The Indian Consensus Guidance on Stroke Prevention in Atrial Fibrillation: A Practical View on the Use of Non-Vitamin K Antagonist Oral Anticoagulants

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Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia characterized by uncoordinated atrial activation with subsequent deterioration of the atrial mechanical function.[1] It is an important risk factor for cardioembolic stroke.[2,3] Non-valvular AF (NVAF) is associated with a fivefold increased risk of stroke,[4] with stroke being more fatal and disabling than in those without AF.[5] The risk of stroke in AF increased from 1.5% at 50-59 years of age to 23.5% at 80 to 89 years.[2] The prevalence of AF in the general population in North America and Europe is 1% to 2%.[6] The United Kingdom (UK)-based West Birmingham Atrial Fibrillation project showed a prevalence of 0.6% in the Indian subset.[3] However, there is paucity of epidemiological data to determine the true incidence and prevalence of AF in India. This paucity seems to be addressed to some extent by the Indian Heart Rhythm Society Atrial Fibrillation (IHRS-AF) registry, REALIZE AF and Indian Subgroup analysis (unpublished) of pivotal randomized controlled trials of the NOACs.[7,8] The mean age of patients in the IHRS-AF registry (n=1537) involving patients from 24 sites was 54.7 years, suggesting that Indian AF patients are about a decade younger than western population. The registry involved 51.5% females.[9] The prevalence of paroxysmal AF as reported in the RE-LY, REALIZE, and IHRS-AF study was 38%, 43% and 19.5% respectively. Permanent AF was reported in 18.6%, 34.3% and 33.7% of participants in the RE-LY, REALIZE, and IHRS-AF registries respectively.[7] In the IHRS-AF registry, paroxysmal AF, persistent AF and permanent AF was present in 20.4%, 33% and 35.1% patients respectively. Despite being younger population compared to westerns, one-third of AF patients were of permanent type. A total of 47.6% patients had rheumatic valvular heart disease. Hypertension and heart failure was present in 31.4% and 18.7% patients respectively. Coronary artery disease and diabetes were present in about 16% patients each.[9] Valvular AF, is associated with a seventeen fold increased risk of stroke.[10] In India, valvular AF comprises patients not just those with mechanical heart valves, but also rheumatic mitral stenosis. A total of 21.8% of patients in the RE-LY trial had valvular heart disease.[11] Indian subgroup analysis (n=1,387) from the 57,262 worldwide patients from the largest global registry (GARFIELD) of non-valvular AF, showed that Indian patients were younger (65.8 vs 69.7 yrs), more diabetic (36.3% vs 22.2%), more coronary artery disease (28.1 vs 21.6%) but less hypercholesterolemic (13.6% vs 41.6%). CHAD2DS2VASc score and HASBLED scores are similar between at diagnosis, but anticoagulant usage was significantly lower (36% vs 66%) in India.[12] Every year, 20 million people worldwide experience a stroke. In the Asia-Pacific region, China and India have the maximum number of deaths resulting from stroke.[3] Approximately 15% of all strokes are associated with atrial fibrillation (AF).[7]

Importantly, longitudinal community-based studies conducted worldwide have shown that there has been a steady increase in AF incidence over the last two decades. This trend is likely to continue over the next few decades with an aging population and higher occurrence of the associated risk factors including cardiac diseases. Despite major advances in its management, AF still remains a significant cause of cardiovascular morbidity and mortality, especially due to stroke and heart failure in such patients.[13]

Stroke Risk Assessment

In patients with non-valvular AF (NVAF), prior stroke or transient ischemic attack (TIA) is the strongest independent predictor of stroke. Apart from this, congestive heart failure (HF), hypertension, increasing age, and diabetes mellitus have consistently emerged as independent risk factors for ischemic stroke associated with NVAF.[14,15] Numerous scores have been devised to predict stroke risk based on the risk factors identified in non-warfarin arms of randomized clinical trial cohorts. However, these scores have been developed nearly two decades ago and need to be revisited with evidence from new epidemiological studies. Two of the most commonly used stroke risk assessment tools are discussed below.

The $CHADS_2$score (comprising of congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism) has been validated in numerous cohorts.[16,17] In the IHRS-AF registry, 68.5 % non RHD AF patients had $CHADS_2$ score of two or more. Though the scoring is simple, most researchers now agree that it does not include many of the common stroke risk factors and has several limitations and hence should not be used in practice.[18,19] The CHA_2DS_2-VASc score (comprising of congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke, vascular disease [e.g., past myocardial infarction

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Table 1: Definition of major and clinically relevant non-major risk factors for stroke in non-valvular atrial fibrillation[6]

Major risk factors	Clinically relevant non-major risk factors
Previous stroke, TIA, or systemic embolism, age >75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF <40%)
	Hypertension - Diabetes mellitus
	Female sex - Age 65–74 years
	Vascular disease[a]

TIA- transient ischaemic attack; LV- Left ventricle; EF- ejection fraction; [a]Prior myocardial infarction, peripheral artery disease, aortic plaque.

(MI), peripheral arterial disease, or aortic atherosclerosis], age 65-74, and sex category [female]) is inclusive of the most common stroke risk factors in everyday clinical practice. The $CHADS_2$ score can be used as a simple initial means of assessing stroke followed by the comprehensive risk factor-based approach using the CHA_2DS_2-VASc score.[10] Table 2 describes the scoring pattern of the CHA_2DS_2-VASc score along with the adjusted stroke rate per year. The net effect of the CHA_2DS_2-VASc score is to increase the proportion of appropriate AF patients for whom anticoagulation is recommended.[20]

The overall goal of stroke risk assessment score is to separate patients at "true low-risk" and identify those who need anticoagulant treatment.[21]

Bleeding Risk Assessment

Thromboprophylaxis with antithrombotic agents is associated with an increased risk of bleeding and requires individual risk assessment before initiation. Many of the risk factors for bleeding overlap with the risk factors for stroke.[22,23] Several bleeding risk assessment tools are available but only few have been derived and validated in patients with AF. These include $HEMORR_2HAGES$ (Hepatic or renal disease, ethanol abuse, malignancy, older age [≥75 years], reduced platelet count or function, re-bleeding risk, hypertension [uncontrolled], anaemia, genetic factors, excessive fall risk and stroke), HAS-BLED (Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [e.g., age >65 years, frailty etc.], drugs/alcohol concomitantly), ATRIA

Table 2: Risk factors in the CHA_2DS_2-VASc score and the adjusted stroke rate[20]

Risk factor	Score assigned
Congestive heart failure/Left ventricle dysfunction	1
Hypertension	1
Age >75 years	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74 years	1
Sex category (i.e. female sex)	1
CHA_2DS_2-VASc score (Total)	**Adjusted stroke rate (%/year)**
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%

TIA- transient ischaemic attack; LV- Left ventricle; EF- ejection fraction; [a]Prior myocardial infarction, peripheral artery disease, aortic plaque.

(AnTicoagulation and Risk factors In Atrial fibrillation) and ABC-Bleeding risk score.[20,24]

The HAS-BLED score has been validated in multiple cohorts. It has performed as good as (sometimes better than) the more complex $HEMORR_2HAGES$ and outperformed the less practical ATRIA score in predicting clinically relevant bleeding.[25,26] A high HAS-BLED score (≥3) is predictive of major bleeding during bridging of chronic anticoagulant therapy.[27] It is recommended to use HAS-BLED score for the assessment of oral anticoagulant-related bleeding risk in clinical practice. Table 3 provides the details of the HAS-BLED scoring system. In the IHRS-AF registry 69.3 % non RHD AF patients had HAS-BLED score of two or less.[9]

The CHA_2DS_2-VASc and the HAS-BLED score have been derived and validated mostly in the Western population. A meta-analysis identified different set of risk factors that are associated with stroke in the Western and the Asian population.[28,29] Another meta-analysis found that the incidence of intracerebral haemorrhage is highest amongst the Asians.[30] In the GLORIA-AF registry, the median CHA_2DS_2-VASc

Table 3: Risk factors of the HAS-BLED scoring system[25]

Risk factor	Score assigned
Hypertension[a]	1
Abnormal renal or liver function (one point each)[b]	1 or 2
Stroke	1
Bleeding[c]	1
Labile INR[d]	1
Elderly (e.g. age >65 years)	1
Drugs or alcohol (1 point each)[e]	1
Maximum total score	9

[a]Hypertension' is defined as systolic blood pressure >160 mmHg; [b]Abnormal kidney function is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L. Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin .2 ×the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/ alkaline phosphatase .3 x upper limit normal, etc.); [c]Bleeding refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc.; [d]Labile INRs refers to unstable/high INRs or poor time in therapeutic range (e.g.<60%); [e]Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc.; INR- international normalized ratio.

score among Asians was 3 (IQR:2 to 4).[31] Although validation of these scores is available in a Chinese population, it is recommended to validate both the CHA_2DS_2-VASc and the HAS-BLEED score in the Indian population for improved management strategies for stroke prevention.[32]

Oral Antithrombotic Agents

Vitamin K Antagonist (VKA)

Oral anticoagulation has a long history of more than seven decades.[33] Warfarin, is an old oral anticoagulant used in clinical practice since several years.[34] Until 2009, Vitamin K antagonist (VKA) (such as warfarin) was the only class of oral anticoagulant approved for the prevention of stroke in AF. Warfarin is a coumarin derivative that inhibits vitamin K epoxide reductase responsible for the cyclic interconversion of vitamin K and vitamin K epoxide. Vitamin K is an essential cofactor for the carboxylation of coagulation factors II, VII, IX and X and therefore their biological activation. Antagonism of vitamin K reduces the rate at which these factors are produced by the liver, thereby creating a state of anticoagulation.[35]

A meta-analysis of data from six randomized clinical trials that compared a VKA with placebo or

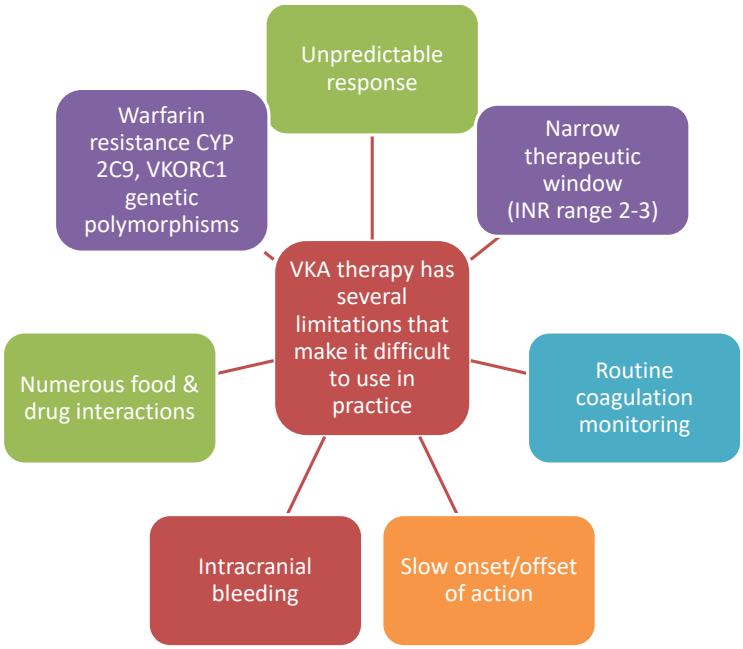


Fig. 1: Limitations of Vitamin K antagonist therapy

control found that adjusted-dose warfarin reduced the relative risk (RR) of stroke by 64% (95% confidence interval [CI] 49-74) versus placebo or control. The relative risk reduction for ischemic stroke with adjusted-dose warfarin was 67% (95% CI 54-77) while the reduction in all-cause mortality was 26% (95% CI 3-43).[36] The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study showed that treatment with VKA (target INR of 2-3) was superior to aspirin 75 mg daily in reducing the primary endpoint of fatal or disabling stroke, intracranial haemorrhage (ICH), or clinically significant arterial embolism by 52%. The risk of major haemorrhage was comparable between the two groups.[37] The target INR should protect from ischemic stroke as well as haemorrhagic complications. Many studies and meta-analysis have reported the risk of stroke and/or major bleeding events in relation to INR, or the time spent in therapeutic range (TTR).[38-40] It is evident that the risk of ischemic stroke with insufficient warfarin anticoagulation (INR<2) and that of bleeding with over anticoagulation (INR>3) is significantly higher relative to patients with NVAF maintained within an INR of 2 to 3. For the primary prevention of stroke in patients above 75 years, a target INR of 2 (range 1.6 to 2.5) is recommended while a target of 2.5 (range 2 to 3) is favourable for patients below 75 years (Figure 1).[1,41] The effectiveness and safety of warfarin treatment depends on the extent of time spent in the recommended INR range. A meta-analysis found that patients receiving warfarin spent 61% of time within, 13% of time above and 26% of time below the therapeutic range (INR range 2 to 3). Gallagher et al[42] evaluated the association between TTR and the risk of stroke and mortality with warfarin anticoagulation treatment. The average time spent in the therapeutic range was 63.1%. Reduction in stroke was the highest (79%) when the patients spent at least 70% of time within the therapeutic range when compared to patients with ≤30% time in the recommended range. Significant reduction in the risk of stroke was observed when time spent in therapeutic range was more than 61% as compared to those who did not receive any antithrombotic therapy. The risk of mortality was reduced by 81% in warfarin users who spent at least 70% of time in the therapeutic range.

Because warfarin undergoes hepatic metabolism and is highly protein bound, it is particularly prone to drug interactions. Warfarin has two active isomers, the S-isomer being 2 to 4 times more potent than the R-isomer. The S-isomer is metabolized primarily by the cytochrome P450 2C9 (CYP2C9) and the R-isomer is metabolized by cytochrome P450 1A2 and 3A4 isozymes. The effect on INR is typically observed within 3 to 5 days for drugs with short half-lives and is delayed further for drugs with longer half-life. Some important interactions of warfarin are listed in Table 4. In addition warfarin has several other limitations and challenges such as a narrow therapeutic window, increased risk of bleeding particularly ICH, need for frequent intensive INR monitoring and dose adjustment.[43] Limitations of warfarin therapy are illustrated in Figure 1.[44,45]

Other important limitations of warfarin include high coefficient of inter-lab variation in INR estimation; INR is not reflective of monthly or long-term control (TTR as measured by the Rosendaal method along with Finn method may be estimated for more appropriate control); certain drugs like amiodarone may themselves affect INR

Table 4: Food and drug interactions with warfarin

Potentiate the effect of warfarin
Acetaminophen
Alcohol (if concomitant liver disease)
Fenofibrate
Mango
Miconazole vaginal suppositories
Quilinggao
Amoxicillin/clavulanate
Azithromycin
Celecoxib
Clarithromycin
Danshen
Fluorouracil
Fluvastatin
Fluvoxamine
Gemcitabine
Grapefruit juice
Interferon
Levamisole/fluorouracil
Levofloxacin
Paclitaxel
Paracetamol
Ritonavir
Ropinirole
Tolterodine
Tramadol
Troglitazone
Acarbose
Amiodarone induced toxicosis
Amoxicillin
Chloramphenicol
Danazol
Miconazole topical gel
Ofloxacin
Trastuzumab
Inhibit the effect of warfarin
Mercaptopurine
Mesalamine
Ribavirin
Trazodone
Azathioprine
Bosentan
Ginseng
Ritonavir
Sulfasalazine
Terbinafine
Ubidicarenone
Green tea
Furosemide
Propofol
Furosemide

Table 5: Summary of pharmacokinetic parameters of NOACs

	Dabigatran (Pradaxa®)[52]	Rivaroxaban (Xarelto®)[53,54]	Apixaban (Eliquis®)[55]	Edoxaban (SAVYASA)[56]
Bioavailability	3–7%	66% without food; almost 100% with food	50%	62%
Time for peak effect	2–3 hours	2–4 hours	3–4hours	1–2hours
Plasma half life	12–17hours	5–13hours	12hours	10–14hours
Metabolism	Via P-gp transporter	Via CYP450 and P-gp transporter	Via CYP450 and P-gp transporter	Via CYP450 and P-gp transporter
Clearance non-renal/renal	20%/80%	73%/27%	50%/50%	65%/35%

and thus, interpretation of the patient's INR in those taking co-medications becomes difficult; patients with INR between 2 and 3 can still bleed or have a stroke.[44,45]

Warfarin-related nephropathy is a newly described entity in those with an acutely increased INR of more than 3 soon after the initiation of warfarin. This, if confirmed, is especially serious in patients with CKD in whom it is more often associated with an unexplained acute increase in serum creatinine and an accelerated progression of CKD. In 4006 patients with CKD and INR exceeding 3, the one year mortality was 31.1% compared with 18.9% without warfarin-related nephropathy. The bottom line is that INR should be kept below 3 in all patients soon after starting warfarin, but especially in those with CKD or who use anti-thrombin inhibitors.[46]

Even with the advent of NOACs, in India, there will always be a role for the relatively cheaper VKAs due to the cost factor. VKAs should be used in AF patients on mechanical heart valves or those with creatinine clearance less than 15 ml/min.

Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

The NOACs fall into two major categories: direct thrombin (factor IIa) inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). As compared to warfarin, these NOACs have a predictable pharmacokinetic profile and fewer food-drug and drug-drug interactions, and do not require routine anticoagulant monitoring.[22] Following rigorous phase III clinical trials, dabigatran received United States Food and Drug Administration (US FDA) approval to prevent stroke in patients with NVAF in 2010. This was followed by rivaroxaban approval in 2011 and apixaban approval in 2012. All the three drugs are also approved in Europe. Edoxaban has received US FDA and EMA approvalsfor prevention of stroke/systemic embolism in NVAF in 2015.

In the IHRS-AF registry, the stroke prevention strategy was oral anticoagulation (VKAs) in 70% patients and antiplatelets in the remaining 30% patients. Of the RHD patients, 83% received oral anticoagulants. The mean INR for warfarin was 1.8.[9] The results of GLORIA-AF Phase II showed that in most regions (except Asia) majority of AF patients received a NOAC rather than a VKA. Overall, 79.9% patients received oral anticoagulants and 47.6% patients received NOAC.[31] The results of GARFIELD-AF registry, evaluating anticoagulant practice in patients with NVAF in the Netherlands showed progressive increase in the uptake of NOAC from 0% in 2009–2011 to 14.5% in 2013–2014.[47] Anticoagulants are overused in patients at low risk and underused in those at high risk of stroke.[48] A systematic review and meta-analysis has shown that risk of fatality cases related to major bleeding events in AF patients is reduced with NOACs.[49]

Dabigatran

Targeting thrombin is a rational choice because of its multiple roles in the process of coagulation. Apart from being involved in the final process of blood coagulation, thrombin also converts fibrinogen to fibrin and makes fibrin resistant to fibrinolysis. Inhibition of thrombin reduces the formation of fibrin and avoids intensification of coagulation. Additionally, thrombin is also a potent platelet agonist.[50] Dabigatran etexilate is an oral prodrug that is rapidly converted by serum esterase-mediated hydrolysis to dabigatran,a potent, direct competitive inhibitor of thrombin.[51] A summary of the pharmacokinetics of dabigatran has been described in Table 5.[52-56]

Dabigatran offers an advantage over indirect thrombin inhibitors like heparin, as it inhibits both free and fibrin-bound thrombin. The reversible binding of dabigatran is comparable to injectable direct thrombin inhibitor (DTI), bivalirudin. DTIs have anti-platelet effect as well due to reduced thrombin-mediated activation of platelets. They produce more predictable anticoagulant response than heparin as they do not bind to plasma proteins and lack immune-mediated thrombocytopenia.[57-59]

The pivotal RE-LY (Randomised Evaluation of Long term anticoagulant therapY) trial compared two blinded doses of dabigatran etexilate (110 mg[D110] or 150 mg[D150] twice daily) with an open-label, adjusted-dose of warfarin for stroke/systemic embolism in NVAF.[11] The study design and baseline characteristics have been elaborated in Table 6.[11,55,60,61]

The D150 arm was superior ($p<0.001$ for superiority) while the D110 arm was non-inferior ($p<0.001$ for non-inferiority) versus the warfarin arm for the primary efficacy end point of stroke or systemic embolism prevention in this trial. In the RE-LY trial, dabigatran 150 mg BD was superior to 110 mg BD dose in ischemic stroke prevention. Both doses of dabigatran reduced the annual rate of haemorrhagic stroke significantly. The annual rate of major bleeding was significantly lower with dabigatran 110 mg. Intracranial bleeding in the dabigatran group was observed at less than one-third than the rate observed with warfarin, without a reduction in efficacy against ischemic stroke. Gastrointestinal bleeding was the most important adverse effect of the higher dose of dabigatran. A numerically higher rate of MI was observed with both doses of dabigatran. However the difference was not statistically significant when compared to warfarin. Overall, dabigatran 110 mg BID (twice daily)was non-inferior to warfarin in efficacy but had lower rates of major bleeding episodes, and dabigatran 150 mg BID was superior to warfarin in efficacy but had similar rates of major bleeding episodes.[11] Only dabigatran 150 mg BD regimen was associated with a lower risk of ischemic stroke than warfarin, possibly because of the its dose-dependent capacity to inactivate fibrin bound thrombin which may be responsible for local hypercoagulable state due to intensification of coagulation and activation of platelets.[62] The efficacy

Table 6: Study design and baseline characteristics of Phase III pivotal trial with NOACs

	Dabigatran[11]	Rivaroxaban[60]	Apixaban[55]	Edoxaban[61]
Study acronym	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AFTIMI-48
Study design	Randomized, open-label	Randomized, double blind	Randomized double blind	Randomized double blind
No. of patients	18,113	14,264	18,201	21,105
	D150; n=6076	R20; n= 5619	A5 n=8692	
	D110; n=6015	R15; n=1462	A2.5=428	
	Warfarin; n= 6022	Warfarin n=7133	Warfarin n=9081	
Follow-up period, yrs	2	1.9	1.8	2.8
Randomized groups	Dose-adjusted warfarin (W) vsdabigatran 110 mg BID (D110), dabigatran 150 mg BID (D150)	Dose-adjusted warfarin (W) vsrivaroxaban 20 mg OD (R20)	Dose-adjusted warfarin (W) vsapixaban 5 mg BID (A5)	Dose adjusted warfarin (W) vs Low dose edoxaban 30 mg OD
				High dose edoxaban 60 mg OD
Dose adjustment	None	15 mg OD in CrCl- 30 to 49 ml/min	2.5 mg BID if (any two of) age ≥80 years, body weight <60 kg, serum creatinine level ≥ 1.5 mg/dl	Dose was halved if estimated CrCl 30 to 50 ml/min, body weight ≤ 60 kg, or the concomitant potent
				P-gp inhibitors (verapamil or quinidine)
Age, yrs	71.5 ± 8.7 (mean ± SD)	73 (65–78)[†]	70 (63–76)[†]	72 (64–78)[†]
Male, sex %	63.6	61.3	64.5	62.5
$CHADS_2$ score (Mean)	2.1	3.5	2.1	2.8

RE-LY- Randomised Evaluation of Long term anticoagulant therapy; ROCKET-AF Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE- Apixaban for Reduction In STroke and Other ThromboembolLic Events in atrial fibrillation; ENGAGE AF-TIMI 48-Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; BID- twice daily ; OD- once daily; CrCl- Creatinine clearance; P-gp-P-glycoprotein; [†]median (interquartile range)

and safety outcomes of the trial have been elucidated in Table 7. [11,55,60,61]

In a subgroup analysis of the RE-LY trial for treatment effects, dabigatran was compared with warfarin for secondary prevention in patients with prior stroke or TIA; both doses of dabigatran were associated with lower rates of stroke or systemic embolism than warfarin (RR 0.84 for D110 and 0.75 for D150).[63] A significant treatment-by-age interaction was also observed in a subgroup analysis of RE-LY trial. D110 was associated with a lower risk of major bleeding in patients below 75 years of age (1.89% versus 3.04%; p<0.001) and with similar risk in those aged 75 years and above (4.43% versus 4.37%; p=0.89; p for interaction <0.001). Similarly, D150was associated with a lower risk of major bleeding in those aged <75 years (2.12% versus 3.04%; p<0.001) and showed a trend towards higher risk of major bleeding in those aged ≥75 years (5.10% versus 4.37%; p=0.07; p for interaction <0.001).[64] Recently, subgroup analysis of dabigatran versus warfarin from the RE-LY trial according to different age groups is published. The analysis compared benefits and risks in the age group of patients less than 75 years, 75-79 years, 80-84 years and >85 years of age. The benefits for stroke prevention and intracranial bleeding with dabigatran were maintained across all age groups. The rates of extracranial major bleeding were lower with both doses of dabigatran than warfarin in younger patients (150 mg BD HR 0.78 (95%CI 0.62-0.97); 110 mg BD HR 0.72(95% CI 0.57-0.90). The rates of extracranial major bleeding in elderly patients (>80 years of age) were similar with 110 mg BD (HR 1.50; 95% CI 1.03-2.18) and higher with 150 mg BD (HR 1.68; 95% CI 1.18-2.41).[65]

Real-world evidence on the safety and effectiveness of dabigatran versus warfarin is available for a total of more than 2,50,000 patients; more than 1,18,000 of these were new users of dabigatran who were propensity-score matched or propensity-score-weighed to new users of warfarin.[66-70] Dabigatran was associated with a reduced risk of ischaemic stroke (HR, 0.80; 95% CI, 0.67–0.96), ICH (HR, 0.34; 95% CI, 0.26–0.46) , and death (HR, 0.86; 95% CI, 0.77–0.96) compared with warfarin. Rates of major bleeding (HR, 0.97; 95% CI, 0.88-1.07) and MI (HR, 0.92; 95% CI, 0.78–1.08) were similar with both dabigatran and warfarin, however the risk for major GI bleeding (HR, 1.28; 95% CI, 1.14–1.44) was increased with dabigatran versus warfarin.[66] Importantly, these findings from large populations in clinical practice were consistent with the favorable safety and efficacy profile of dabigatran indicated in the pivotal RE-LY study. Two year follow up data from the GLORIA-AF registry are recently published. In this study, a total of 2932 patients received at least one dose of dabigatran. The probability of dabigatran persistence after two years was 69.2%. The switch over rate to factor Xa and VKA was approximately 7% and 6% respectively.[71]

Factor Xa Inhibitors

Factor Xa (FXa) is an attractive target for novel anticoagulants as it acts at the convergence point of the intrinsic and extrinsic coagulation pathway. One molecule of FXa catalyses the formation of 1000 thrombin molecules together with factor Va (as the prothrombinase complex). Inhibition of FXa activity blocks the amplification of thrombin generation, thereby limiting thrombin-mediated activation of coagulation and platelets without affecting existing thrombin levels.[72]

Rivaroxaban

Rivaroxaban is a highly selective, reversible direct oral FXa inhibitor.[73] It is rapidly absorbed after oral administration and attains maximum plasma concentration after 2 to 4 hrs. The pharmacokinetic parameters of rivaroxaban have been elucidated in Table 5[52-56] and the prominent Drug interactions of rivaroxaban have been detailed in Table 8.[74]

The 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) was a double-blind, double-dummy study conducted in 45 countries worldwide. The study design and patient characteristics of ROCKET-AF have been detailed in Table 6.[60]

Table 7: Summary of efficacy and safety outcomes of NOACs

	Dabigatran[11] (RE-LY)			Rivaroxaban[60] (ROCKET-AF)		Apixaban[55] (ARISTOTLE)		Edoxaban[61] (ENGAGE AFTIMI-48)		
Outcome (% per yr)	W (n=6022)	D110 (n=6015) RR, 95% CI, p value	D150 (n=6076) RR, 95% CI, p value	W (n=7133)	R20 (n=7131) HR (95% CI, p value)	W (n=9081)	A5 (n=9120) HR (95% CI, p value)	W (n=7035)	E30 (n=7034) HR (95% CI, p value)	E60 (n=7035) HR (95% C, I p value)
Stroke or systemic embolism	1.71	1.54(0.90; 0.74–1.10; p<0.001; NI)	1.11(0.65; 0.52–0.81; p<0.001 (NI, Sup)	2.4	2.1 (0.88; 0.75–1.03; p<0.001; NI)	1.6	1.27(0.79; 0.66–0.95; p<0.001 NI, p=0.01 Sup)	1.50	1.61 (1.07; 0.87–1.31; p=0.005; NI)	1.18 (0.79; 0.63–0.99; p<0.001; NI)
Ischemic stroke	1.21	1.34 (1.11; 0.88–1.39; p=0.35)	0.92 (0.76; 0.59–0.97; p=0.03)	1.42	1.34 (0.94; 0.75–1.17; p=0.581)	1.05	0.97 (0.92; 0.74–1.13; p=0.42)	1.25	1.77 (1.41; 1.19–1.67; p<0.001)	1.25 (1.00; 0.83–1.19; p=0.97)
Hemorrhagic stroke	0.38	0.12 (0.31; 0.17-0.56; p<0.001)	0.10 (0.26; 0.14–0.49; p<0.001)	0.44	0.26 (0.59; 0.37–0.93; p=0.024)	0.47	0.24 (0.51; 0.35–0.75; p<0.001)	0.47	0.16 (0.33; 0.22–0.50; p<0.001)	0.26 (0.54; 0.38–0.77; p<0.001)
Major bleeding	3.57	2.87 (0.80; 0.70–0.93; p=0.003)	3.32 (0.93;0.81–1.07; p=0.31)	3.4	3.6 (1.04; 0.90–1.20 p=0.58)	3.09	2.13 (0.69; 0.60–0.80; p<0.001)	3.43	1.61 (0.47; 0.41–0.55; p<0.001)	2.75 (0.80; 0.71–0.91; p<0.001)
Intracranial bleeding	0.76	0.23 (0.30; 0.19–0.45; p<0.001)	0.32; 0.41 (0.28–0.60) p<0.001	0.7	0.5 (0.67; 0.47–0.93 p=0.02)	0.80	0.33 (0.42; 0.30–0.58; p<0.001)	0.85	0.26 (0.30; 0.21–0.43; p<0.001)	0.39 (0.47; 0.34–0.63; p<0.001)
Gastrointestinal bleeding	1.07	1.15; 1.08 (0.85–1.38) p=0.52	1.56; 1.48 (1.18–1.85) p=0.001	2.2	3.2 (p<0.001)	0.86	0.76 (0.89; 0.70–1.15; p=0.37)	1.23	0.82 (0.67; 0.53–0.83; p<0.001)	1.51(1.23; 1.02–1.50; p=0.03)
Myocardial infarction	0.64	0.82 (1.29; 0.96–1.75; p=0.09)	0.81 (1.27; 0.94–1.71; p=0.12)	1.1	0.9 (0.81; 0.63–1.06; p=0.12)	0.61	0.53 (0.88; 0.66–1.17; p=0.37)	0.75	0.70 (0.94; 0.74–1.19; p=0.60)	0.89 (1.19; 0.95–1.49; p=0.13)
All cause mortality	4.13	3.75 (0.91; 0.80–1.03; p=0.13)	3.64 (0.88; 0.77–1.00; p=0.051)	2.2	1.9 (0.85; 0.70–1.02; p=0.07)	3.94	3.52 (0.89, 0.80–0.99; p=0.047)	4.35	3.80 (0.87; 0.79–0.96; p=0.006)	3.99 (0.92; 0.83–1.01; p=0.08)
Net clinical benefit outcome	7.91	7.34 (0.92; 0.84–1.01; p=0.09)	7.11 (0.90; 0.82–0.99; p=0.02)	-	-	7.20	6.13 (0.85; 0.78–0.92; p<0.001)	8.11	6.79 (0.83; 0.77–0.90; p<0.001)	7.26 (0.89; 0.83–0.96; p=0.003)

W- dose-adjusted warfarin; D110- Dabigatran 110 mg twice daily; D150- Dabigatran 150 mg twice daily; R20- Rivaroxaban 20 mg once daily; A5- Apixaban 5 mg twice daily; E30- Edoxaban 30 mg once daily; E60- Edoxaban 60 mg once daily

Table 8: Drug Interactions with NOACs[74]

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Amiodarone	+12-60 %	No PK data	+40 %	Minor effect (use with caution if CrCl <50 ml/min
Antacids	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Atorvastatin	No dose adjustment	No data yet	No dose adjustment	No dose adjustment
Clarithromycin/Erythromycin	No dose adjustment	No data yet	Reduce NOAC dose by 50 %	+30-54 %
Cyclosporin/Tacrolimus	Not recommended	No data yet	+ 73 %	Extent of increase unknown
Digoxin	No dose adjustment	No data yet	No dose adjustment	No dose adjustment
Diltiazem	No dose adjustment	+40 %	No data yet	Minor effect (use with caution if CrCl 15-50 ml/min
Dronedarone	Contraindicated	No PK/PD data; caution	Reduce NOAC dose by 50 %	Moderate effect but no PK/PD data: caution and try to avoid
HIV protease inhibitors	No data yet	Strong increase	No data yet	Contraindicated
Ketoconazole, Itraconazole, Voriconazole, Posaconazole	Contraindicated	Contraindicated	Reduce NOAC dose by 50 %	Contraindicated
Carbamazepine, Phenytoin, Phenobarbitone, Rifampicin	Minus 66 %	Minus 54 %	Minus 35 %	Up to minus 50 %
Quinidine	+53 %	No data yet	+77 %	Extent of increase unknown
Verapamil	+12-180 %	No PK data	+53 % (Slow release)	Minor effect (use with caution if CrCl 15-50 ml/min

Contraindicated	Dose reduction required	Consider dose reduction if ≥ 2 yellow is present	No dose adjustment required	Reduction in NOAC plasma levels. This may also constitute a contraindication for simultaneous use	Decrease in plasma level but not clinically relevant. Avoid if possible

The trial results showed that rivaroxaban was non-inferior to warfarin in both the primary efficacy end point of stroke and systemic embolism prevention (p<0.001 for non-inferiority) as well as the safety end point of major and clinically relevant non-major bleeding. The trial results have been elucidated in detail in Table 7.[60] Major bleeding from a gastrointestinal site was significantly higher in the rivaroxaban group (3.2%), as compared to the warfarin group (2.2%, P<0.001).Though there was no significant difference in the rates of major and clinically relevant non major bleeding between the two groups, intracranial bleeding and fatal bleeding occurred less frequently with rivaroxaban.[60]

A subgroup of patients (20.7%

of the enrolled population) with moderate renal impairment (CrCl 30-49 ml/min) received a lower dose of rivaroxaban, 15 mg OD. For patients with moderate renal impairment, the rate of stroke and systemic embolism, major and clinically relevant non-major bleeding events were higher than those with CrCl≥50 ml/min. Comparative treatment effects for rivaroxaban versus warfarin were similar for all major outcomes, including bleeding events, for those with and without renal impairment. Gastrointestinal bleeding was more frequent than warfarin in this subgroup of patients (4.1% versus 2.6% for warfarin, p=0.02).[75]

A subgroup analysis of ROCKET-AF investigated the efficacy and safety of rivaroxaban in patients aged ≥75 years and in those aged <75 years. There was no significant interaction between treatment and age for the primary outcome of stroke or systemic embolism (p=0.31) or for major bleeding (p=0.34). Clinically relevant non-major bleeding was significantly higher for patients aged ≥75 years compared with patients aged <75 years (p=0.01).[76]

One real world study which included atrial fibrillation patients compared 3654 rivaroxaban with 14,616 matched warfarin patients. Rivaroxaban was associated with similar rates of major bleeding (HR, 1.08; 95% CI: 0.71–1.64), ICH (HR, 1.17; 95% CI: 0.66– 2.05) and GI bleeding (HR, 1.27; 95% CI: 0.99–1.63) when compared with warfarin. Rates of composite stroke and systemic embolism for rivaroxaban and warfarin were also similar (HR, 0.77; 95% CI: 0.55–1.09).[77] In the REVISIT-US study, rivaroxaban use was associated with significant decrease in the combined endpoint of ischemic stroke or intracranial hemorrhage as compared to warfarin (HR 0.61, 95% CI 0.45–0.82) in NVAF patients. Rivaroxaban was associated with significantly lower rate of intracranial hemorrhage (HR 0.53, 95% CI 0.35–0.79) and non-significantly lower rate of ischemic stroke (HR 0.71, 95% CI 0.47–1.07) than warfarin.[78] The XANTUS study (n=6784) prospectively evaluated safety and efficacy of rivaroxaban in NVAF patients. Patients in this study were followed for one year or for at least 30 days after permanent discontinuation with mean treatment duration of 329 days. The incidence of treatment-emergent major bleeding was 2.1 events per 100 patient-years whereas mortality rate and stroke rate was 1.9 events per 100 patient-years and 0.7 events per 100 patient-years respectively.[79]

Apixaban

Apixaban is a selective, reversible direct oral inhibitor of factor Xa. The important pharmacokinetic parameters have been detailed in Table 5[55] while the common drug interactions with apixaban have been detailed in Table 8.[74]

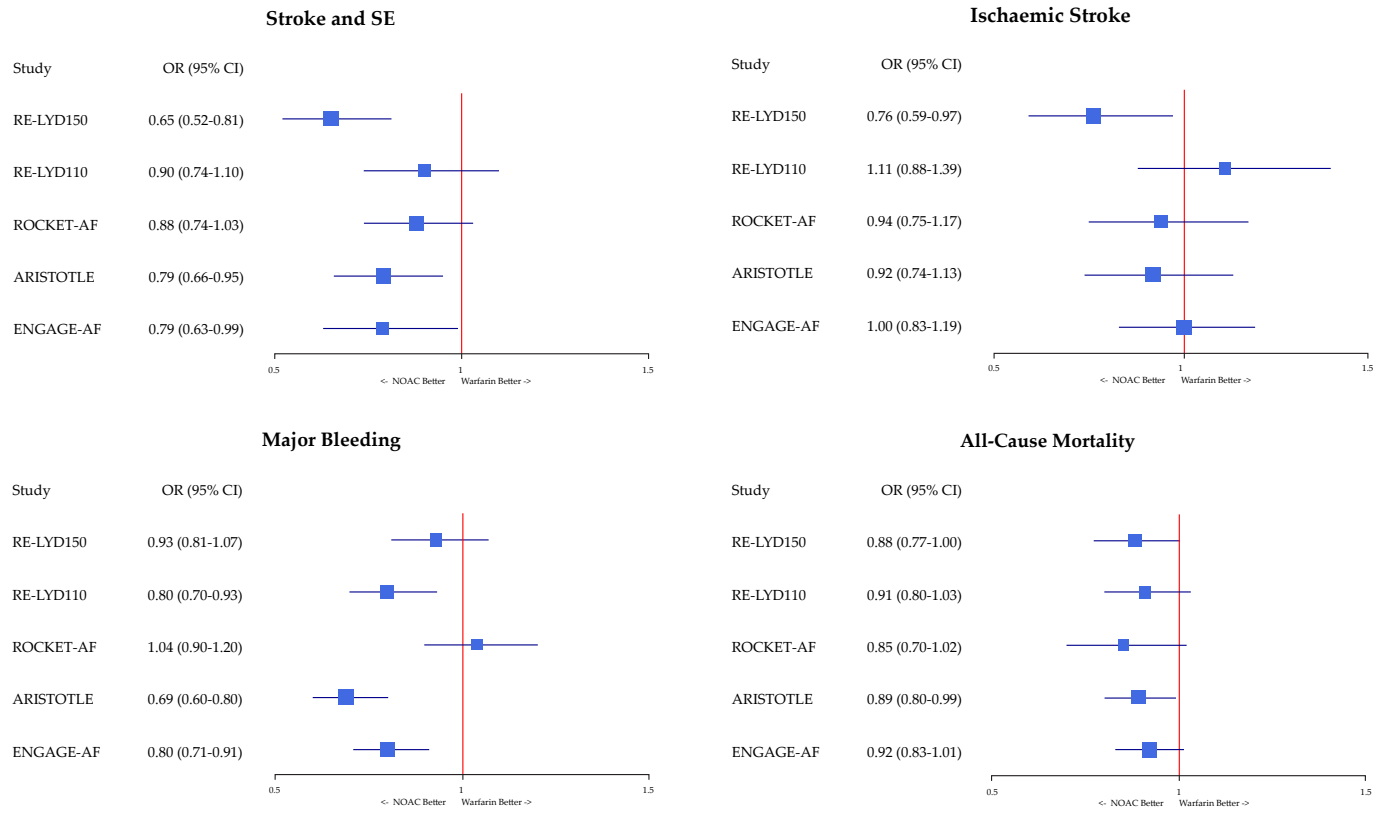
The Apixaban for Reduction In STroke and Other ThromboembolIc Events in atrial fibrillation (ARISTOTLE) trial included patients with NVAF and at least one of the following risk factors for stroke: age of at least 75 years, previous history of stroke, TIA, or systemic embolism, symptomatic heart failure within the previous 3 months or left ventricular ejection fraction of no more than 40%; diabetes mellitus; or hypertension. The ARISTOTLE study design and the patient characteristics of the study patients enrolled have been detailed in Table 6.[55] It is important to note that 26.4% of patients had mild to moderate valvular heart disease along with AF in the ARISTOTLE study.[55]

The ARISTOTLE trial proved superiority of apixaban over dose adjusted warfarin in preventing stroke and systemic embolism (p<0.01 for superiority).The major efficacy and safety results of ARISTOTLE have been detailed in Table 7.[55] The protocol of apixaban defined major bleeding as clinically overt bleeding accompanied by a decrease in the haemoglobin level of at least 2 g/dl or more over a 24 hour period along with the other clauses of the definition as per the International Society on Thrombosis and Haemostasis (ISTH).However, it remains unclear whether the final results captured the major bleeding rates using this definition or not. Rates of haemorrhagic stroke and intracranial bleeding were significantly lower (p<0.001 for superiority) in patients treated with apixaban than with warfarin. Gastrointestinal bleeding was similar between the treatment arms. There was no significant difference in the incidence of ischemic stroke. Pre-defined subgroup analyses in the ARISTOTLE trial found no significant interaction between the TTR with warfarin treatment and any of the other efficacy or safety outcomes. However, a significant interaction (p=0.003) was observed for major bleeding between diabetics (3.0% per year) and non-diabetics (1.9% per year) when treated with apixaban.[55] Thus, in patients with NVAF and increased risk of stroke, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.[55] The effect of apixaban in preventing stroke and reducing mortality was significantly better than warfarin across all age groups, and was associated with less major bleeding, less total bleeding, and less intracranial haemorrhage regardless of age (p interaction >0.11 for all).[80] However, the ARISTOTLE study did not allow patients to be on dual antiplatelet therapy and the predefined dosing in the study probably ensured that patients with a higher risk of bleeding got a lower dose (2.5 BID).In the REVIST-US study,apixaban us was associated with non-significant reduction in the combined endpoint of ischemic stroke or intracranial hemorrhage compared with warfarin (HR 0.63, 95% CI 0.35–1.12) and decreased risk of intracranial hemorrhage (HR 0.38, 95% CI 0.17–0.88) in NVAF patients.[78]

Edoxaban

Edoxaban is also an oral, selective inhibitor of Factor Xa. The pharmacokinetics of edoxaban has been detailed in Table 5[56] and important drug interactions of Edoxaban are tabled in Table 8.[74]

The Effective Anticoagulation with Factor XaNext Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) was a double-blind, double-dummy trial that compared two doses of edoxaban (60 mg and 30 mg once daily) with warfarin (target INR 2.0 to 3.0). The study characteristics have been detailed in Table 6.[61] Both once-daily regimens of edoxaban were non-inferior (p<0.005 for E30 group and p<0.001 for E60 group for non-inferiority) to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. The key efficacy and safety results of the ENGAGE-AF TIMI48 study have been detailed in Table 7.[61]



Efficacy and Safety of Noacs Versus Warfarin in NVAF

The NOACs have been evaluated and tested extensively in large trials for their efficacy and safety, including "real life" follow-up data. The pivotal randomized trials were mostly designed as non-inferiority studies and thus powered to show that NOACs are at least as good as warfarin in prevention of stroke in AF. It is evident that dabigatran 150 mg BID and apixaban 5 mg BID was superior to warfarin in reducing stroke (or systemic embolism). Dabigatran reduced ischemic stroke (or systemic embolism) by 35% and apixaban reduced it by 21%. More importantly only dabigatran 150 mg BID showed significant reduction in the incidence of ischemic stroke. All NOACs reduced the risk of haemorrhagic stroke when compared with warfarin (Figure 2). In the ROCKET-AF study, patients (n=1474) with a CrCl of 30 to 49 ml/min received lower dose of rivaroxaban15 mg OD. In the ARISTOTLE study, few patients (n=428) received half the dose of apixaban (2.5 mg BID). In the ENGAGE AF-TIMI 48 study, the dose of edoxaban was reduced from 60 mg OD to 30 mg OD (n=1787) in the high dose arm or from 30 mg OD to 15 mg OD (n=1784) in the low dose arm. Thus, all the three studies included dose adjusted subset of population in the primary efficacy and safety analysis that may add to some bias in the endpoints. Dabigatran was also evaluated at a lower dose, however no further dose adjustments were made and all patients in each subgroup showed comparable baseline characteristics.

Currently there are no head to head trials comparing the efficacy of NOACs. Several authors have performed meta-analysis of these trials. Differences in trial designs along with definition of safety and efficacy endpoints pose a challenge to the meta-analysis of these trials. A systematic review evaluated the results of the NOAC versus warfarin trials (RE-LY, ROCKET-AF and ARISTOTLE) and concluded that overall mortality was decreased in patients with AF receiving NOACs (risk difference estimated to be 8 [95% CI 3–11] fewer deaths per 1000 patients, RR 0.88, 95% CI 0.82–0.96).[81] In the meta-analysis that also included ENGAGE AF-TIMI, all-cause mortality was also significantly reduced with NOACs (2022 events in 29292 patients [6.9%]) versus warfarin (2245 events in 29221 patients [7.7%], RR 0.90, 95% CI 0.85–0.95, p=0.0003).[82] In a meta-analysis of 50,578 patients from three randomized trials (RE-LY, ROCKET-AF and ARISTOTLE), NOACs were found to significantly decrease the rate of stroke or systemic embolism as well lower the rates of intracranial bleeding. NOACs were associated with a significant 18% reduction in the composite of stroke or systemic embolism when compared to warfarin (2.8% versus 3.5%, odds ratio [OR] 0.82, 95% CI [0.74-0.91.p<0.001; I^2=0% for heterogeneity; p=0.62). All-cause mortality (6.0% versus 6.3%, OR 0.88, 95% CI [0.82-0.95], p=0.001; I^2=0% for heterogeneity; p=0.76) and rate of haemorrhagic stroke (0.3% versus 0.8%, OR 0.79, 95% CI [0.71-0.88], p<0.001; I^2=59% for heterogeneity; p=0.09) was significantly lower for NOACs as compared to warfarin. NOACs were associated with lower rates of intracranial bleeding (0.6% versus 1.3%, p<0.001) and higher rates of gastrointestinal bleeding (2.3% versus1.3%, p=0.036), however heterogeneity among the trials was high for these endpoints. There was no difference in the rates of myocardial infraction.[83] Yet another meta-analysis

found that the risk of intracranial bleeding with NOACs was lower than with warfarin (RR 0.46; 95%CI 0.33-0.65) but the risk of non-haemorrhagic stroke and systemic embolism was comparable to warfarin (RR 0.93; 95% CI 0.83-1.04).[84] This meta-analysis also observed the influence of geography on treatment outcomes. With NOACs, Asian patients experienced significantly lesser stroke and systemic embolism in RE-LY and ARISTOTLE studies in comparison to non-Europeans, whereas no significant difference was observed in ROCKET-AF.

Valvular heart disease in AF

The definition of non-valvular atrial fibrillation is usually a definition of exclusion. The ESC-2016 referred valvular AF as AF patients with either rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves.[21] Inconsistencies in the definition of non-valvular heart disease (NVHD) leads to confusion which may cause some hesitation in some clinicians mind to prescribe NOACs to patients with any form of valvular heart disease (VHD). The optimal anticoagulant treatment during initial post-biological valve replacement period is unknown. VKAs are the important agents during early period after surgery; however, NOACs may provide similar efficacy.[21]

The RE-LY, ROCKET AF and ARISTOTLE trialsincluded 21.8%, 14%, 26.4%patients of VHD patients respectively. The doses of NOACs used in these studies are shown in Table 9.[11,55,60]

Overall, there does not seem to be differential effect of warfarin over NOACs in patients with and without VHD in relation to efficacy and safety outcomes.[85] When oral anticoagulation is started in AF patient who needs non vitamin-K-antagonist oral anticoagulant, NOAC is recommended over vitamin K antagonist.[21]

We feel that the current definitions of *"valvular"* and *"nonvalvular"* AF are misleading and NOACs are *attractive alternatives* to VKAs because the coexistence of VHD does not affect the overall relative efficacy or safety of NOACs. The use of NOACs should be permitted in most patients with VHD. "Mechanical And Rheumatic Mitral valvular AF" (*MARM-AF)* could be useful to identify the true high risk AF patients for whom VKAs are the anticoagulants of choice.[86]

NOACs in Asian Population

The Asian subgroup analysis of Phase III trials of dabigatran,apixaban and edoxaban are detailed in Table 10 with respect to the major efficacy and safety end points. Further analysis of the RE-LY trial revealed that the rates of bleeding outcomes (major, major gastrointestinal, life-threatening, minor, total, intracranial, and haemorrhagic stroke) when on warfarin were numerically higher in the Asian subjects than in non-Asians. A significant interaction (p=0.008) between treatment effect and the geographical region was observed when comparing D150 versus warfarin in Asians and non-Asians.[87] A previous report on AF patients treated with warfarin found a 4-fold higher HR for ICH in Asians compared with the whites.[88] A Japanese subgroup analysis of ROCKET-AF trial is also available and it showed non-inferiority of rivaroxaban to warfarin in the primary efficacy end point of stroke and systemic embolism (HR for rivaroxaban 0.49, 95% CI 0.24–1.00) and demonstrated no significant differences in the incidence of major haemorrhage between the treatment groups.[89]

Gastro-intestinal bleeding with NOACs

In individual studies major GI bleeding risk was significantly increased with rivaroxaban, edoxaban (higher dose) and dabigatran (higher dose), albeit there was no increase in GI major bleeds with dabigatran (lower dose) and apixaban. However, a recently published subgroup analysis of ARISTOTLE trial has shown numerically increased rate of non-major lower GI bleeding with apixaban versus dose adjusted warfarin.[90] a meta-analysis by Ruff CT et al, all NOACs together increased gastrointestinal major bleeding (1·25, 1·01–1·55; p=0·04).[82] Upon searching for MedDRA preferred terms for non-adjudicated GI bleeding AEs as reported in www.clinicaltrials.gov,similar or higher rates of GI bleeding AEs were observed with standard dose NOACs versus warfarin.[91] Table 11 describes the GI bleeding incidences in NOAC studies.[82]

NOACs in elderly patients(>75 years)

A meta-analysis by Sardar P and colleagues suggests that risk of major or clinically relevant bleeding was not significantly different between NOACs and conventional therapy in elderly adults. In atrial fibrillation (AF) trials, NOACs were more effective than conventional therapy in prevention of stroke or systemic embolism in an elderly population with AF. Hence the group recommends that age should not be a limiting factor for use of NOACs.[92] Lower dosage may be required in some situations (Table 12).[93-97]

Table 9: Doses of NOACs in RE-LY, ROCKET-AF and ARISTOTLE study

	RE-LY[11]	ROCKET-AF[60]	ARISTOTLE[55]
Anticoagulant used	Dabigatran 110 mg or 150 mg BD	Rivaroxaban 20 mg OD (15 mg OD with CrCl 30-49 ml/min)	Apixaban 5 mg BD (2.5 mg BD with ≥2 of the following: age ≥80 yrs, weight ≤60 kg, or serum creatinine ≥1.5mg/dl)
Comparator	Warfarin	Warfarin	Warfarin
Target INR	2.5	2.5	2.5

Table 10: Summary of efficacy and safety outcomes of NOACs in Asian population subgroup analysis*

	Dabigatran (RE-LY)		Apixaban (ARISTOTLE)	Edoxaban ENGAGE AF-TIMI 48		Rivaroxaban ROCKET-AF
RR (95 % CI)	D150 (n=2782)[87]	D110 (n=2782)[87]	Study 2 using 5 mg (n=1993)[55]	30 mg once daily (n=3383)[61]	60 mg once daily (n=3383)[61]	20 mg once daily (n=932)[89]
Stroke or systemic embolism	0.45 (0.28–0.72)	0.81 (0.54–1.21)	0.74 (0.50–1.10)	Annualized Rate 1.83% versus 2.37% (Warfarin)	Annualized Rate 2.43% versus 2.37% (Warfarin)	0.76 (0.42–1.37)
Major bleeding	0.57 (0.38–0.84)	0.57 (0.39–0.80)	0.53 (0.35–0.80)	Annualized Rate 1.87% versus 4.12% (Warfarin)♯	Annualized Rate 3.51 % versus 4.12 % (Warfarin)♯	0.63 (0.37–1.09)
Intracranial bleeding	0.20 (0.07–0.60	0.41 (0.27–0.63)	0.36 (0.18–0.71)	NA	NA	0.23 (0.08–0.68)
All cause death	0.90 (0.78–1.04)	0.98 (0.73–1.32)	1.02 (0.70–1.50)	NA	NA	0.70 (0.40–1.25)

*From phase III trials. ‡Dose adjustments were made in all trials on the basis of renal function, and in some trials on the basis of body mass and concurrent administration of other drugs. ♯Hazard ratio not provided. Abbreviations: NA, not available; RR, relative risk.

NOACs in rheumatic heart disease

NOACs are approved for treatment of non-valvular AF. Patients with valvular AF i.e. patients with mechanical prosthetic heart valves or with moderate to severe mitral stenosis (usually of rheumatic origin) were excluded from all NOAC trials. Atrial fibrillation in patients with valvular problems other than these is defined as 'non-valvular', and such patients were included in the trials. Atrial fibrillation with biological valves or after valve repair constitute a grey area, however, patients with these were included in some trials on 'non-valvularAF'.Recently published AHA/ACC guideline for the management of patients with valvular heart disease recommend anticoagulation in patients with AF and a CHA2DS2-VASc score >2 with native aortic valve disease, tricuspid valve disease, or MR. According to the guideline, it is reasonable to use a direct oral anticoagulants as an alternative to a VKA these patients.[98] According to the ESC/EACTS 2017 guidelines, NOACs should be considered as an alternative to VKAs in AF patients with aortic stenosis, aortic regurgitation and mitral regurgitation. In patients having AF associated with surgical or transcatheter aortic valve bioprosthesis, NOACs should be considered alternative to VKAs after the third month of implantation. NOACs are not recommended in patients with AF and moderate to severe mitral stenosis and contraindicated in those with a mechanical valve.[99]

Table 11: Non adjudicated GI bleeding with NOACs[82]

Study	Warfarin	NOAC standard dose	NOAC low dose
RE-LY	1.37	1.93	1.42
ROCKET-AF	2.68	3.52	-
Aristotle	1.59	1.93	-
Engage-AF	3.19	3.28	2.33

All values in % patients per year

Treatment with NOACs

Pharmacokinetics and Drug-Drug Interactions

Treatment with NOACs needs consideration of their pharmacokinetics and interaction with concomitant medication and co-morbidities. Table 5 summarizes the pharmacokinetic profile[52-56] and Table 8 drug interactions of NOACs.[74]

Absorption of NOACs is dependent on P-glycoprotein (P-gp) and various drugs and food components are P-gp modulators.[100] The prodrug of dabigatran, dabigatran etexilate is a P-gp substrate and the bioavailability of dabigatran varies with P-gp modulation. As dabigatran is primarily excreted by the kidneys, P-gp inhibitors when administered in cases of renal insufficiency may increase the bioavailability of dabigatran. Many drugs used in AF are substrates for P-gp (e.g., verapamil, dronedarone, amiodarone, and quinidine) and may increase the bioavailability of both F IIa and FXa inhibitors.[101] NOACs should be avoided with concomitant administration of strong inducers of P-gp and FXa are contraindicated when used in combination with strong inhibitors of both CYP3A4.[95] A recently published retrospective study from Taiwan involving 91 330 patients with NVAF showed higher risk of major bleeding when NOACs are concomitantly used with amiodarone, fluconazole, rifampin, and phenytoin.[102] Further details on specific interaction with NOACs are presented in table 8.[74]

Dose Recommendations

Renal function is one of the most important criteria which affects the excretion of NOACs, and hence should be assessed at least once a year for patients with normal or mild impairment of renal function. Since most of the NOAC trials used Cockroft Gault formula for calculating the creatinine clearance of the patients, we recommend using the same.

Table 12 describes the dosing recommendations for NOACs.[93-97]

Monitoring Anticoagulant Effect

Anticoagulation therapy with warfarin needs dose adjustment to achieve an INR of 2.0 to 3.0. Because of significant inter- and intra-patient variability of effective doses and various food and drug interactions, regular anticoagulation monitoring is required to keep all patients in the target INR range. When a patient is started on warfarin, INR monitoring should be performed daily for at least two days until the target INR is achieved.[103]

Table 12: Dosing recommendation of NOACs for thromboprophylaxis in atrial fibrillation

	Dabigatran[93]	Rivaroxaban[94]	Apixaban[95,96]	Edoxaban[97]
Dosing recommendation	150 mg twice daily with or without food	20 mg once daily with evening meal	5 mg twice daily	60 mg once daily
Dose adjustment in renal dysfunction	CrCl 30-50 mL/min: 150 mg twice daily. Patients aged 80 years or above: 110 mg hard capsules twice daily	CrCl >50 mL/min: 20 mg orally, once daily with evening meal CrCl 15 - 50 mL/min: 15 mg orally, once daily with evening meal	Serum creatinine ≥ 1.5 mg/dL associated with age ≥ 80 years or body weight ≤ 60 kg, dose reduction is required CrCl 15-29 mL/min: 2.5 mg twice daily End-stage renal disease patients maintained on hemodialysis: 5 mg twice daily For ESRD patients maintained with hemodialysis (age ≥80 years or body weight ≤60 kg: 2.5 mg twice daily	CrCL >50 to ≤ 95 mL/min: 60 mg once daily CrCL 15-50 mL/Min: 30 mg once daily
Dose adjustment in Hepatic impairment	Patients with active liver disease including but not limited to the persistent elevation of liver enzymes ≥ 2 Upper Limit Normal (ULN), or hepatitis A, B or C were excluded in clinical trials	Avoid in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy	Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk; not recommended in patients with severe hepatic impairment Caution in patients with mild or moderate hepatic impairment (Child Pugh A or B) No dose adjustment in patients with mild or moderate hepatic impairment	Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B and C) No dose reduction needed in mild hepatic impairment (Child-Pugh A)
Not recommended	CrCl<30 ml/min	Consider dose adjustment or discontinuation in patients who develop acute renal failure while on rivaroxaban	CrCl<15ml/min	CrCL > 95 mL/min CrCL < 15 mL/min

CrCl- creatinine clearance

Table 13: Anticoagulant monitoring assay[103-109]

Parameter	Description	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (SAVYASA)
Time for peak effect	-	2-3 hrs	2-4 hrs	3 – 4hrs	1-2hrs
Plasma trough level	-	12-24 hrs after ingestion	16-24 hrs after ingestion	12-24 hrs after ingestion	12-24 hrs after ingestion
Activated partial thromboplastin time (aPTT)	Test for the intrinsic system; measures kininogen, prekallikrein, XII, XI, IX, VIII, X, V, and thrombin	Qualitative At trough: >2XULN Suggest excess bleeding risk	Not useful	Not useful	Not useful
Ecarin clotting time (ECT)	Specific assay for thrombin generation	Quantitative At trough: ≥3 XULN Suggest excess bleeding risk	Not affected	Not affected	Not affected
Prothrombin time (PT)	Test of the extrinsic pathway, measures factor VII, X,V, thrombin and fibrinogen	Not useful	Qualitative	Not useful	Not useful
Thrombin time	Functional test of fibrinogen concentration and fibrin formation	Qualitative	Not useful	Not useful	Not useful
Diluted TT (dTT)	Uses the Hemoclot thrombin inhibitor assay	Quantitative analysis	Not useful	Not useful	Not useful
Anti-factor Xa	Measures factor X activation directly using a chromogenic substrate	Not affected	Quantitative; cut off values for bleeding or thrombosis risk not established		

ULN- upper limit of normal

NOACs do not require routine monitoring of coagulation. However, quantitative assessment may be required to assess drug exposure and anticoagulant effect in emergency situations. INR is not an effective option for monitoring anticoagulation in NOAC-treated patients. Given the direct anticoagulant activity of NOACs, rapid onset/offset of anticoagulation effects, and relatively short half-lives, the exact time of last dose intake relative to the time of blood sampling is of prime importance.[104]

The activated partial thromboplastin time (aPTT) and the prothrombin time (PT) may provide a qualitative assessment for the presence of dabigatran and rivaroxaban, respectively.[105] The relation between dabigatran and aPTT is curvilinear. In patients undergoing chronic therapy with dabigatran, the median peak aPTT was approximately twofold that of control. The median aPTT, 12 hours after the last dose was 1.5 fold that of the control. If the aPTT level at trough (i.e., 12-24 hrs after ingestion) still exceeds two times the upper limit of normal, there may be a high risk of bleeding. Dabigatran has little effect on the PT and INR assays. Therefore, they are not suitable for quantitative assays. The ecarin clotting time (ECT) assay provides a direct measure of thrombin inhibition activity. Greater than threefold elevation in the ECT value at trough are associated with the risk of bleeding. Hemoclot® is a diluted thrombin time (dTT) test developed with appropriate calibrators for interpretation in the context of dabigatran use. When dabigatran is used with twice daily dosing, the dTT measured at trough is associated with an increased risk of bleeding.[106]

The choice of measurement methods for direct FXa inhibitors is an anti-Xa assay. A number of *in vitro* and ex-vivo studies indicated that anti-Xa chromogenic assays are more specific and sensitive than routine clotting test-based assays. Commercial anti Xaamidolytic assays are mainly designed for measurement of anti-Xa activity of LMWHs and some may require modifications for use with peak and trough levels of direct Xa inhibitors in treated patient plasma. LMWH reference standard cannot be recommended as the mechanisms of action of the two are different. Product-specific calibrators must be used for accurate estimation of plasma level expressed in mass concentration (e.g. mg/l). Factor Xa-inhibitors demonstrate a concentration dependent prolongation of PT. However, it is subjected to huge variation because of differences in PT reagents.[107] At present, there are no USFDA approved assays for the measurement of Factor Xa inhibitors. Currently, PT and anti-factor Xa chromogenic assays (where available) are considered appropriate for qualitative and quantitative measurement of Factor Xa inhibitors respectively. However, the interpretation of these results is complicated as no therapeutic ranges exist.[108,109] Also, usage of the appropriate calibrator needs to be ensured if Anti-factor Xa chromogenic assay is to be performed (specifically, heparin calibrators are not to be used).

Table 13 provides an overview of the anticoagulant monitoring assay with particular application to the NOACs.[103-109]

NOAC Overdose

In terms of management of overdose of a NOAC, it is important to distinguish between an overdose with and without bleeding complications. Overdose associated with bleeding complication should be managed as discussed in the section on management of complications. Coagulation tests can help to determine the risk of bleeding and its severity.

Activated charcoal may be considered to reduce absorption of any NOAC.[104] In addition dialysis can be used to reverse dabigatran's anticoagulant effect. In the absence of specific reversal agents a wait and watch strategy is recommended; since the half-life of NOACs is relatively shorter.

Reversal Agents of NOACs

Idarucizumab, a humanized mouse monoclonal antibody fragment (Fab) binds specifically to dabigatran with an affinity that it 350-fold greater than the affinity of dabigatran for thrombin. Rapid reversal of anticoagulant activity of dabigatran was observed in rats administered an intravenous bolus injection of idarucizumab. The first-in-human, single-rising-dose study found that idarucizumab achieved rapid peak plasma concentration, had rapid elimination, had no endogenous thrombin potential nor did it affect any coagulation parameters.[110] The

RE-VERSE AD™ was conducted to evaluate the extent of reversal of the anticoagulant effect of 5 g of intravenous idarucizumabin 503 patients with uncontrolled bleeding (group A), and in those requiring urgent surgery (group B) forwhich normal haemostasis is desirable.The results of RE-VERSE AD™ study showed immediate reversal of dabigatran-mediated anticoagulation in majority of the patients. Median maximum reversal in four hours was observed100% for both diluted thrombin time and ecarin clotting time (95% CI: 100–100). The reversal was quick and independent of age, gender, kidney function and baseline concentration of dabigatran.

In patients with uncontrolled bleeding, the median time to the cessation of bleeding was 2.5 hours. In patients undergoing urgent surgery, the median time required for initiation of procedure was 1.6 hours with normal periproceduralhemostasis in 93.4% patients. Incidence of thrombotic events at 90 days was 6.3% and 7.4% in group A and B respectively.[111] So far, no major safety concerns have been reported with idarucizumab, which has been approved by USFDA, EMA and Indian regulatory authorities. Idarucizumab received approval of USFDA in October 2015 whereas EMA approved it in November 2015. Indian regulatory authority approved it in January 2017.

Andexanet alpha (PRT064445), a truncated form of enzymatically inactive factor Xa, dose-dependently reversed the inhibitory activity and corrected the prolongation of *ex vivo* clotting time by apixaban and other factor Xa inhibitors.[112] Currently, andexanet alfa is an investigational compound and is not approved in any country. In phase 2 double-blind studies intravenous andexanet alpha (420 mg) neutralized the anti-factor Xa effects of apixaban and rivaroxaban by 91% and 53% (as compared to placebo) respectively.[113,114] Both these phase II studies have shown that anticoagulation returns to its pre-treatment state within several hours of the bolus infusion, thus, constant infusion of this agent may be required for reversing anticoagulation for a longer period of time.[113,114] Edoxaban 60 mg once daily was reversed by 52% after a bolus of 600 mg andexanet and by 73% after a bolus of 800 mg, each followed by an infusion of 8 mg/min for 1 hour.[114] Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration without evidence of clinical toxic effects. The effects sustained for the time of infusion. The ANNEXA-4 study evaluated effect of andexanet in patients with acute major bleeding. The response was evaluated by changes in anti–factor Xa activity and clinical hemostatic efficacy. After the bolus dose of andexanet, reduction in the median anti– factor Xa activity was 89% (95% CI 58 to 94) forrivaroxaban and 93% (95% CI, 87 to 94) for apixaban. The levels did not change during the 2-hour infusion. After12 hours of infusion, effective clinical hemostasis was acheived in 79% patients (n=47). Thrombotic events occurred in 18% (n=67) patients during 30-day follow-up period.[115] Andexanet was not tested in patients who need emergency surgery. Andexanet alfa was submitted for FDA review in December 2015 and accepted for review by EMA in August 2016.

Ciraparantag (PER977) is a small synthetic and cationic molecule that binds direct Xa inhibitors, direct thrombin inhibitors, and unfractionated and low molecular weight heparin (LMWH) through non-covalent hydrogen bonds and charge–charge interactions.It completely reversed the anti-Xa activity of rivaroxaban and apixaban in a dose-dependent manner ex vivo in human plasma. When administered to weight-matched rats over-dosed with rivaroxaban, apixaban, and dabigatran, aripazine decreased bleeding by >90% and the reduction was within the normal range for un-anticoagulated rats in a standard tail transaction bleeding model.[116] The dose of ciraparantag is 100 mg intravenously. There is a little published data on the exact mechanism of the molecule. Aripazine has undergone first-in-human studies in volunteers pre-treated or untreated with edoxaban. In this Phase I study, hemostasis was restored from the anticoagulated state within 10–30 min after administra- tion of 100 to 300 mg of Aripazine and was sustained for 24 h.[117] It is currently in phase II study.[118]

Current research related to antidote is focused on control of bleeding in patients with atrial fibrillation on oral anticoagulants. However, these agents may also have extended uses other than prevention and treatment of bleeding with oral anticoagulants. Excessive hemorrhage is the main cause of early mortality after injury and a risk in any major surgical procedure.[119] Reversal agents can also play an important role in restoring hemostasis in patients with excessive and uncontrolled bleeding after major surgery or trauma.

Treatment of Hypertrophic Cardiomyopathy (HCM) with AF using NOACs

Anticoagulation is indicated in HCM with AF irrespective of the CHA2DS2-VASc score.[120] The ESC-2016 guideline[21] recommends lifelong oral anticoagulation for prevention of stroke in patients with HCM who develop AF (Class of recommendation I; level of evidence B).However, the choice of anticoagulation depends upon the patient profile as there is no data available to support one anticoagulant over another.

Management of Bleeding Complications and Reversal of Anticoagulation

Anticoagulant therapy carries the risk of bleeding which may be due to dosing errors, haemorrhagic diatheses or emergency medical procedures. Though the risk of major bleeding, particularly intracranial bleeding and life-threatening bleeding was significantly lower with the NOACs, as compared to warfarin (Table 7), an effective plan is required for the management of bleeding in a real world clinical setting.

It is known that the anticoagulant effects of heparins and VKA can be reversed with protamine sulphate and prothrombin supplementation respectively.[121] Administration of protamine sulphate may be associated with the potential for allergic response with ensuing hypotension and bronchoconstriction.[122] Reversal of the anticoagulant effect of VKA with oral or parenteral vitamin K has a slow onset (at least 12 to 24 hours) while fresh frozen plasma or coagulation factors may restore coagulation more rapidly.[121]

Several papers provide recommendations on the use of idarucizumab in emergency situations, where reversal of dabigatran anticoagulant effect is imminent.[123,124] The Anticoagulation Education

Table 14a: Possible measures to take in case of bleeding[121]

Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-life threatening bleeding	
• Record the dosage regimen and time of last dose intake	Record the dosage regimen and time of last dose intake
• Delay next dose or discontinue treatment as appropriate	Delay next dose or discontinue treatment as appropriate
• Consider factors influencing homeostasis (concomitant antiplatelet medications) and those affecting plasma concentrations (CYP3A4 and P-gp modulators)	
Estimated time for normalization of hemostasis:	Estimated time for normalization of haemostasis: 12–24 hrs
Normal renal function: 12–24 hrs	
CrCl 50–80 ml/min: 24–36 hrs	
CrCl 30–50 ml/min: 36–48 hrs	
CrCl ,30 ml/min: ≥48 hrs	
Standard supportive measures	Standard supportive measures
• Mechanical compression	• Mechanical compression
• Surgical hemostasis	• Surgical hemostasis
• Fluid replacement (colloids if needed)	• Fluid replacement (colloids if needed)
• RBC substitution if necessary	• RBC substitution if necessary
• Platelet substitution (in case of thrombocytopenia ≤60 × 109/L or thrombopathy	• Platelet substitution (in case of thrombocytopenia ≤60 × 109/L or thrombopathy
• Fresh frozen plasma as plasma expander	• Fresh frozen plasma as plasma expander
• Tranexamic acid can be considered as an adjuvant	• Tranexamic acid can be considered as an adjuvant
• Desmopressin can be considered in special cases (coagulopathy or thrombopathy)	• Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
• Maintain adequate diuresis	
• Consider dialysis (preliminary evidence: -65% after 4 h)	
• Charcoal hemoperfusion not recommended (no data)	
Life-threatening bleeding	
All of the above	All of the above
PCC 25 U/kg (may be repeated once or twice) (but no clinical evidence)	PCC 25 U/kg (may be repeated once or twice) (but no clinical evidence)
aPCC(50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available	a PCC 50 IE/kg; max. 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available
Activated factor VII (rFVIIa; 90 mg/kg) no data about additional benefit + expensive (only animal evidence)	Activated factor VII (rFVIIa; 90 mg/kg) no data about additional benefit + expensive (only animal evidence)

CrCl, creatinine clearance; PCC, prothrombin complex concentrate; aPCC- activated Prothrombin complex concentrates

Task Force White Paper provides guidance on when reversal of NOACs may be appropriate in line with the idarucizumab label. Conditions where there is definite need for a reversal agent include life-threatening bleeding, bleeding in a closed space or critical organ, persistent major bleeding even after using local haemostatic measures, risk of recurrent bleeding because of delayed NOAC clearance, and emergency surgery or intervention in patients at risk of procedural bleeding. Reversal agent may be required in urgent surgery or intervention in patients with acute renal failure. Reversal agent is generally not required in elective surgery, gastrointestinal bleeding which responds to supportive measures, high drug levels or excessive anticoagulation without associated bleeding and surgery/ intervention which can be postponed until drug is cleared.The White Paper recommends idarucizumab to reverse dabigatran anticoagulation in patients requiring emergency surgery or with life-threatening bleeding.[122] EHRA practical guidance on use of NOACs recommends idarucizumab use in patients with severe or life-threatening bleeding on dabigatran.[125]

Management of Bleeding in Patients on Anticoagulants

The common measures for management of bleeding in anticoagulated patients include mechanical compression of bleeding sites, assessment of hemodynamic status, measurement of blood pressure, blood count, estimation of coagulation parameters and renal function tests. Table 14a summarizes the management strategy discussed in these guidelines.[121] Anticoagulation history should be taken to understand the last dose of NOAC or VKA. Further management is decided based on the severity of bleeding and type of anticoagulant taken (Table 14b). Idarucizumab 5 g intravenously can be given in patients with life threatening bleeding.

Switching Between Anticoagulant Regimens

When switching between different anticoagulant therapies, it is of paramount importance to maintain the anticoagulation effect while minimizing the risk of bleeding at the same time.

Switching to and from VKAs to NOAC

INR monitoring is required while transitioning patients from VKAs to a NOAC to avoid over anticoagulation. While switching from NOAC to warfarin, parenteral therapy is not required. Warfarin is initiated, when INR is in range and NOAC is stopped. Option of short overlap of NOAC with VKA therapy can also be considered.

Switching to and from parenteral anticoagulants to NOACs

NOAC should be initiated up to 2 hours before the next dose of the parenteral agent when transitioning from a parenteral agent to an NOAC. The prescribing information of each of the NOACs describes the strategy for switching between these therapies.[93,95,126,127] Table 15 summarizes the transition between different treatment regimens whereas Table 16 provides recommendations for the use of NOACs.

Cardioversion or Ablation in NOAC Treated Patients

Today, catheter ablation of AF is the most commonly performed ablation procedure in major medical centers worldwide. The procedure is associated with several complications including thromboembolic and bleeding events. Such complications may be minimized with uninterrupted anticoagulation with a VKA. VKA is commonly used at the time of AF ablation However, most AF patients are on NOAC prior to ablation. Therefore, VKA strategy requires transition to non-VKA therapy. NOACs have established efficacy and safety for stroke prevention in patients with AF. However, data on the outcomes of AF ablation with uninterrupted NOAC

Table 14b: Management of bleeding in bleeding in patients on anticoagulants

	VKA	NOAC
Minor bleeding	Delay VKA till INR is <2	Delay NOAC for 1 dose or 1 day
Moderate to severe bleeding	Symptomatic management (fluid therapy, blood transfusion, treatment of the cause of bleeding)	Symptomatic management (fluid therapy, blood transfusion, treatment of the cause of bleeding)
	Consider vitamin K (intravenous dose of 1 to 10 mg)	Consider oral charcoal (if NOAC is recently ingested)
Severe or life-threatening bleeding	Consider PCC and FFP	Consider specific antidote (PCC if antidote is not available)
	Replacement of platelets (if required)	Replacement of platelets (if required)

Table 16: Recommendations on the use of NOACs[104,128,129]

Condition	Dabigatran 150 mg bid	Dabigatran 110 mg bid	Rivaroxaban 20 mg OD	Apixaban 5 mg bid	Edoxaban* 60 mg OD
Patients with high risk of stroke/ Systemic embolism					
CHA_2DS_2-VASc ≥2					
HAS-BLED >3					
Severe heart valve disease					
Prosthetic Heart Valve					
Mild to moderate valvular heart disease	Limited evidence. May consider any of the NOAC.				
AF and hypertrophic cardiomyopathy	irrespective of the CHA2DS2-VASc score patient should be anticoagulated				
Patients with high risk of bleeding					
Moderate renal impairment (CrCl 30 – 50 ml/ min)			Low dose preferred (Dose - 15mg OD)		
Severe renal impairment (CrCl <30 ml/ min)			15 mg OD when CrCl 15–49 mL/ min	CrCl 15–29 mL/ min: 2.5 mg BID At least 2 of these factors are present: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/ min
Concomitant antiplatelets			Low dose may be considered (dose -15mg OD)	Low dose may be considered (dose-2.5 mg BD)	Low dose may be considered (dose-30 mg OD)
Patients >75 yrs					
Patients >80 yrs				Low dose preferred (dose-2.5 mg BD)	
	Preferred		May be considered		Not recommended

*Edoxaban is not yet approved in India.

Table 15: Transition between anticoagulant regimens

VKA to NOAC	INR <2.0: immediate
	INR 2.0–2.5: immediate or next day
	INR >2.5: use INR and VKA half-life to estimate time to INR <2.5
Parenteral anticoagulant to NOAC: Intravenous unfractioned heparin (UFH)	Start once UFH discontinued ($t_{½}$=2h). May be longer in patients with renal impairment
Low molecular weight heparin (LMWH)	Start when next dose would have been given
NOAC to VKA	Administer concomitantly until INR in appropriate range
	Measure INR just before next intake of NOAC
	Re-test 24 hours after last dose of NOAC
	Monitor INR in first month until stable values (2.0–3.0) achieved
NOAC to parenteral anticoagulant	Initiate when next dose of NOAC is due

VKA: Vitamin K antagonist; NOAC- Non-Vitamin K Oral anticoagulants; INR- international normalised ratio

therapy are limited. The RE-CIRCUIT™ study evaluated safety and efficacy of uninterrupted anticoagulation with dabigatran (150 mg BID) versus warfarin in AF patients undergoing catheter ablation.[130] The primary endpoint of this study was incidence of adjudicated ISTH major bleeding events from venous access up to 8 weeks post-ablation. A total of 678 patients were randomized to either dabigatran 150 mg BID (n=339) or warfarin (n=339). Patients on uninterrupted dabigatran had significantly fewer MBEs as compared with patients on warfarin (1.6% vs 6.9%). The absolute risk difference was -5.3% (95% CI -8.4%,-2.2%). The relative risk reduction was 77.2%. There were no thromboembolic events in either group. One incidence of TIA occurred in a patient on warfarin. The rates of minor bleeding events were similar in the two groups. There were no deaths in the study.

The VENTURE-AF, a small study assessed the safety of uninterrupted treatment with rivaroxaban versus warfarin in patients undergoing AF ablation.[131,132] In the post-ablation period, event rates with uninterrupted rivaroxaban were similar to those for uninterrupted VKA therapy. Thromboembolic event occurred in two patients on VKA therapy (n=124) whereas none of the patients in rivoroxaban 20 mg OD group (n=124) had thromboembolic event. Bleeding events occurred in 21 patients (major=0; non-major= 21) in rivoroxaban group and 18 in VKA group (major=1; non-major=17). Other procedure-attributable events were observed in five patients in both groups.[131]

Research is ongoing on uninterrupted use of apixaban and edoxaban during ablation. AXAFA-AFNET 5 is an ongoing investigator initiated study evaluating use of uninterrupted apixaban versus VKA.[133,134] The AEIOU study is evaluating uninterrupted apixaban versus interrupted apixaban.[135] The findings suggests similar rates of major and minor bleeding with uninterrupted or interrupted by a single dose as

that of uninterrupted warfarin in patients who underwent ablation for atrial fibrillation.[136] The ELIMINATE-AF study is evaluating outcomes of uninterrupted edoxaban versus VKA therapy.[137]

Interventions like ablation increase the bleeding risk and require temporary discontinuation of the NOAC. In patients scheduled to undergo ablation, it is reasonable to perform the procedure 24 h after stopping the NOAC. It is recommended to perform a transesophageal echocardiography before the procedure, to rule out left atrial thrombi, as it is possible to have a left atrial thrombus in spite of adequate oral anticoagulation. Pulmonary vein isolation (PVI) carries a risk of serious bleeding. In practice, PVI is performed in VKA-treated patients without the interruption of VKA treatment and such an approach is associated with not only a reduction in thromboembolic events, but also leads to less bleeding. Comparable rates of thromboembolic events and bleeding rates were observed with NOACs compared to uninterrupted VKA. An individualized approach must be taken to decide on changing patients to uninterrupted VKA, or uninterrupted NOAC therapy, or of a well-planned cessation of NOAC. Studies are ongoing to evaluate the use of uninterrupted NOAC therapy before ablation. NOACs can be restarted 4 h after the sheath removal provided there is no evidence of pericardial effusion and adequate hemostasis has been achieved.[138]

In patients with documented AF >48 h duration or AF of unknown duration, cardioversion should be performed only after 3 weeks of effective oral anticoagulation or if a transesophageal echocardiography (TOE) has ruled out Left Atrial (LA) thrombi. If the TOE detects a LA thrombus, the patient should not be subjected to cardioversion, as it can increase the risk of embolization.If AF duration is of less than 48 h, it is recommended to treat the patient with LMWH, supplement with TOE, and take a call to cardiovert the patient. The patient can then be started on NOACs for at least 4 weeks, irrespective of the patient's CHA2DS2-VASc score.[125]

The ESC (20116) guidelines recommend that patients anticoagulated with VKAs should continue therapy during ablation (INR 2–3). So far, no safety signal has been seen in observational studies evaluating use of uninterrupted NOACs. During ablation, heparin should be used to maintain an ACT >300s. In all patients, anticoagulation should be maintained for at least eight weeks after ablation. General anticoagulation recommendations should be followed for OAC use after catheter ablation.[21] For patients undergoing AF catheter ablation therapeutically anticoagulated with dabigatran or rivaroxaban, performance of the ablation procedure without interruption of dabigatran (Class of recommendation I; level of evidence A) or rivaroxaban(Class of recommendation I; level of evidence B-R) is recommended by the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement.[139]

Planned/Emergency Surgical Intervention

Patient characteristics (age, kidney function, previous bleeding complications, and concomitant medication) and surgical factors should be considered when deciding on the interruption and restart of NOAC drug. Interventions that carry no clinically important risk of bleeding (e.g., dental procedures, cataract or glaucoma) can be performed at the trough concentration of the NOAC and then restart after 6hours. For procedures involving minor risk of bleeding, it is recommended to discontinue NOACs 24hours before the elective procedure, provided the kidney functions normal. For procedures involving a major risk for bleeding cease the NOAC treatment 48 hours before the intervention. Though NOAC can be resumed in 6-8 hours after the intervention, for a few surgical interventions resuming full dose anticoagulation within the first 48-72 hours of the procedure may carry a bleeding risk that outweighs the risk for cardio-embolism. An emergency intervention should be deferred, if possible, for at least 12 hours and ideally 24 hours after the last dose of NOAC.[140]

Management of Acute Coronary Syndrome (ACS) and AF

Coronary artery disease may coexist in approximately 20-30% of patients with AF which is an indication for continuous antithrombotic treatment.[141,142] A considerable number of these patients is candidates for coronary revascularization to reduce risk of recurrent ischemic events with percutaneous coronary interventions (PCI), with stentimplantation. Management of patients with NVAF and acute coronary syndrome (ACS) either as ST elevation myocardial infarction (STEMI) or as non-ST elevation ACS (NSTE-ACS), is often challenging given the multiplicity of therapeutic options.[143] Moreover, stenting requires follow-up treatment with antiplatelets, which puts anticoagulatedpatients at higher risk of bleeding.

For stroke prevention in atrial fibrillation (SPAF), anticoagulants are more effective than antiplatelets. Anticoagulants are recommended in treatment guidelines for all AF patients except those with very low stroke risk. Dual antiplatelet therapy (DAPT) (ASA + clopidogrel) is highly effective for prevention of stent thrombosis and other major ischaemic events in post-PCI patients. For PCI in patients with AF, triple therapy (ASA + clopidogrel + OAC) is recommendedfor most patients. However, it is associated with increased bleeding risk compared to DAPTor anticoagulation alone.[144]

A meta-analysis was performed to evaluate the efficacy and safety of adding NOAC (apixaban, dabigatran, rivaroxaban, and ximelagatran) to single (aspirin) or dual (aspirin and clopidogrel) antiplatelet therapy in patients presenting with ACS.When compared with aspirin alone the combination of an oral anticoagulant and aspirin reduced the incidence of major adverse cardiovascular events (MACEs) [hazard ratio (HR) and 95% CI 0.70; 0.59-0.84], but increased clinically significant bleeding (HR: 1.79; 1.54-2.09). Compared to dual antiplatelet therapy with aspirin and clopidogrel, adding an oral anticoagulant decreased the incidence of MACE modestly (HR: 0.87; 0.80-0.95), but doubled the incidence of bleeding (HR: 2.34; 2.06-2.66).[145]

EHRA 2015 guidelines also mention that triple therapy with dual antiplatelet agents and a NOAC is associated with at least doubling the risk of major bleeding.[104] The WOEST trial[146] and the nationwide registry from Denmark[147] reported twice the number of bleeding episodes with triple therapy as compared to double therapy with warfarin and clopidogrel than aspirin. Hence it cannot be said that NOACs behave differently from VKAs.

High risk of CV events in patients with AF undergoing PCI can be reduced with anticoagulants as part of dual or triple therapy. A retrospective review of 426 patients with AF undergoing PCI with stenting between 2001 and 2006 was performed. Out of these 373 patients completed follow-up. Major adverse cardiac events (MACE) (p=0.01), embolism (p=0.02), death (0.02) and target vessel failure (p<0.01) was significantly less in patients in whom anticoagulant was a part of dual or triple therapy (n=195) compared to antiplatelet alone (n=178). The rate of major bleeding was similar in both the groups (p=0.19)[148] Currently, data on the use of NOACs with DAPT in AF are limited. In the RE-LY® study, 4.5% patients received DAPT. A total of 32% patients received ASA alone whereas 1.9% received clopidogrel alone[149] In ROCKET-AF,[60] ARISTOTLE study[55] and ENGAGE AF-TIMI 48 study[61] DAPT was not permitted. 36% patients in the ROCKET-AF study[60] received ASA alone whilein the ARISTOTLE study[55] 31% patients received ASA alone and 1.9% received clopidogrel alone whereas in the ENGAGE AF-TIMI 48 study,[61] 29% patients received ASA alone. Clopidogrel alone was used in 2.3 % patients. RE-LY® is the only NOAC AF trial in which concomitant ASA plus clopidogrel use was allowed. In this subgroup, lower major bleeding rates were seen with both doses of dabigatran versus warfarin.[149]

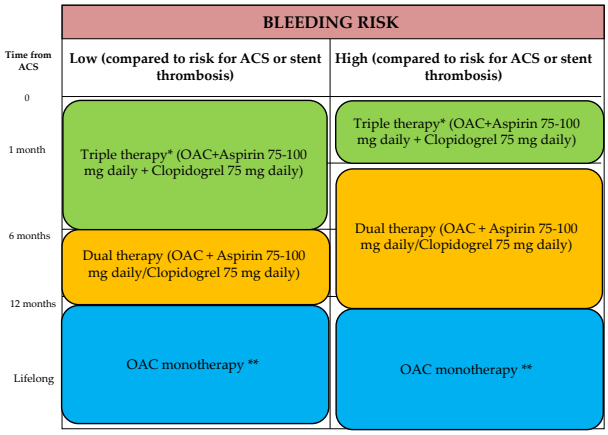
Currently, safety and efficacy data are available with rivaroxaban and dabigatran in such group of patients. The PIONEER AF-PCI™ study compared regimens of rivaroxaban with single or dual antiplatelet therapy. In this multicentre, randomized, exploratory, open-label trial, 2124 patients with paroxysmal, persistent or permanent AF, undergoing PCI (with stent placement) were randomized to receive either low-dose rivaroxaban (15 mg OD) plus a P2Y12 inhibitor for 12 months (Group 1), very-low-dose rivaroxaban (2.5 mg BID) plus dual antiplatelet therapy (DAPT) for 1, 6, or 12 months (Group 2), or standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months (Group 3). In groups 2 and 3, the duration of triple therapy (1, 6, or 12 months) was decided by the treating physician.[150,151] The primary safety endpoint was the percentage of patients experiencing either Thrombolysis In Myocardial Infarction (TIMI) major bleeding, minor bleeding, or bleeding requiring medical attention by the end of 12 months. At 12 months, the primary composite endpoint of major bleeding, minor bleeding, and bleeding requiring medical attention was significantly lower in the groups receiving rivaroxaban compared with warfarin triple therapy (both P<0.001). However, this difference in the primary endpoint was driven by the high incidence of bleeds requiring medical attention. There were no significant differences between groups in the incidence of TIMI major bleeding or minor bleeding [major bleeding (Group 1 vs Group 3: HR: 0.66; 95% CI: 0.33–1.31; P=0.23) (Group 2 vs Group 3: HR: 0.57; 95% CI: 0.28–1.16; P=0.11) minor bleeding (Group 1 vs Group 3: HR: 0.51; 95% CI: 0.20–1.28; P=0.14) (Group 2 vs Group 3: HR: 0.50; 95% CI: 0.20–1.26; P=0.13); bleed requiring medical attention (Group 1 vs Group 3: HR: 0.61; 95% CI: 0.47–0.80; P<0.001) (Group 2 vs Group 3: HR: 0.67; 95% CI: 0.52–0.86; P<0.001)]. The secondary analyses showed similar efficacy of each of the two doses of rivaroxabanas that of warfarin-based triple therapy. However, the trial was not adequately powered to definitively establish either superiority or non-inferiority of the efficacy end point.[151] The RE-DUAL PCI™ trial, a multicentre, randomized, open-label study following a PROBE designtested the hypothesis of non-inferiority in safety of dual therapy with dabigatran versus triple therapy with VKA. . The primary safety end point of the RE-DUAL PCI™ study was time to first ISTH (International Society on Thrombosis and Haemostasis) major bleeding event or ISTH clinically relevant non-major bleeding event. The RE-DUAL PCI™ study compared the safety of dual antithrombotic therapy with dabigatran plus P2Y12 inhibitor vs triple therapy (warfarin + P2Y12 inhibitor + ASA). The study used dabigatran dose which has shown favourable safety and efficacy in the prevention of stroke in patients with AF. The incidence of primary end point of major or clinically relevant non-major bleeding event during follow-up (mean follow-up, 14 months) was significantly lower with 110-mg dual-therapy compared with triple therapy (15.4% vs 26.9%; HR 0.52; 95% CI, 0.42 to 0.63; P<0.001 for non-inferiority; P<0.001 for superiority). The rates for 150-mg dual-therapy versus triple therapy were 20.2% versus 25.7% respectively (HR 0.72; 95% CI, 0.58 to 0.88; P<0.001 for non-inferiority). Incidence of serious adverse events was not significantly different among the groups.[152] Studies are also ongoing with Factor Xa inhibitors plus DAPT in AF.[153] The AUGUSTUS study is evaluating use of apixapan in patients with NVAF in a recent acute coronary syndrome or those undergoing PCI. The ENTRUST-AF-PCI trial will provide information on edoxaban versus VKA in patients with PF undergoing PCI.[154]

The recommendations for management of AF post ACS and elective PCI after stent are shown in Figure 3.[21]

Management of Acute Ischemic Stroke while on Oral Anticoagulants

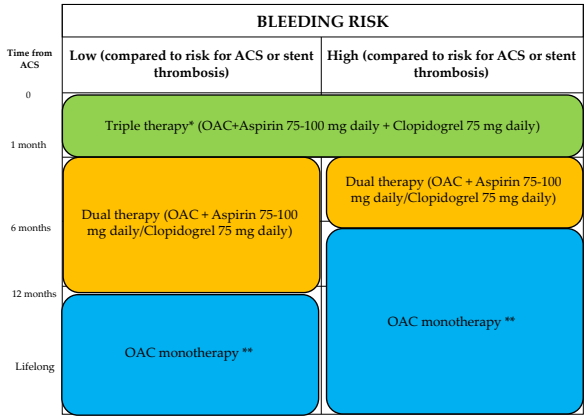
Intravenous recombinant tissue plasminogen activator (rtPA) is an effective thrombolytic agent for acute ischemic stroke and is approved when administered within 4.5 hours' time window from onset of stroke symptoms.[155] The American Heart Association/ American Stroke Association (AHA/ASA) guideline[156] allow the use of intravenous tissue plasminogen activator in warfarin-treated patients whose INR≤1.7 and are not associated with an increased risk of symptomatic ICH.[157] The plasma half-lives of NOACs lies in the range of 8 to 17 hours, hence thrombolytic treatment cannot be administered within 48 hours of the last administration of the NOAC. In case of uncertainty about the last administered NOAC, coagulation test (aPTT and PT) should be ordered. A prolonged aPTT in case of dabigatran and a prolonged PT in case of factor Xa inhibitors are indicators of *in vivo* anticoagulation; thus, thrombolytic should not be administered. The EHRA 2015 guidelines recommend that if NOACs have been given within 24-48 hours and coagulation tests are not available or are abnormal, mechanical recanalization of occluded vessels may be considered.[125]

Idarucizumab can play an important role in acute ischaemic stroke treatment in patients treated with dabigatran.A retrospective study from Germany reported use of idarucizumab in 31 patients with stroke (ischemic stroke



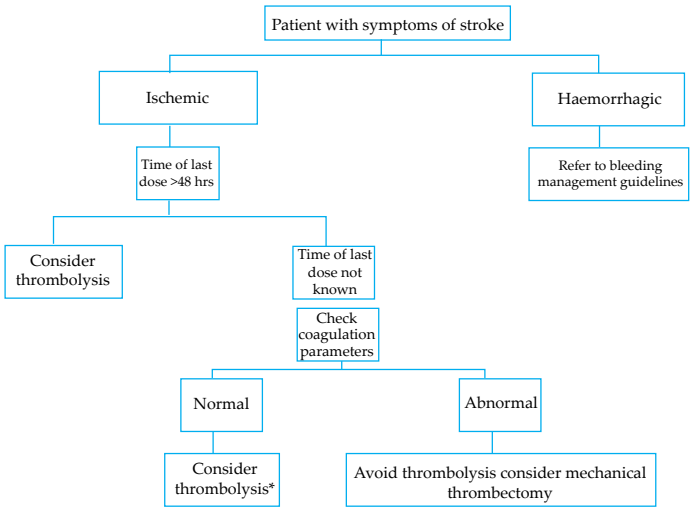
ACS: Acute coronary syndrome; OAC: oral anticoagulant; PCI: percutaneous coronary intervention
*Dual therapy i.e. OAC plus single antiplatelet agent (aspirin/clopidogrel) may be considered in some patients especially those not receiving a stent or patients at a longer time from the index event
** Dual therapy i.e. OAC plus single antiplatelet agent (aspirin/clopidogrel) may be considered in patients at high risk of coronary events

Fig. 3a: Management of atrial fibrillation after acute coronary syndrome[21]



ACS: Acute coronary syndrome; OAC: oral anticoagulant; PCI: percutaneous coronary intervention
*Dual therapy i.e. OAC plus single antiplatelet agent (aspirin/clopidogrel) may be considered in selected patients
** Dual therapy i.e. OAC plus single antiplatelet agent (aspirin/clopidogrel) may be considered in patients at high risk of coronary events

Fig. 3b: Management of atrial fibrillation after elective PCI with stent[21]



* If patient is on dabigartan, idarucizumab can be given to reverse its activity.

- For FXa inhibitors, PT may provide quantitative information, but the effect is dependent on the FXa inhibitor and the reagent used

Fig. 4: Stroke management in patients on NOACs: (<4.5hrs of symptom onset)[105,158]

n=19; intracranial bleeding n=12). The study reported benefit of rt-PA thrombolysis after idarucizumab in 79% patients without bleeding complications. Low mortality rate (6.5%) with improvement in NIHSS score suggests that thrombolysis with rt-PA after reversal of dabigatran activity with idarucizumab is an effective and safe approach.Idarucizumabis a new option for patients receiving dabigatran treatment presenting with ischemic stroke.[158]

Initiation or resumption of anticoagulation depends mainly on the severity of stroke as assessed by the NIHSS (National Institute of Health Stroke Scale) score. The thumb rule of 1-3-6-12 day may be applied, wherein the anticoagulant treatment may be resumed after 1 day in patients with transient ischemic attack; after 3 days in case of small, non-disabling infarct; after 6 days in patients with moderate stroke and not before 2 (or even 3) weeks in case of large infarcts /severe stroke.[105] Figure 4 depicts the stroke management flowchart when the patient is on a NOAC. Table 17 has detailed the recommendations for stroke prevention in AF patients.[21]

Candidates suitable for treatment with idarucizumab followed by rt-PA include patient treated with dabigatran, no intake of dabigatran within last 24 hours (96 hours if creatinine clearance is<30 ml/min), acute ischemic stroke (bleeding excluded by CT or MRI) within 4.5 hours and no additional contraindications for rt-PA.

Initiation of anticoagulation after intracranial hemorrhage

There are no prospective studies evaluating effect of initiation of OAC after intracranial haemorrhage. Patients with a history of intracranial bleeding were excluded from the randomized trials comparing NOACs with VKAs. ESC-2016 guidelines recommend that with well informed discussion between patient or caregiver and multidisciplinary team, OAC may be initiated or restarted after 4-8 weeks with an agent having low risk of intracranial bleedingafter the treatment or control of the cause of bleeding or risk factor (Evidence-class IIb evidence and Level of recommendation-B).[21] If there is a contraindication for use of OAC in patients with intracranial bleed while on OAC, occlusion of left atrial appendage may be tried

Table 17: ESC-2016 recommendations for stroke prevention in non-valvular AF[21]

Category	Recommendations
Stroke risk assessment	The CHA2DS2-VASc score is recommended for stroke risk prediction in patients with AF
Bleeding risk assessment	Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.
Renal function assessment	The assessment of kidney function by serum creatinine or CrCl is recommended in all AF patients to detect kidney disease and to support correct dosing of AF therapy.
	All AF patients treated with oral anticoagulation should be considered for at least yearly renal function evaluation to detect chronic kidney disease.
Antithrombotic therapy	Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2-VASc score of ≥2.
	Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA2DS2-VASc score of ≥3.
No antithrombotic therapy	In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention
	Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.
	Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk
	After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended
NOACs contraindication	NOACs should be avoided in pregnancy and in women planning a pregnancy
	Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves
	NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves or moderate-to-severe mitral stenosis .

CrCl- Creatinine clearance; NOACs- new oral anticoagulants; AF- atrial fibrillation; OAC- oral anticoagulants; VKA- vitamin K antagonist; INR- International normalized ratio

(Evidence-class IIb evidence and Level of recommendation-C).[21] If there is no contraindication for use of OAC, careful judgement of withholding or reinitiating OAC should be taken. Factors supporting reinitiation of OAC include bleeding while on VKA or overdose, bleeding due to treatable or traumatic cause, younger age group, hypertension under control, bleeding from basal ganglia, absence/mild white matter lesions, surgical removal of subdural haematoma, subarachnoid bleed (aneurysm clipped or coiled) and high-risk of ischaemic stroke.The factors which support withholding OAC include bleeding on adequate dose of NOAC, bleeding after treatment interruption underdosing, elderly patient, uncontrolled hypertension, cortical bleeding, severe intracranial haemorrhage, presence of multiple microbleeds, untreatable or unremovable cause of bleeding, chronic alcohol abuse and requirement of dual antiplatelet therapy after PCI.[21]

Right Dose for the Right Patient

Appropriate dosing with NOAC is essential as under-dosing can cause ischemic stroke or systemic embolism whereas over-dosing may cause bleeding. A recently published study evaluated effectiveness and safety of lower doses of NOACs [dabigatran 110 mg (n=8875), apixaban 2.5 mg (n=4400), rivaroxaban 15 mg (n=3476)) versus warfarin (n=38,893)]. In this study patients on only low NOAC doses were included.[159] Apixaban 2.5 mg was associated with non-significantly higher (weighted) event rate of ischaemic stroke/systemic embolism (4.8%). The event rate of ischaemic stroke/systemic embolism with dabigatran 110 mg, rivaroxaban 15 mg and warfarin was 3.3%, 3.5% and 3.7% respectively.All-cause mortality was significantly higher in apixaban (HR: 1.48 (95% CI 1.31-1.67)) and rivaroxaban groups (HR: 1.52 (95% CI 1.36-1.70)) but similar in dabigatranvs warfarin.Compared to warfarin, any bleeding was significantly less in dabigatran group (HR: 0.80 (95% CI 0.70-0.92)) but was similar in apixaban and rivaroxaban groups. There was similar trend for major bleeding but this did not reach significance. The rates of hemorrhagic stroke were lower for all but significantly so for dabigatran (HR: 0.46 (95% CI 0.29-0.72).[159]

In the RE-LY study,equal number of patients receiveddabigatran 150 mg BID(n=6076) and 110 mg BID(n=6015) without predefined indications for lower dose.[11]

In the ARISTOTLE study, only 428 patients (about 5%) received the 2.5 mg BID dose of apixaban, based on specific selection criteria i.e. ≥2 criteria of the following: age ≥80 years, weight ≤60 kg and serum creatinine ≥1.5 mg/dL (133 µmol /L).[55,160] In the real world clinical practice, apixaban is often under dosed.

ROCKET-AF provides fewer data for the use of rivaroxaban 15 mg OD (n=1474) than for 20 mg OD (n=5637).[75] In the ROCKET-AF study, 20 mg and 15 mg OD doses were analysed as one treatment group.[60]

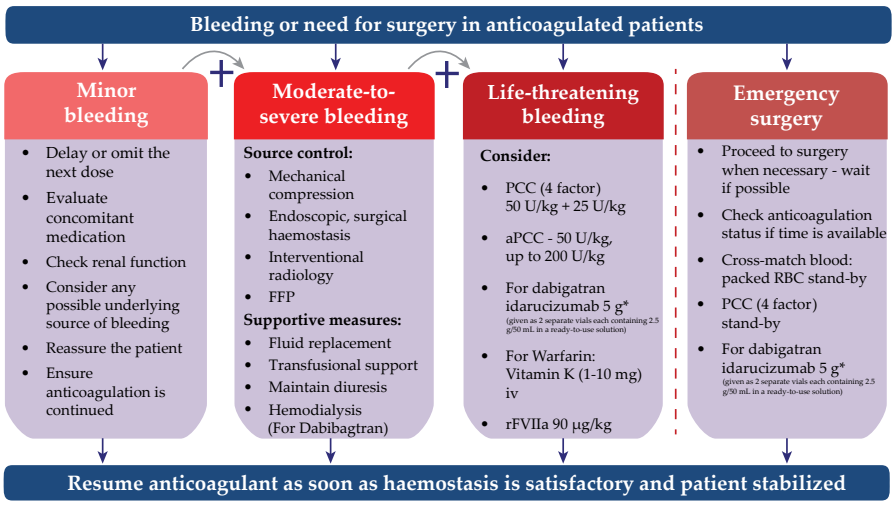
A recently published study evaluated NOAC dosing patterns and outcomes in patients with atrial fibrillation and renal impairment.Of thepatients with renal cause for dose reduction (n=1473), 43.0%received higher dose which was associated with increased risk of major bleeding (HR: 2.19; 95% CI: 1.07 to 4.46). Of the patients without renal cause for dose reduction (n=13,392), 13.3% received lower dose which was associated increased risk of stroke (HR: 4.87; 95% CI: 1.30 to 18.26).[161] Dosing of NOACs is described in table 12.

Individual thromboembolic and bleeding risk assessment for dabigatran is required in patients between 75–80 years, moderate renal impairment, gastritis, oesophagitis, gastro-oesophageal reflux and increased risk of bleeding (e.g. receiving concomitant ASA/clopidogrel).[101]

In routine clinical practice, NOAC doses are often inconsistent with drug labelling. These prescribing patterns lead to overdoing and under dosing. In order to over this and prescribe appropriate dose, every AF patient should undergo a CHADS-VASc and HAS-BLED scoring.

Summary of Recommendations

Several committees have reviewed the available data on NOACs and provided recommendations to guide clinical practice. The EHRA 2015 offers a practical guide on various treatment related challenges of NOACs.[124] The 2016 focused update



FFP - Fresh Frozen Plasma; PCC - prothrombin complex concentrate; aPCC - activated prothrombin complex concentrate; RBC - red blood cells
Anticoagulation Education task Force White Paper: Ageno et al. Thromb Haemost 2016; Dienner et al. Int J Stroke 2016; Heidbuchel et al. Eurospace 2015

Fig. 5: Suggested bleeding management protocol in India

of the ESC guidelines also provides recommendation for the prevention of stroke in NVAF and guidance for use of NOACs.[21] In view of the observations that individuals with Asian ethnicity are at disproportionately higher risk of stroke and are more prone to warfarin-associated haemorrhages, Sabir et al[129] reviewed the use of NOACs in the management of AF in Asian populations.[129] Table 17 summarizes the important recommendations on stroke prevention in patients with AF using NOACs.[21]

To summarize, for patients with NVAF, direct thrombin inhibitors (Dabigatran) or factor Xa inhibitors (rivaroxaban or apixaban) may be preferred to all patients and specially those who are unable to maintain the target INR levels with warfarin, Similarly, for patients who are unable or unwilling to submit to the frequent periodic testing of INR levels, dabigatran, rivaroxaban or apixabanmay be offered.Edoxaban may be included in any upcoming guidelines and as more clinical experience accumulates, the management of stroke prevention in NVAF may see more refined recommendations.

Suggested bleeding management protocol in India is given in Figure 5.

Future Scope for Research

There is limited data on the community prevalence of AF and focussed studies are needed to delineate the rural and urban prevalence of AF separately. The utility of the CHA2DS2-VASc and HAS-BLED scoring in Indian populations has not been studied and further studies focussing on validating these scores in an Indian population are required. As AF patients in India often have a rheumatic valvular component, the utility of NOACs in this population without mechanical valves need to be studied in detail.

NOACs are now well proven, established and widely accepted treatment options for several thromboembolic conditions. Still there are several unmet needs in anticoagulant therapy. More research is required on the use of NOACs prior and after cardioversion and catheter ablation. Prevention of recurrent cardiovascular events after acute coronary syndrome, heart failure, and secondary prevention of recurrent strokes after ischemic stroke of undetermined cause arefew more areas where research is required. The consensus statement will be updated as and when the results of these trials become available.

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