Balancing Efficacy and Bleeding Risk in the Prevention of Stroke Due to Atrial Fibrillation with Newer Oral Anticoagulants

M. B. Agarwal · Subhash Verma · Manoranjan Mahapatra ·
A. K. Tripathi · Abhay Bhave · Anand Deshpande ·
Amit Vora · Jamshed J. Dalal · A. B. Shah · S. Bichu

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Abstract With the evaluation and approval of newer oral anticoagulants such as the factor IIa inhibitor, dabigatran etexilate and the factor Xa inhibitors, rivaroxaban and apixaban, strategies for stroke prevention in atrial fibrillation need a thorough re-evaluation of current options. Clinicians are naturally excited about the imminent introduction of these newer drugs that do not need international normalized ratio (INR) monitoring, besides having no drug–food and minimal drug–drug interactions. However, as with all new drugs, it is always prudent to use these judiciously so that they stay in our therapeutic armamentarium for a long time. More than 56 years after the introduction of warfarin we now have three drugs, viz., dabigatran 150 mg bid, rivaroxaban 20 mg od, and apixaban 5 mg bid which were effective in comparison with warfarin in reducing the risk of stroke and bleeding in the landmark trials, RE-LY, ROCKET-AF, and ARISTOTLE respectively. There is a thin dividing line between

physiological hemostasis and pathological thrombosis. Routine INR monitoring may not be required but in special situations, such as prior to major surgery, overdose, non-compliance or stroke while on the anticoagulant, one may wish to know whether there are any laboratory measures of efficacy or means of reversal of over anticoagulation. Similar questions may be raised about other situations such as renal dysfunction, cardioversion, ablation procedures, post-stenting, or switch to and from warfarin, heparin or LMWH? This document is an attempt to address these concerns based on available evidence and give physicians a perspective and practice guidelines on how best to use these agents, both old and new, for optimal patient outcomes, maximizing efficacy and minimizing risk.

Keywords Stroke · Atrial fibrillation · INR · Dabigatran · Rivaroxaban · Apixaban

M. B. Agarwal (✉) · S. Bichu
Bombay Hospital, Mumbai, India
e-mail: mb.agarwal@yahoo.in

S. Bichu
e-mail: shrirangbichu@gmail.com

S. Verma
PGI, Chandigarh, India
e-mail: suvarma@hotmail.com; suvarma@gmail.com

M. Mahapatra
All India Institute of Medical Sciences,
New Delhi, India
e-mail: mrmahapatra@hotmail.com

A. K. Tripathi
C.S.M. Medical University, Lucknow, India
e-mail: tripathiak2010@hotmail.com

A. Bhave · A. Vora
Lilavati Hospital, Mumbai, India
e-mail: bhaveabhay@hotmail.com

A. Vora
e-mail: amvora@hotmail.com

A. Deshpande
Hinduja Hospital, Mumbai, India
e-mail: dr_adeshpande@hindujahospital.com;
dr_adeshpande@yahoo.co.in

J. J. Dalal
Kokilaben Dhirubhai Ambani Hospital, Mumbai, India
e-mail: jjdalal@hotmail.com

A. B. Shah
Saifee Hospital, Mumbai, India
e-mail: arun.1950@hotmail.com

Introduction and Scope

VKAs have so far been the mainstay of stroke prevention in patients with atrial fibrillation. However, their application in clinical practice is challenging due to problems such as a narrow therapeutic index, drug–drug and drug–food interactions, inter- and intra-patient variability, variable INR reporting, genetic polymorphisms, etc. Also, physicians are more concerned about the risk of bleeding and therefore tend to use low, fixed dose warfarin or anti-platelet agents or combinations. It has been clearly shown that well adjusted warfarin is more effective and safer than a combination of a lower fixed dose of warfarin with anti-platelet therapy. Guidelines, based on this evidence, also recommend against using such combinations. Ideally patients should be maintained on well adjusted warfarin but in reality very few patients are able to be maintained in the desired time in therapeutic range. When the newer OACs become available, if doctors wish to switch patients from this combination to the newer oral anticoagulant, ideally the concomitant aspirin and/or clopidogrel, if given for SPAF and not for concomitant IHD, needs to be stopped. Warfarin has been available for about 58 years now and doctors are familiar with managing the bleeding complications. What about the newer oral anticoagulants, which have been shown to be safer than warfarin, but also have bleeding as an inevitable side effect? How does one measure the anticoagulant effect knowing that INR is not required? Is there an antidote and in the absence of such an antidote how does one manage bleeding complications? Are there any recommendations on when to stop these newer OACs before surgery? These are some of the questions that this document addresses as also the fine line between physiological haemostasis and pathological thrombosis.

This document covers the existing, approved and/or available OACs in India (dabigatran etexilate) for stroke prevention in atrial fibrillation till date, and may not necessarily capture in-depth information on all the other newer oral anticoagulants.

Systematic evidence on use of anti-coagulants and/or anti-platelet agents in SPAF in India is lacking due to extremely sparse published data in the Indian context. At best there are 43 case reports on Pub Med.

However, independent research conducted by a research agency concludes that the Indian practice scenario in SPAF is dominated by a very high use of combination therapy with either single or dual antiplatelets or with low-dose warfarin.¹

There is a huge body of evidence for the efficacy of adjusted-dose warfarin alone without any combinations in the prevention of stroke. Multiple historical trials have

repeatedly proven the efficacy of adjusted-dose warfarin compared with not only aspirin and placebo but also with combination therapies with antiplatelets and with low fixed-dose warfarin [1].

Numerous studies have compared the safety and efficacy of warfarin with that of aspirin in the prevention of stroke in AF. Table 1 lists the studies and their findings.

As is evident from the results, warfarin has consistently shown higher efficacy compared with aspirin. A meta-analysis of all these trials demonstrated that adjusted dose warfarin is associated with a relative risk reduction of 38 % [2] (95 % CI 18–52 %) versus aspirin for both ischaemic and haemorrhagic stroke as seen in Fig. 1 [2].

The differences in the bleeding rates for warfarin and aspirin in all these trials are highlighted in Fig. 2 [3] and it is evident that the bleeding rates were comparable in both the treatment groups in all the trials except for the SPAF II trials. In the SPAF II study, the apparent difference in bleeds was seen largely in the older population. This was observed to be related mostly to the intensity of the anticoagulation in these patients, with most of the intracranial bleeds observed in patients with an INR >3.0 [3].

Though combination therapies are rampantly prescribed in the Indian practice scenario, clinical studies have demonstrated that adjusted-dose warfarin is superior to combination therapy.

The ACTIVE-W study has compared the safety and efficacy of warfarin with that of combination therapy with aspirin and clopidogrel in prevention of stroke in AF. Over 6,000 patients with AF and 1 or more risk factors were enrolled to receive adjusted warfarin (INR 2–3) or clopidogrel (75 mg/d) plus aspirin (75–100 mg/d). Outcomes were occurrence of stroke, non-CNS emboli, myocardial infarct (MI), or vascular death. This is another instance where the study was stopped early because of clear evidence on the benefits of Oral Anticoagulant (OAC) over combination antiplatelet treatment. As shown in Fig. 3 [4], adjusted-dose warfarin was associated with a 72 % relative risk reduction of stroke compared with aspirin plus clopidogrel [4].

The study also demonstrated that the dual combination therapy was associated with a significantly higher bleeding risk as compared with adjusted-dose warfarin (Fig. 4) [4]. This was despite similar risk profiles for bleeding, particularly with regard to prior stroke or hypertension and age [4].

Studies have shown that combination of low, fixed-dose warfarin with aspirin and/or clopidogrel is inferior to adjusted-dose warfarin in SPAF. SPAF III was an open-label study conducted in 1,044 patients with AF and one thromboembolic risk factor, who were randomized to either fixed-dose warfarin (initial dose adjustment done on the basis of INR of 1.2–1.5) and aspirin (325 mg/d) or adjusted-dose warfarin (INR 2.0–3.0). This study demonstrated

¹ India Physician Quantitative Research (n = 382); data weighted by doctor and patient number by doctor. Boehringer-Ingelheim India Pvt. Ltd. Data on File.

Table 1 List of studies comparing warfarin with aspirin

Study	Years	2° prev (%)	Patients (n) (W/A)	Warfarin target INR	Aspirin dosage	RRR for stroke (%)	P value
AFASAK I	1989	6	335/336	2.8–4.2	75 mg/day	45	NS
EAFT	1993	100	225/230	2.5–4.0	300 mg/day	67	<0.05
sPaf II	1994			2.0–4.5	325 mg/day		
Age ≤75 years		6	358/357			10	NS
Age >75 years		9	197/188			10	NS
pataf	1997	0	131/141	2.5–3.5	150 mg/day	20	NS
AFASAK ii	1998	8	170/169	2.0–3.0	300 mg/day	–23	NS
Vemmos et al.	2006	0	16/15	1.6–2.5	100 mg/day	100	NS
Chinese ATAFS	2006	19	335/369	2.0–3.0	150–200 mg/day	43	NS
WASPO	2007		36/39	2.0–3.0	300 mg/day	NC	–
All trials	–	21	1803/1844	–	–	38	95 % CI: 18–52 %

Fig. 1 Forest plot graph comparing warfarin with aspirin **Fig. 2** Comparison of bleeding rates between warfarin and aspirin

that adjusted-dose warfarin was far superior to fixed-dose low-intensity warfarin plus aspirin for stroke prevention with comparable bleeding rates.

Figure 5 [5] demonstrates that adjusted-dose warfarin was associated with a relative risk reduction of 74 % compared with fixed-dose warfarin and aspirin [5].

Furthermore, adjusted-dose warfarin was not associated with any increase in the bleeding risk and with comparable

rates of major haemorrhage in both the treatment groups (refer to Fig. 6) [5].

Thus, adjusted-dose warfarin resulted in all the benefits for SPAF without any increase in major bleeding. In fact, a subgroup analysis in a high-risk cohort demonstrated that combination therapy resulted in not just a higher rate of stroke but also a higher rate of bleeding compared with adjusted-dose warfarin as shown in Fig. 7 [5].

Fig. 3 Graph showing differences in stroke rate for dual antiplatelet therapy versus warfarin

Fig. 4 Graph showing rates of major bleeding with dual antiplatelet therapy as compared with warfarin

Fig. 5 Adjusted dose warfarin associated with 74 % relative risk reduction versus fixed-dose warfarin + aspirin

Role of VKAs in Anticoagulation and the Newer Targets for Novel Antithrombotic Agents (Factor IIa and Factor Xa Inhibitors) in the Coagulation Cascade

Warfarin inhibits the synthesis of clotting factors II, VII, IX, and X, as well as the naturally occurring endogenous anticoagulant proteins C and S. The anticoagulant and antithrombotic activity of warfarin depends on the

clearance of functional clotting factors from the systemic circulation once the drug is administered.

Warfarin results in a two-thirds reduction in stroke on the basis of a meta-analysis of the randomized controlled trials. However, warfarin is grossly underused. In a relatively healthy insured population, ~55 % of eligible patients with AF received warfarin, and the rates dropped off substantially in the elderly, who have the greatest need.

Fig. 6 Comparable rates of bleeding in adjusted warfarin and combination of warfarin and aspirin group

Fig. 7 Combination results both in higher stroke and bleeding SPAF III results—high risk cohort

This low proportion of use and even greater underuse in higher-risk patients have been consistent findings across the clinical settings. In addition, not only is warfarin underused, but when it is used, it is used suboptimally.

Reasons for underuse of warfarin and inability to consistently achieve target INR, at least in part, relate to pharmacological properties of the drug, including unpredictable anticoagulant effects, genetic variability in metabolism, multiple drug and food interactions, a narrow therapeutic window, and the resulting need for inconvenient monitoring. However the INR has been reported to be in the recommended range (2.0–3.0) in almost 66 % of individuals with intracranial bleeds [6].

Oral anticoagulants with targeted action against individual coagulation factors, specifically direct factor Xa and IIa inhibitors appear to have pharmacokinetic and pharmacodynamic properties that overcome the limitations of the VKAs. Dabigatran is a direct factor IIa inhibitor, and rivaroxaban and apixaban are direct factor Xa inhibitors.

These newer agents have the potential to dramatically change the nature of oral anticoagulant therapy. In preparation for this change, clinicians need to carefully consider

the clinical trials that support the use of these agents, as well as their pharmacokinetic and pharmacodynamic characteristics, so that these agents will be used safely for appropriate indications.

Patient and Physician Values and Preferences

Patients are more concerned of developing a stroke. Doctors are more concerned about bleeding episodes, both major and minor. Laboratory reports of INR are highly variable and therefore doctors tend to under dose warfarin rather than adjust dose of warfarin to maintain the INR between 2.0 and 3.0. Doctors in India prefer to maintain their patients at an INR range between 1.6 and 2.5, as was seen in the IMPACT survey (see foot note), and then add aspirin and/or clopidogrel without realizing that this regimen only increases bleeding risk but does not decrease stroke risk.

Evaluation of stroke risk with CHADS₂ and CHA₂DS₂ VASc and of bleeding risk with HAS-BLED help doctors decide what's best for their patients in line with the evidence and guidelines. For example, per the ESC guidelines on AF management in 2010, if CHA₂DS₂VASc is 0, the recommendation is either no anti-thrombotic therapy or low dose aspirin (former preferred), if CHA₂DS₂VASc is 1, then it's either low dose aspirin or oral anti-coagulant (latter preferred), and if CHA₂DS₂VASc is ≥ 2 then it's only OAC.

Early Symptoms and Signs of Bleeding When on a Newer Oral Anti-Coagulant

One should look out for signs and symptoms of anemia. One should do baseline hemoglobin estimation, and, if below 10 g/dl one should be cautious, weigh benefit to risk

ratio, and decide. One can also do an aPTT and if above 70–80 s at trough one should be cautious and perhaps withdraw the oral anti-coagulant before the bleeding becomes major.

Thrombocytopenia, history of a coagulation disorder, recent GI or intracranial hemorrhage, and moderate renal impairment are other factors which increase the risk of bleeding. When patients on warfarin have labile INR or are on and off with warfarin due to poor adherence, and are then switched to the newer oral anti-coagulants the risk of bleeding increases. Also, if patients are on low dose warfarin with an INR range below 2.0–3.0 with aspirin and/or clopidogrel for SPAF (not for concomitant IHD) and are then switched to the newer oral anti-coagulants the bleeding risk increases.

Need for Measuring Activity of Newer oral Anti-Coagulants in Clinical Practice

In contrast to warfarin which needs INR monitoring and frequent dose adjustments, one does not need to monitor INR with the factor IIa and factor Xa inhibitors. Nevertheless, if there is a need for measuring anti-factor IIa or anti-factor Xa activity, e.g., suspected overdose or non-compliance, trauma, before surgery, stroke while on the newer OACs, then one may consider measuring the activity of these new OACs.

Effect of Dabigatran on Coagulation Assays [7]

In general, higher dabigatran plasma concentrations result in prolonged clotting times, although coagulation assay tests behave differently with increasing concentrations of dabigatran.

The time curves for activated partial thromboplastin time (aPTT), prothrombin time [PT, expressed as international normalised ratio (INR)], thrombin clotting time (TT) and ecarin clotting time (ECT) values parallel the plasma concentration–time curve of dabigatran.

The maximum effect of dabigatran on clotting parameters occurs at the same time as maximal plasma concentrations, indicating that thrombin inhibition by dabigatran is a direct effect linked to the central plasma compartment.

When interpreting a coagulation assay it is essential to know when dabigatran etexilate was administered relative to the time of blood sampling. In contrast, the timing of blood sampling to drug administration is not so relevant for warfarin because of the prolonged activity of the coagulation factors arising from its long half-life (days).

Both the TT and ECT tests are highly sensitive tests for measuring the anticoagulant effects of dabigatran, each showing a linear relationship for dabigatran concentrations up to 400 ng/ml. The ECT and the thrombin time (TT) are available worldwide and especially the aPTT is a commonly used laboratory method.

In emergency situations, the aPTT and TT are the most effective qualitative methods widely available for determining the presence or absence of anticoagulant effect in patients receiving dabigatran.

The aPTT may be also useful for qualitative assessment, especially in smaller centers where alternative methods are not available. An aPTT which is >80 s at trough 10–16 h after the last dose is indicative of a high bleeding risk.

Thrombin clotting time (TCT) directly assesses the activity of thrombin. At therapeutic levels, TT is a sensitive measure of dabigatran's anticoagulant effect. But TT has not been established as a standard anticoagulant test in the clinical setting Fig. 8.

A diluted TT assay (Hemoclot® thrombin inhibitor assay), using dabigatran standards is another precise, sensitive and robust TT method suitable for the quantitative assessment of dabigatran concentrations in human citrated plasma; however, this test is still not yet commercially available outside Europe. The Hemoclot® TT assay (HYPHEN BioMed, France) is a chronometric, standardized and calibrated coagulation assay proposed for the quantitative determination of thrombin inhibitors in plasma. Calibration of the Hemoclot® assay with lyophilized dabigatran standards is the currently preferred method for the determination of clotting time in a dabigatran-treated patient—the back-calculation of dabigatran concentration is also possible. The Hemoclot® assay covers a dabigatran concentration range up to 4,000 nM, which is far beyond the maximum dabigatran plasma concentrations expected in patients. For

Fig. 8 Thrombin time versus dabigatran plasma concentration [7]

dabigatran 150 mg bid mean $C_{max,ss}$ ~ 2 h after ingestion is 175 (117–275) ng/ml and mean $C_{trough,ss}$ 10–16 h after ingestion is 91 (61–143). For dabigatran 110 mg bid mean $C_{max,ss}$ is 126 (85–200) ng/ml and mean $C_{trough,ss}$ is 65 (43–102) ng/ml. It is easy to perform; it requires a standard ball coagulometer, which is routine equipment for laboratories. CE certification (Europe) for the Hemoclot® TT assay is complete.

There are limited data on the use of activated clotting time (ACT). Prothrombin time (INR) is less sensitive than other assays and cannot be recommended. Similarly, tests of anti-factor Xa activity are being evaluated.

Evaluation of Anticoagulant Activity of Dabigatran

In emergency situations it is advisable to assess the anticoagulation status of a patient receiving dabigatran. There is a close correlation between the plasma concentration of dabigatran and the degree of anticoagulant effect. The half-life of dabigatran is 12–14 h; after this period of time, 80 % of dabigatran is renally cleared. Please be aware that in patients with renal impairment the half-life of dabigatran will be prolonged accordingly [7, 8].

Time Point of Blood Sampling

The anticoagulant response depends on the time when the blood sample was taken in relation to the last dose administered [8].

Level of Anticoagulant Activity

The most sensitive test is the TT test. A normal TT measurement indicates no clinically relevant anticoagulant effect of dabigatran [8].

In the absence of commercially available sensitive tests in India, a normal activated partial thromboplastin time (aPTT) remains the most relevant measure to assess the level of anticoagulant activity of dabigatran. A normal aPTT is indicative of no pharmacologically relevant anticoagulant activity of dabigatran.

Certain Tests are Not Recommended

Prothrombin time (INR) is not sufficiently sensitive for the evaluation of the anticoagulant activity of dabigatran. Please note: point-of-care devices for measurement of INR

have shown falsely elevated values of INR (2–4-fold false high) [8, 9].

Evaluation of Anticoagulant Activity of Rivaroxaban [10–12]

Anti-FXa activity is the test of choice to measure the anticoagulant activity of Rivaroxaban. While its unavailability is a point of concern, it's just a matter of time before this will be routinely available in most laboratories.

Prothrombin time (PT) is also a good test for this drug, can be standardized, but is dependent on the type of reagent used.

Dilute Russell viper venom test (dRVVT). Good linearity and responsiveness. Standardisation might be an issue depending on the type of phospholipids and purity of snake venom used for testing. The future will look at laboratories standardizing the ECT and dilute TT for dabigatran and PT or anti-Xa assay for rivaroxaban as recommended tests.

Special Situations with Additional Bleeding Risk Considerations

Presentation with ACS and/or Requiring PCI/Stents

As per the ESC guidelines on AF management in 2010, [13] such patients are put on aspirin and clopidogrel with warfarin for the first month if it is a bare metal stent, and for 3–6 months for drug eluting stents. During the next 6 months, one can reduce dual anti-platelet therapy to one anti-platelet agent along with warfarin, and from 1 year onwards one needs to only continue warfarin. This is because after 1 year the risk of stent thrombosis is ~ 0.5 % but the risk of stroke is still as high as it was prior to the stenting. Also, if one were to continue with the anti-platelet agent along with warfarin, this only increases the bleeding risk (~ 1.5 %). Data on use of dabigatran or the factor Xa inhibitors in this setting is awaited but it may be reasonable to presume that the same may be judiciously considered. There is no data on use of prasugrel or ticagrelor in this setting and the chances of bleeding could be higher when these newer drugs are combined with OACs. Also the guidelines below refer to the use of newer drug-eluting stents. Warfarin is also reported to have a cardioprotective effect perhaps because of its effect on inhibiting activated factor VII-tissue factor complex which stabilizes the coronary atheromatous plaque [14].

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0–2)	Elective	Bare-metal	1 month: triple therapy of VKA (INR 2.0–2.5) + aspirin $\leq$ 100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
		Drug-eluting	3 (-olimus ^a group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0–2.5) + aspirin $\leq$ 100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal/ drug-eluting	6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin $\leq$ 100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	Elective	Bare-metal ^c	2–4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin $<$ 100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
High (e.g. HAS-BLED score $\geq$ 3)	ACS	Bare-metal ^c	4 weeks triple therapy of VKA (INR 2.0–2.5) + aspirin $\leq$ 100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone

ACS acute coronary syndrome, AF atrial fibrillation, INR international normalized ratio, VKA vitamin K antagonist

Gastric protection with a proton pump inhibitor (PPI) should be considered where necessary

^a Sirolimus, everolimus, and tacrolimus

^b Combination of VKA (INR 2.0–3.0) + aspirin $\leq$ 100 mg/day (with PPI, if indicated) may be considered as an alternative

^c Drug-eluting stents should be avoided as far as possible, but, if used, consideration of more prolonged (3–6 months) triple antithrombotic therapy is necessary

Adapted from Lip et al. [61]

Acute Coronary Events and Coronary Intervention While on Dabigatran

Consideration should be given to discontinuing dabigatran in the setting of acute myocardial infarction (MI) if invasive procedures such as percutaneous coronary revascularisation or coronary artery bypass surgery are indicated. Such patients should be treated according to current clinical guidelines. If patients are candidates for thrombolysis, the aPTT, TT and ECT tests are sensitive measures of dabigatran activity and are recommended where there is a high bleeding risk, such as coronary revascularisation. Activated clotting time (ACT), which is sensitive to dabigatran in vitro may also be used, although relevant ACT prolongation has not been tested in this clinical setting. A recent study in stable coronary heart disease patients showed that a short course (3 days) of dabigatran 110 or 150 mg bid given in combination with dual antiplatelet therapy prior to elective percutaneous coronary intervention (PCI) did not provide sufficient anticoagulation

compared with unfractionated heparin (UFH) given during the procedure. At present, dabigatran should be interrupted before PCI and replaced by an alternative anticoagulant. Further studies are necessary to identify the optimal approach for patients receiving dabigatran who require PCI. If UFH or LMWH is indicated, treatment should be delayed if possible, for at least 12 h after the last dose of dabigatran or until the aPTT is less than 1.5 times the upper limit of normal (ULN). If aPTT is >1.2 and $<1.5 \times$ ULN, UFH can be started without a loading dose and LMWH can be initiated. If the aPTT is $>1.5 \times$ ULN, this should be repeated every 4 h until $<1.5 \times$ ULN at which time heparin or other anticoagulation can be started. For patients with AF on an oral anticoagulant who require PCI stenting, current guidelines advocate the use of bare metal stents rather than drug-eluting stents due to the shorter duration of triple oral therapy after the procedure (4 weeks vs. 12 months) and the associated lower potential risk of subsequent bleeding events. Triple therapy with aspirin, clopidogrel and dabigatran after revascularisation can be

given for a short period but requires close observation for bleeding events [15].

Newer OAC and Radiofrequency Ablation for Atrial Fibrillation

Thromboembolic and bleeding risks during atrial fibrillation ablation can be minimized by pre-procedural transesophageal echocardiography, optimal intra-procedural anticoagulation (maintaining ACT of 300–400 s), and use of intra-cardiac echo, irrigated catheters and access sheaths with constant heparinized saline flow. Additionally, a strategic approach to peri-procedural anticoagulation that includes continuation of warfarin, bridging with low-molecular-weight heparin (LMWH), is essential in the balance of thrombotic and hemorrhagic risks. Newer anticoagulants (direct thrombin inhibitors or anti-Xa inhibitors) have provided further options.

The use of dabigatran peri-ablation appears safe, with no evidence of thromboembolism and bleeding, in one small reported series. In a study by Winkle et al. [16] there were no pre-procedural or intra-procedural thromboembolic episodes or bleeding in patients receiving dabigatran for AF ablation. Patients were specifically instructed to halt use of dabigatran 36 h before ablation procedure. This approach presents a more suitable, best practice approach for the use of dabigatran, in this clinical setting and is in line with the label recommendations. Recent guidelines [17] on RF ablation for AF have approved the use of newer OAC—direct thrombin and factor Xa inhibitors post-ablation.

Cardioversion

Dabigatran etexilate is a viable alternative to warfarin for stroke prevention at cardioversion. This means that patients can remain on dabigatran etexilate while being cardioverted [18].

A subgroup analysis of the RE-LY® trial has investigated patients who underwent cardioversion during the study [19]. A total of 1983 cardioversions were performed in 1,270 patients during the trial and the majority of cardioversions were electric (>80 %). Efficacy (rate of stroke and systemic embolism) and safety (rate of major bleeding) within 30 days following cardioversion were assessed. Trans-oesophageal echocardiography (TEE) was performed before conversion in more patients assigned to dabigatran than in those assigned to warfarin

($P < 0.0001$ for each dose of dabigatran vs. warfarin). For patients undergoing TEE, there was no difference across the three treatment arms in the incidence of left atrial spontaneous echo contrast or left atrial appendage thrombus.

Patients discharged in normal sinus rhythm following cardioversion were similar (~90 % in all groups). Rates of stroke within 30 days of cardioversion were low and comparable across all groups. The event rate was not statistically significantly different in patients with TEE and patients without TEE prior to cardioversion.

Pre-operative

Renal function (CL _{CR} , ml/min)	Half-life (hours) ^a	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk of bleeding ^b (days)
≥80	13 (11–22)	24 h	2–4
≥50 to <80	15 (12–34)	24 h	2–4
≥30 to <50	18 (13–23)	At least 2 days (48 h)	4

Other procedures such as spinal anesthesia may also require hemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (e.g., major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy

^a Data from renal impairment study in healthy volunteers (11), geometric mean (range)

^b Types of surgery associated with a high risk of bleeding (or in major surgery where complete hemostasis may be required) include but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ

Re-Starting dabigatran

Re-initiation of dabigatran following completion of surgery depends on the nature of the surgery, the urgency for restarting thromboprophylaxis and the haemostatic state of the patient. Where wound haemostasis is satisfactory, dabigatran can generally be re-started with a single capsule (110 or 150 mg depending on the dose prescribed) 1–4 h after surgery with the usual regimen started the following day. When resuming dabigatran in a patient with renal impairment it is important to remember that there is a rapid onset of action with peak levels around 2 h which, in combination with higher peak plasma concentrations and overall exposure, may place

the patient at risk of bleeding if given too close following surgery [15].

Thrombolysis in Patients with Acute Ischaemic Stroke

In the setting of acute ischaemic stroke, intravenous administration of recombinant tissue plasminogen activator (rtPA) is proven if given to eligible patients within 4.5 h of symptom onset. Warfarin-treated patients with stroke are not considered eligible for thrombolysis unless the INR ≤ 1.7 , although an increased risk of symptomatic intracerebral haemorrhage after thrombolytic treatment has been reported even in those with subtherapeutic INR levels. The use of thrombolysis in patients receiving concurrent dabigatran or rivaroxaban or apixaban has not been studied and may increase the risk of bleeding. There are few anecdotal reports. De Smedt et al. reported successful use of rtPA in a patient 4.5 h after onset of an ischaemic stroke and 7 h after receiving dabigatran. Matute et al. reported use of tPA 15 h after dabigatran when plasma concentration of dabigatran was low and aPTT was normal, suggesting absence of anticoagulant effect, which could have favoured the absence of complications. In both of the above cases anticoagulation tests suggested a low risk of bleeding. In patients who are considered possible candidates for thrombolysis, measurement of the aPTT, TT, or ECT are appropriate initial tests. A normal result from one of these assays generally indicates that the risk of bleeding is low, although there is also the possibility that one or more doses of dabigatran may have been missed. Since the INR is insensitive to dabigatran, a recommendation based on INR is not useful. Whether thrombectomy with the Penumbra or Solitaire, revascularisation devices is possible in patients treated with dabigatran has not been evaluated but this could be an option [15].

Initiation of Dabigatran After Transient Ischaemic Attack or Ischaemic Stroke

In RE-LY, patients with transient ischaemic attack (TIA) or ischaemic stroke were excluded if the event had occurred within the previous 2 weeks. However, there is no reason to assume that dabigatran carries a higher bleeding risk than warfarin when initiated early after the event. Since dabigatran achieves full anticoagulant activity 2 h post dose it should only be commenced when the patient is suitable for full anticoagulation. In patients with a TIA, it seems reasonable that dabigatran can be started as soon as imaging tests have excluded a cerebral haemorrhage. We recommend that treatment can be initiated 3–5 days after a

mild stroke, 5–7 days after a moderate stroke and 2 weeks after a severe stroke [15].

Management of Bleeding in Acute Trauma Patients

All medications prescribed to manage blood coagulation, including warfarin, dabigatran etexilate, acetylsalicylic acid (ASA), and clopidogrel increase the risk of bleeding associated with injuries. The management of major bleeding in trauma patients treated with these medications is therefore of paramount importance and options are available to manage emergency situations.

When treating patients on dabigatran who present with trauma in the emergency room, a number of options are available to assess the degree of anticoagulation and to rapidly reverse the anticoagulation effect of dabigatran.

These options include: [9].

- Delay or discontinue treatment with dabigatran as appropriate
- Symptomatic treatment
- Mechanical compression
- Surgical intervention
- Fluid replacement and hemodynamic support
- Blood product transfusion
- Oral charcoal application (if dabigatran ingestion is <2 h before)
- Hemodialysis/Charcoal filtration

As dabigatran has a low protein binding (which is different to the other new OACs as well as to warfarin) it can additionally be removed by dialysis.

Although there is no specific antidote to reverse the anticoagulation effect of dabigatran, there are clear recommendations available on how to counteract bleeding with dabigatran. These measures should be used depending on clinical requirements, at the discretion of the treating physicians, and include the administration of blood transfusion products, prothrombin complex concentrate (PCC) and recombinant Factor VIIa.

Recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) is an approved potent procoagulant and general haemostatic agent that can initiate haemostasis at sites of bleeding by directly activating thrombin on the surface of platelets in the absence of tissue factor [20]. As a result, it has been proposed that this agent may have potential in reversing the effects of a variety of anticoagulants, including the new oral thrombin inhibitors. It has been successfully used “off-label” in patients with refractory life-threatening haemorrhage [21].

Similarly, prothrombin complex concentrates (PCC) which contains all the Vit K dependent coagulation factors has thrombogenic potential and may prove useful in restoring normal hemostasis [22]. At present, there is only experimental evidence to support the role of these hemostatic agents in reversing the anticoagulant activity of dabigatran in life threatening bleeding [15].

In case of moderate to severe bleeding with the use of dabigatran etexilate therapy, blood products, i.e., packed red cells and/or fresh frozen plasma (FFP) should be transfused depending on associated anemia or coagulopathy. FFP should be used in the dose of 10–15 ml/Kg body weight and should be preferably ABO blood group compatible. FFP prepared from units of whole blood or from plasmapheresis are therapeutically equivalent in terms of hemostasis and side-effect profile. The use of platelet concentrates may be considered where thrombocytopenia is present or long acting anti-platelet drugs have also been used.

It is also important to note that, vitamin K alone is not effective in rapidly reversing the anticoagulation effect of VKAs such as warfarin in emergency situations; even if given intravenously, it takes up to 12 h to fully reverse the anticoagulation effect of VKAs [23].

These recommendations regarding emergency or overdosing situations were established in the RE-LY® trial where a significantly lower rate of life-threatening bleedings and a numerically lower rate of fatal bleedings were observed for patients treated with dabigatran

compared to patients treated with well controlled warfarin [24, 25].

Managing Over Anti-Coagulation with Dabigatran

Dabigatran is dialysable due to its relatively low (~35 %) plasma protein binding [9]. In cases of overdose or severe bleeding, where more rapid reversal of the anticoagulant effects of dabigatran is required, haemodialysis could be effective in accelerating plasma clearance of dabigatran, especially in patients with renal impairment. This is supported by data from an open-label study, in which a single 50 mg dose of dabigatran etexilate was administered to six patients with end-stage renal failure on maintenance haemodialysis. Mean inlet- and outlet line dialysis concentrations were 12.6 and 4.4 ng/ml, respectively, at 2 h after dosing and 8.9 and 3.4 ng/ml at 4 h after dosing. Based on the mean concentration differences at the inlet- and outlet lines, the mean fraction of the drug removed by dialysis was 62 % at 2 h and 68 % at 4 h.

Administering prothrombin concentrate may also lead to removal of the clotting inhibition. In the event of an overdose or bleeding, Dabigatran administration should be halted. Depending on the type and cause of the bleeding, measures should be taken, according to the physician's evaluation that rapidly stop the bleeding and remove the clotting inhibition of dabigatran.

As with other bleeding, established symptomatic measures to stop bleeding can be used for dabigatran, such as: [9].

*Recommendation based only on limited non-clinical data, there is no experience in volunteers or patients

Similar data is awaited on reversal of over anticoagulation with factor Xa inhibitors.

Antidote to Dabigatran

There is currently no specific antidote for Dabigatran or the factor Xa inhibitors. However, there is also no antidote available for antiplatelet agents or LMWH. For VKAs there is also no fast acting reversal agent. The administration of vitamin K for the reversal of vitamin K antagonists lasts hours to days to reverse the anticoagulant effect. The relatively shorter half-life time of dabigatran compared to VKAs is of advantage as the anticoagulant effect will last much shorter.

Antibody clone 22 demonstrated the following properties:

- Highly potent and specific binding to dabigatran (K_d 30 pM)
- Binding correlated with complete inhibition of dabigatran anticoagulant activity, both in human plasma and whole blood, with an IC_{50} of 2–5 nM
- Complete inhibition of anticoagulant activity of dabigatran in ex vivo studies

The engineered antibody clone 22 showed potent and selective reversal of dabigatran anticoagulation, without affecting normal haemostasis. Clone 22 is currently under further development for use in the clinic, as a compassionate use program. It may allow rapid and specific reversal of dabigatran where required in the future.

Use of Newer oral Anticoagulants for Stroke Prevention in Patients with Chronic Kidney Disease (CKD) and AF

AF rate in patients with CKD is 10–20-fold higher than in the general population [26]. Patients with CKD compared to the general population, are at increased risk of major bleeding as well as strokes [27]. Hence the decision to recommend anticoagulation therapy for patients with AF and CKD needs special consideration of its benefit and risk. Fortunately there is high quality evidence to support the use of anticoagulation therapy in patients with AF and an eGFR as low as 30 ml/min per 1.73 m^2 who have a CHADS₂ score of ≥ 1 [28, 29].

All three trials, RE-LY, ARISTOTLE, and ROCKET-AF, evaluated the efficacy and safety of oral anticoagulant therapy in patients with stage 3 CKD (eGFR 30–59 ml/min) in subgroup analysis. The three newer agents were compared with warfarin for prevention of stroke and systemic embolism. Dabigatran was found to be superior to

warfarin at a 150 mg dose and non-inferior at 110 mg dose in RE-LY. Apixaban at 5 mg twice daily was superior to warfarin in ARISTOTLE. Rivaroxaban at 20 mg once daily was non-inferior to warfarin. Hence in this group of CKD patients in whom oral anticoagulation therapy is considered, one of the newer agents should be preferred over warfarin.

For patients with AF and stage 4 CKD (eGFR 15–29 ml/min per 1.73 m^2) or stage 5 CKD (eGFR less than 15 ml/min per 1.73 m^2) in whom anticoagulation is considered warfarin is preferred over the newer anticoagulants. This is based mainly on the wide clinical experience with warfarin use, as all good clinical trials done so far have a very small number of patients with AF and CKD stage 4 and 5. This group of patients was entirely excluded from all the three randomized trials with newer anticoagulants. The starting dose of warfarin should be 2.5 mg daily with more frequent monitoring of INR for patients in this group as the bleeding risk is higher.

Renal excretion of apixaban is 25 % and that of rivaroxaban and dabigatran is 66 % and 80 % respectively. eGFR should be checked by Cockcroft and Gault equation before starting the medication in all patients and then every 6 monthly. More frequent monitoring of eGFR is need for patients who have CKD. The recommended dose of Dabigatran is 150 mg BID in patients with a eGFR of more than 30 ml/min per 1.73 m^2 . For those with a high bleeding risk and eGFR between 30 and 50 ml/min per 1.73 m^2 , a dose of 110 mg per day should be considered. For apixaban and rivaroxaban a dose of 2.5 mg BID and 15 mg OD respectively are considered in patients with an eGFR between 30 and 50 ml/min per 1.73 m^2 . All these agents are at present are not recommended in patients with an eGFR of less than 30 ml/min per 1.73 m^2 .

While switching from warfarin to dabigatran one should stop warfarin and measure INR on a daily basis. As soon as INR is below 2.0 start dabigatran. When converting from dabigatran to warfarin, adjust the starting time of warfarin based on eGFR as follows: for eGFR >50 ml/min per 1.73 m^2 , start warfarin 3 days before discontinuing dabigatran; for eGFR 31–50 ml/min per 1.73 m^2 , start warfarin 2 days before discontinuing dabigatran. Those patients currently receiving a parenteral anticoagulant (intravenous unfractionated heparin) who are to be switched over to dabigatran, start dabigatran 0–2 h before the due time for the next dose of the parenteral drug. For patients currently taking dabigatran, wait for 12 h (eGFR ≥ 30 ml/min per 1.73 m^2) to 24 h (eGFR <30 ml/min per 1.73 m^2) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant. Data for switching from warfarin and heparin/LMWH to the factor Xa inhibitors and vice versa is not yet available.

Drug Interactions with Newer OACs

Newer OACs have much lower potential of drug–drug interactions as compared to warfarin.

Dabigatran does not interact with the cytochrome P450 system. The main clinically relevant interaction is with drugs that inhibit the P-gp efflux transporter as the prodrug (dabigatran etexilate) is a substrate. Thus, plasma concentrations of dabigatran are increased when given with strong P-gp inhibitors such as amiodarone, verapamil and ketoconazole, and reduced when given with potent inducers such as rifampicin, carbamazepine or phenytoin. Data from RE-LY indicate that co-administration of P-gp inhibitors (mainly amiodarone or verapamil) resulted in modest increases in dabigatran plasma concentrations (12 % overall increase) compared with that observed in healthy volunteer studies. Further, the combination of P-gp inhibitors with dabigatran did not influence the overall benefits of dabigatran for stroke prevention, major bleeding events or intracranial haemorrhage relative to warfarin. In view of the relatively small increases in exposure, dose modification is not required when dabigatran is administered with amiodarone or quinidine. Co-prescription with a PPI such as pantoprazole may slightly reduce dabigatran exposure and peak concentrations although these effects are not likely to reduce the efficacy of dabigatran. In RE-LY, use of PPIs decreased exposure by 12.5 % with no impact on efficacy outcomes. Caution is recommended if considering co-administration of dabigatran with other anticoagulants or antiplatelet agents due to the increased risk of bleeding. Among patients receiving concomitant aspirin or clopidogrel in RE-LY, there was an increased risk of major bleeding (HR 1.76, 95 % CI 1.55–2.00), which was similar for dabigatran 110, 150 mg or warfarin. Data are lacking concerning the use of dabigatran in conjunction with new antiplatelet treatments such as prasugrel and ticagrelor [15].

The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP 3A4 and P-gp. Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution. Co-administration of rivaroxaban with the strong CYP 3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP 3A4 inducers [e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort (*hypericum perforatum*)] may also lead to reduced rivaroxaban plasma concentrations. Strong CYP 3A4 inducers should be co-administered with caution [30].

Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP 3A4 and P-gp, led to a twofold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban C_{max} . The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir). After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg single dose), an additive effect on anti-Factor Xa activity was observed. Due to an increased bleeding risk, care is to be taken if patients are treated concomitantly with any other anticoagulants apixaban should be used with caution when co-administered with NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, acetylsalicylic acid and clopidogrel in a clinical study in patients with acute coronary syndrome. Agents associated with serious bleeding are not recommended concomitantly with apixaban such as: unfractionated heparins and heparin derivatives (including low molecular weight heparins (LMWH)) [31].

Perspective on Newer Oral Anticoagulants

The randomized evaluation of Long-term anticoagulation therapy (RE-LY) trial, a prospective randomized open-label, blinded endpoint (PROBE) design, which included 18,113 patients with AF (578 of which were from India) and at least 1 risk factor for stroke, demonstrated that dabigatran is safe and effective compared with warfarin. Warfarin was used with an INR target of 2.0–3.0, which was achieved 64 % of the time in the trial on an average (49 % in India). Two doses of dabigatran (110 and 150 mg twice daily) were studied. Although it was a non-inferiority trial, dabigatran 150 mg not only met the NI margin but was also shown to be superior to well controlled warfarin in reducing the incidence of ischemic (25 %) and hemorrhagic (74 %) stroke and systemic embolism by 35 % ($P < 0.001$) with no significant difference in major bleeding. Dabigatran 150 and 110 mg were superior to well controlled warfarin in reducing the risk of intracranial bleeding by 59 and 70 % respectively. Dabigatran 150 mg was also superior to well controlled warfarin in reducing life-threatening bleeding by 20 % and vascular mortality by 15 %. Dabigatran 110 mg was non-inferior to warfarin in preventing stroke and systemic embolism and was associated with a 20 % relative risk reduction in major bleeding compared with warfarin ($P < 0.003$). Dyspepsia was more common with dabigatran (11.8 % of patients

with 110 mg and 11.3 % of patients with 150 mg compared with 5.8 % with warfarin; $P < 0.001$ for both) [24, 25].

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, randomized comparison of rivaroxaban 20 mg once daily (with dose adjustment for renal function) versus dose-adjusted warfarin (INR target between 2.0 and 3.0, which was achieved on an average 55 % of the time). The trial targeted high-risk patients with a CHADS₂ score of ≥ 2 , and approximately half had history of prior stroke. There was a 12 % relative risk reduction in the occurrence of stroke and systemic embolism in AF patients treated with rivaroxaban that did not reach statistical significance and it was non-inferior to warfarin. The rates of bleeding and adverse events were similar. In terms of major bleeding there was a significant increase in the drop in hemoglobin by ≥ 2 g/dl ($P = 0.019$) and in the need for transfusion ($P = 0.044$) but this was offset by the significant decrease in critical organ bleeding ($P = 0.007$) and bleeding causing death ($P = 0.003$). There were significant reductions in intracranial hemorrhage [32].

The ARISTOTLE trial compared apixaban with warfarin for the prevention of stroke and systemic embolism in patients with AF and at least 1 additional risk factor for stroke. Compared with warfarin, apixaban reduced stroke (49 % hemorrhagic stroke; 8 % ischemic stroke—not significant) and systemic embolism by 21 % ($P < 0.01$), resulted in 31 % less major bleeding ($P < 0.001$), and resulted in 11 % lower all-cause mortality ($P < 0.047$), although in terms of vascular mortality the difference was not statistically significant. Apixaban was better tolerated than warfarin, with fewer drug discontinuations [33].

Please note that the three trials had different designs, different patient populations, and bleeding definitions were different; therefore they cannot be compared directly. However it is unlikely that head to head, well designed, appropriately powered studies may be available in the near future.

Newer OACs Versus Warfarin

New data on the efficacy and safety of the oral factor Xa inhibitors, rivaroxaban and apixaban, in comparison to warfarin for stroke prevention in AF, as well as information on their clinical pharmacology, are available. In addition to these long-term benefits, the shorter half-life of direct thrombin or factor Xa antagonists compared to VKA suggests that the management of bleeding complications and the antithrombotic regimen during operations and invasive

procedures could become simpler with those substances than with VKA. A remaining concern would still be the lack of a specific antidote for these new drugs. One recent small trial in 12 healthy subjects found that the use of PCC 50 IU/kg (Cofact) immediately and completely reversed the anticoagulant effect seen with rivaroxaban (as measured by prothrombin time, endogenous thrombin potential), and both PCC and recombinant factor VII have been shown to be effective in cases of over anticoagulation with dabigatran.

Warfarin is not renally excreted and can be given to patients with CrCl < 30 ml/min, who are contraindicated for the newer oral anticoagulants. It has a long biological half-life and even if a patient misses a dose, it still confers protection. It is dosed once daily which is convenient and facilitates compliance. In rheumatic valvular heart disease with AF and in those AF patients with mechanical heart valves, currently only warfarin should be used since there is no data on the newer OACs in this setting. Warfarin's acquisition cost in India will be lower than that of the newer oral anticoagulants. Warfarin's MOA makes it cardioprotective. Inhibition of factor VIIa and tissue factor complex helps stabilize coronary atherosclerotic plaques.

Disclaimer This document is based, where possible, on available scientific literature, and existing guidelines on newer oral anticoagulants (OACs) that are approved and available in India (dabigatran etexilate) for stroke prevention in atrial fibrillation. At the current moment both rivaroxaban and apixaban have not yet been approved for SPAF in India. An update will follow when in-depth information on the use of other newer oral anticoagulants becomes available. Some advice is, however, based on clinical experience and extrapolation of existing knowledge about the coagulation system and anticoagulant drugs. This guide should therefore not be considered as a formal recommendation but as the provision of pragmatic advice for the use of vitamin K antagonists (VKAs) or newer OACs in daily practice. It is possible that the content of this document does not apply to individual cases or circumstances. The authors cannot be held liable for the outcomes resulting from this guidance. These guidelines will be reviewed with the emerging data on the other newer agents as and when they will become approved for SPAF.

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