic prosthetic valves were included in ARISTOTLE and ENGAGE-AF; however, the data regarding this subset of patients has not been published.

Although patients with biologic prosthetic valves have not been subject to large-scale comparative studies with NOACs, the reason for anticoagulation is the presence of AF and not the prosthetic valve. Consequently, the authors believe that the prevailing practice of off-label prescription of NOACs to patients with AF harboring biologic surgical valves or post-TAVR should not be discouraged, even though these patients have not been extensively studied in NOAC trials.

A separate newly diagnosed entity is restricted valve mobility presumed to be related to some degree of leaflet thrombosis in biological aortic valve replacement or TAVR. This condition seems to favorably respond to anticoagulation, but neither warfarin nor NOACs have been extensively evaluated for efficacy and safety in this condition.

8.3 | Valvular Heart Disease

Coexisting AF and ≥ moderate rheumatic mitral stenosis poses excessive thromboembolism risk; thus, it should not be evaluated by CHA_2DS_2-VASc score. These patients were excluded from major NOAC trials, so safety and efficacy of NOACs in these patients have not been established. Most NOAC trials included other native valvular abnormalities and subset analysis of these patients had comparable outcomes with VKAs and NOACs.

9 | PRACTICAL CONSIDERATIONS

9.1 | Cost Analysis

Outcomes analysis based on NOAC fundamental trials suggests that NOACs may reduce overall medical costs (excluding drug costs) relative to VKAs.[48] A subsequent analysis that incorporated NOAC drug

TABLE 4 OAC for AF in Specific Clinical Scenarios[43–47]

Category	Recommendations
Stable CAD and PAD	NOAC mostly without use of antiplatelet agents
After coronary stenting	Triple therapy with VKA (target INR 2–2.5) or reduced-dose NOAC[a], aspirin 75–100 mg/d, and clopidogrel 75 mg/d
	Consider: BMS, abbreviated 6-mo DAPT for DES, or omission of aspirin if bleeding propensity is high
Secondary stroke prevention	NOACs preferred over VKAs unless TTR >70
	No addition of antiplatelet agent to OAC is needed
Acute stroke	r-tPA only if anticoagulation by test or history is minimal
	Mechanical thrombectomy for proximal intracranial occlusion
Acute ischemic stroke after neuroimaging (repeat imaging pre-OAC for moderate to severe ischemic stroke)	TIA: start OAC immediately
	Mild ischemic stroke: start OAC after 3 days
	Moderate ischemic stroke: start OAC at 5–7 days
	Severe ischemic stroke: start OAC at 12–14 days
History of GI bleed	Preference to apixaban and low-dose dabigatran
End stage renal disease and dialysis	VKA or Apixaban 5 mg b.i.d or Rivaroxaban 15 mg/d
Cardioversion	VKAs and NOACs appear to be similarly effective
AF ablation	Preferred VKA over NOACs (limited data on edoxaban)
Mechanical valves	VKA target INR based on valve type, site, and associated conditions, along with aspirin 75–100 mg daily
Moderate/severe rheumatic mitral stenosis	VKA target INR 2–3

Abbreviations: AF, atrial fibrillation; b.i.d., twice daily; BMS, bare-metal stents; CAD, coronary artery disease; CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; GI, gastrointestinal; INR, international normalized ratio; NOAC, new oral anticoagulant; OAC, oral anticoagulants; PAD, peripheral artery disease; r-tPA, recombinant tissue plasminogen activator; TIA, transient ischemic attack; TTR, time in therapeutic range; VKA, vitamin K antagonist.

[a]Apixaban 2.5 mg b.i.d.; rivaroxaban 15 mg daily with food; dabigatran 110 mg b.i.d.

costs suggested that NOACs are cost-effective alternatives to VKAs.[49] A recent analysis showed that average combined patient and insurer anticoagulant spending in the first 6 months after initiation was > $900 greater for patients initiating a NOAC.[50]

9.2 | New Oral Anticoagulant Usage Distribution

A recent evaluation of anticoagulation practices in Europe shows a clear increase in the use of NOACs in AF. The overall usage in Europe is 6%, with considerable regional variability. Germany and Spain have the highest rates of prescription, at 11%, which is attributed to the availability of NOACs through their health scare systems. However, VKA remain the predominant choice.[51] Usage of NOAC therapy in the United States is significantly influenced by cost; however, there has been a notable rise in their use. New oral anticoagulants accounted for 62% of all new prescriptions in the United States and 98% of all anticoagulant-related costs between 2010 and 2013.[50]

10 | SPECIAL TREATMENT GROUPS

The European consensus articles[44,47] on choosing particular anticoagulants and dosages for stroke prevention in NVAF discuss the choice of OAC and dosing for special treatment groups. These recommendations are summarized in Table 4. Most of these recommendations are based on consensus rather than randomized clinical trials.

11 | CONCLUSION

All subjects with NVAF should undergo initial and periodic risk-benefit assessment to delineate their thromboembolic and bleeding risk. This assessment should be discussed and documented prior to therapy initiation. With very few exceptions, NOACs seem to be equally effective when compared with VKAs in NVAF and provide the benefits of rapid onset and offset, no pharmacodynamic monitoring or diet restrictions, fewer drug interactions, and predictable pharmacodynamics. NOACs are associated with decreased rates of intracranial and fatal bleeding, even without the use of reversal agents. New oral anticoagulants offer a reasonable option for patients undergoing cardioversion and AF ablation and facilitate access to surgical and invasive procedures. The relative safety and efficacy of NOACs in certain patient subsets is not established. For life-threatening bleeding after initial resuscitation, activated charcoal and prothrombin complex concentrate can be used. Specific antidotes such as andexanet alfa (for Xa inhibitors) and idarucizumab (for dabigatran) can further improve outcomes of bleeding or emergency surgery. More dose flexibility and the ability to perform point-of-care pharmacodynamic assessments may provide additional safety and efficacy when committing to lifelong therapy.

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