

DRUG CORNER

Dabigatran – the First Approved DTI for SPAF

Abhijit Trailokya¹, JS Hiremath²**Abstract**

Atrial fibrillation (AF) is commonly occurring arrhythmia in clinical practice. AF is easy to recognize but difficult to treat. Stroke is the most devastating complication of AF and is associated with a huge disease burden on the society. Effective stroke prevention is a priority for patients with AF. Two-thirds of strokes due to AF are preventable with suitable anticoagulant therapy. VKA like warfarin, acenocoumarol remains the gold standard for stroke prevention in AF (SPAF). However, it is associated with numerous limitations such as a high risk of drug-drug, drug-food interactions and need for frequent PT/INR monitoring. Dabigatran etexilate is a selective, specific, reversible direct thrombin inhibitor that has been approved in United States, European countries and in India for SPAF and primary venous thromboembolism prevention and treatment. The efficacy and safety of dabigatran in AF has been established the "Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY)", a randomized clinical trial. As per RE-LY trial 150-mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism, and the 110-mg dose was superior to warfarin with respect to major bleeding. The adverse event profile of dabigatran etexilate was generally similar to that of warfarin in the RE-LY study, except for the incidence of dyspepsia. Dabigatran has edge over VKAs like warfarin and acenocoumarol including predictable pharmacokinetic and pharmacodynamic profile, minimal drug-drug and no drug-food interactions while no monitoring is needed. Dosing schedule is dabigatran 150mg BID patients with normal renal function. 110 mg BID is specifically for elderly patients above 80 years and over, as well as for patients at an increased risk of bleeding and in renal impairment CrCL 15-30 mL/min dosing is 75mg twice daily. Dabigatran is only NOAC with approved specific reversal agent.

Introduction

Atrial fibrillation (AF) is commonly occurring arrhythmia in clinical practice accounts 1/3 of hospital admissions for cardiac rhythm disturbances. AF is easy to recognize but difficult to treat. The consequences of AF have been clearly established in multiple large observational cohort studies and include increased stroke and systemic embolism rates if no oral anticoagulation is prescribed, with increased morbidity and mortality. The estimated number of individuals with AF globally in 2010, was 33.5 million (20.9 million men and 12.6 million women) with significant regional variations and heterogeneity. Mortality associated with AF was increased by 2-fold in both genders from 1990 to 2010.¹ AF does occur in

isolation, but also commonly seen in association with cardiovascular disease like hypertension, sleep apnoea, diabetes and obesity. Stroke is a very common and serious complication of atrial fibrillation (AF), which is the utmost prevalent clinically significant cardiac arrhythmia.² Effective stroke prevention can be done by means of anticoagulation therapy is very important.

AF-related Stroke Is Preventable

AF is the most common cardiac arrhythmia and is associated with increased risk of stroke, heart failure,

hospitalization and death. AF is the main contributor for stroke in elderly. Therefore it is important to actively screen patients for AF.³ Effective stroke prevention is a priority for patients with AF.⁴ Two-thirds of strokes due to AF are preventable with suitable anticoagulant therapy. A meta-analysis of 29 trials in 28,044 patients showed that the vitamin K antagonist (VKA) warfarin reduces the risk of stroke and all-cause mortality. 64% reduction in stroke and 24% reduction in all-cause mortality compared with placebo. Aspirin also reduced the risk of stroke, but less effectively than warfarin (19% reduction compared with placebo).⁵ But Warfarin is used in only 55% of the Eligible Patients with AF. Underuse of warfarin is greatest in elderly patients who are at the highest risk of stroke. About 60% of patients never get VKA, around half of patients who do get it stop taking it especially in the developing world, and of those who still take it only half are in therapeutic range. So, only a small minority are well treated.⁶

The GARFIELD registry, a study of 19 countries in 2009–2011, discovered that 38.0% of patients with high risk of stroke had not received anticoagulant therapy, whereas 42.5% of those at low risk (score 0) did.⁷ The PINNACLE Study in the United States found that less than half of high-risk patients were receiving OACs therapy.

Vitamin K Antagonist Usage in India

India the two most common VKAs are warfarin and acenocoumarol. Successful anticoagulation with VKAs requires to maintained PT/ INR within recommended range and required regular INR monitoring with dosage adjustment. Nevertheless, several

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places in India lack laboratories with standardized measurement of prothrombin time (PT)/INR. One of the retrospective study conducted in India, Out of a total of 1631 PT ratios and INRs recorded, only 17.8% were in the therapeutic range.⁸ In India there are different dietary habits are more prone for VKAs (warfarin and acenocoumarol) food interactions. Green leafy vegetables, cauliflower, cabbage and other foods rich with vitamin K in the Indian diet cause lability in INR values and extremely challenging in maintaining PT/INR in required range. Over the counter medications may also alter INR values and result in under or over anticoagulation. NOACs like dabigatran may overcome the challenges associated with VKAs and improve patient's outcome provided if it is available in economical coast.

Challenges Associated with VKAs

Complications, Compliance, convenience, confidence, convenience and cost are the five Cs of anticoagulation, plays an important role in the anticoagulation management.⁹

Vitamin K antagonists are widely used oral anticoagulants worldwide¹⁰. Oral vitamin K antagonists (VKAs) such as acenocoumarol and warfarin have long been the mainstay of stroke prevention in patients with atrial fibrillation (AF). Nevertheless, the use of warfarin and acenocoumarol in clinical practice is challenging due to problems such as drug-drug and drug-food interactions, a narrow therapeutic index and unpredictable anticoagulant effects, all of which result in the need for regular laboratory monitoring. So there is need to develop an effective oral anticoagulant with reliable pharmacokinetic profile so can be taken as fixed daily dosage, regardless of patient's weight, age, ethnicity or gender. It would be in preventing thromboembolic episodes with good safety profile. It should have no or less interactions with commonly taken medicines and food. An anticoagulant with above mentioned properties would be easy for patients to on long term basis with no need for dosage titration with regular monitoring. These are the objectives behind developing NOACs. NOACs available in India till date are Dabigatran. Rivaroxaban and

apixaban. Assessment of CHA2 DS2 VAS and HAS-BLED scores for stroke and bleeding risk is indicated in patient and guides anticoagulation therapy.

Dabigatran Etexilte

Dabigatran etexilate is indicated for the prevention of stroke and systemic embolism in patients with non-valvular AF (NVAF) and one or more risk factors. It is also indicated for treatment of VTE and prevention of recurrent VTE as well as for the primary prevention of venous thromboembolism (VTE) after total hip or knee replacement.¹¹

Dabigatran etexilate is a small molecule prodrug of dabigatran. Dabigatran is a potent, reversible and competitive direct inhibitor of thrombin, responsible for converting fibrinogen to fibrin in the coagulation cascade. Dabigatran inhibits both free and fibrin-bound thrombin, thereby preventing thrombus formation

Dabigatran Approval Status

On the basis of RE-LY trial dabigatran etexilate has been approved by USFDA and EMA as well as in many other countries worldwide, for Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age \geq 75 years; heart failure (NYHA Class \geq II); diabetes mellitus; hypertension. EMA has approved 150mg twice daily and 110 mg twice daily doses. On other hand USFDA has approved 150 mg twice daily dose and the 75mg twice daily dose in patients with severe renal impairment (creatinine clearance 15-30 ml/ min). In India dabigatran got approval for prevention of stroke, systemic embolism and reduction of vascular mortality in adult patients with atrial fibrillation on Dec 2011 for all the three strengths i.e. 75mg, 110mg and 150 mg by DCGI.¹²

Dabigatran Dosing schedule¹³

Prevention of stroke and SEE in adult patients with NVAF with one or more risk factors (SPAF). The recommended daily dose of Dabigatran is 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term.

For the following groups the recommended daily dose of Dabigatran

is 220 mg taken as one 110 mg capsule twice daily: Patients aged 80 years or above and Patients who receive concomitant verapamil

For the following groups the daily dose of Dabigatran of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding: Patients between 75-80 years, Patients with moderate renal impairment, Patients with gastritis, esophagitis or gastroesophageal reflux, other patients at increased risk of bleeding.

Premature discontinuation of oral anticoagulant, like Dabigatran, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events.

Missed dose of Dabigatran¹¹ If patient miss a dose of dabigatran, he can take it as soon as he remember. If patient's next dose is less than 6 hours away, skip the missed dose. Do not take two doses of dabigatran at the same time.

Pharmacokinetic profile of dabigatran¹¹

A	Absorption: Rapid Bioavailability: 3-7% (approx. 6.5 %) and remains relatively static under fast or fed conditions. Predictable pharmacokinetic profile with low-inter and intra- individual variability
B	Plasma concentration of dabigatran peaks within 1h (delayed 2hrs by food). Half-life elimination: 12-17 hours T max: 2 hrs. (in healthy subjects)
C	Metabolized by microsomal carboxylesterases to active drug dabigatran in the liver. Does not affect CYP activity
D	Approx. 85% renal

Dabigatran in Renal Impairment

As per USFDA labelling the dosage of Dabigatran 150 mg twice daily for patients with CrCL >30 mL/min and for patients with CrCL 15-30 mL/min it is 75 mg orally, twice daily. For CrCL <15 mL/min, no recommendations can be made. As per European regulation Dabigatran is contraindicated in Patients with severe renal impairment (CrCL < 30 mL/min).¹¹

Renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with dabigatran to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min). Renal function should

be assessed during treatment with dabigatran at least once a year or more frequently as needed.¹¹

Hepatic impairment: The pharmacokinetics and pharmacodynamics of dabigatran were not affected by moderate (Child-Pugh class B) hepatic impairment following a single oral dose of dabigatran etexilate 150 mg. Dabigatran is contraindicated in hepatic impairment or liver disease expected to have any impact on survival.¹¹

Contraindication¹¹

Dabigatran is contraindicated in patients with active pathological bleeding, History of a serious hypersensitivity reaction to Dabigatran and Mechanical prosthetic heart valve.

Recommendations for discontinuation of dabigatran etexilate before elective invasive or surgical procedures¹¹

Renal function (CrCL in mL/min)	half-life (hours)	Dabigatran should be stopped prior to elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50 < 80	~ 15	2-3 days before	1-2 days before
≥ 30 < 50	~ 18	4 days before	2-3 days before (> 48 hours)

Types of surgery associated with a high risk of bleeding (or major surgery where complete haemostasis may be required), including, but not limited to, cardiac surgery, neurosurgery, abdominal surgery or surgeries involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function

Recommendations for Converting to or from other Oral or Parenteral Anticoagulants¹¹

Converting from or to Warfarin

When converting patients from warfarin therapy to Dabigatran, discontinue warfarin and start Dabigatran when the INR is below 2.0.

For CrCL ≥50 mL/min, start warfarin 3 days before discontinuing Dabigatran
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For CrCL 30-50 mL/min, start warfarin 2 days before discontinuing Dabigatran
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For CrCL 15-30 mL/min, start warfarin 1 day before discontinuing Dabigatran

For CrCL <15 mL/min, no recommendations can be made.
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Converting from oral to Parenteral Anticoagulants¹¹

For patients currently receiving a parenteral anticoagulant, start Dabigatran 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking Dabigatran, wait 12 hours (CrCL ≥30 mL/min) or 24 hours (CrCL <30 mL/min) after the last dose of Dabigatran before initiating treatment with a parenteral anticoagulant

Patients can stay on Dabigatran while being cardioverted.

Drug Interactions¹¹

Dabigatran etexilate is a substrate for P-glycoprotein (P-gp), there is potential for interaction when it is co-administered with P-gp inhibitors or inducers. Concomitant use of Ketoconazole, Dronedarone, Itraconazole, cyclosporine with dabigatran are contraindicated. Concomitant use of Tacrolimus with dabigatran is not recommended. Cautions to be exercised in case concomitant use with Verapamil, Amiodarone, Quinidine, Clarithromycin, Ticagrelor and Posaconazole.

Co-administration of dabigatran etexilate with P-gp inducers [e.g. phenytoin, rifampicin, carbamazepine, hypericum (St John's wort)] should be avoided. There is no change in dabigatran exposure when dabigatran is co-administered with the P-gp substrate digoxin.

The concomitant use of other oral or parenteral anticoagulants increases major bleeding rates with both dabigatran etexilate by approximately 2.5-fold, mainly related to situations when switching from one anticoagulant to another. Furthermore, concomitant use of anti-platelets, ASA or clopidogrel approximately doubled major bleeding rates with both dabigatran etexilate. UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

When dabigatran was co-administered with pantoprazole, a decrease in the dabigatran AUC of approximately 30 % was observed. Proton-pump inhibitors (PPI) like pantoprazole were co-administered with dabigatran in clinical trials, and concomitant PPI treatment did not appear to reduce the efficacy of dabigatran. Ranitidine administration together with dabigatran had no clinically relevant effect on the extent of absorption of dabigatran.

Pregnancy: Dabigatran category C. Breast-feeding should be discontinued during treatment with Dabigatran. No human data available on fertility.

Common adverse events with dabigatran: Increased Risk of Thrombotic Events after Premature Discontinuation, Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves and Dyspepsia.

Dabigatran prolongs the thrombin time (TT), ECT, and aPTT.

Antidote for Dabigatran

A specific reversal agent (idarucizumab) is available when reversal of the anticoagulant effect of dabigatran is needed: For emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding. On October 2015, the U.S. FDA approved idarucizumab (Praxbind), a monoclonal antibody fragment that binds tightly to dabigatran and nullifies its anticoagulant activity.

Clinical Development of Dabigatran

PETRO Study: Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with non-valvular atrial fibrillation

This was the first evaluation of dabigatran, in patients with atrial fibrillation (AF). Patients (n = 502) were randomized to receive blinded doses of 50-, 150-, or 300-mg dabigatran twice daily alone or combined with 81- or 325-mg aspirin or open-label warfarin administered to achieve an international normalized ratio of 2 to 3 for 12 weeks.

Long-Term Open Label Extension of the Prevention of Embolic and Thrombotic Events on Dabigatran in Atrial Fibrillation (PETRO- Ex study):¹⁴

The results of Prevention of Embolic

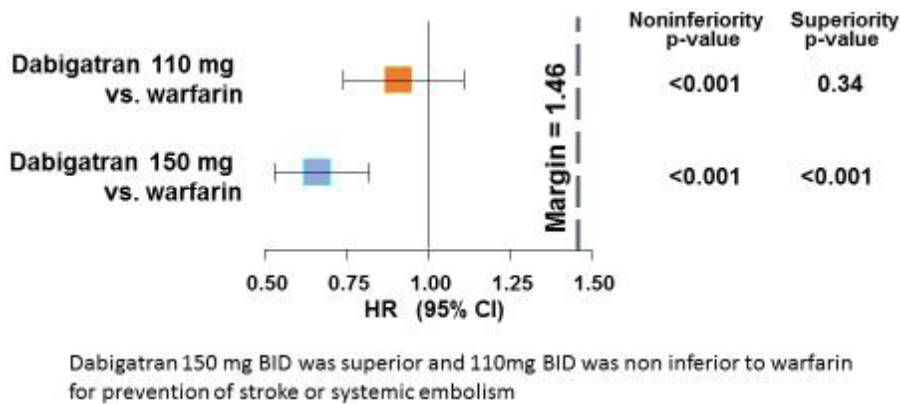


Fig. 1: RE-LY study, primary outcome: stroke or systemic embolism

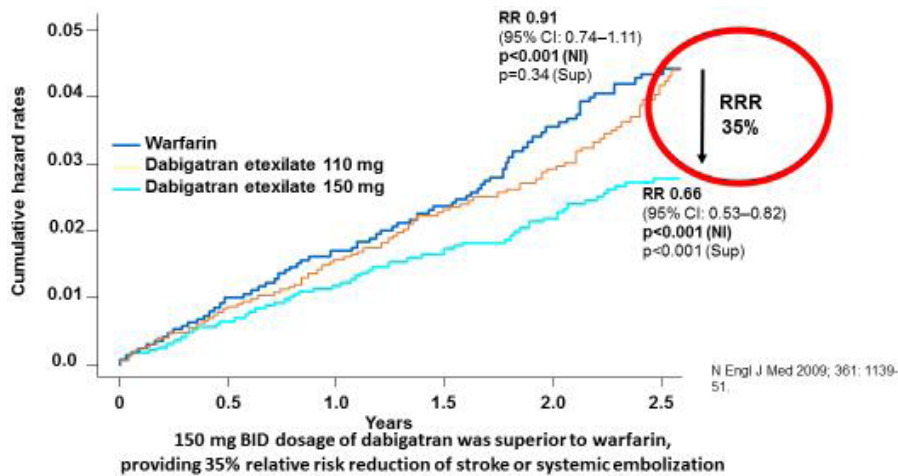


Fig. 2: RE-LY study, primary outcome: stroke or systemic embolism

and Thrombotic events in patients with persistent atrial fibrillation-Extension (PETRO-Ex) trial, an extension of the 3-month PETRO study, also showed that 50 mg twice-daily and 150-mg daily doses of dabigatran etexilate were not effective and that the 300-mg twice daily dose resulted in high major bleed rate. No serious liver toxicity was observed. PETRO- Ex study, suggests that 150 mg twice daily is an appropriate dose for further study in the prevention of stroke in high-risk patients with atrial fibrillation because Thromboembolic event rates were lowest in the dabigatran 150 and 300 mg BID groups.¹⁵ Major bleeding was most frequent in the 300 mg BID group. No significant liver function abnormalities were noted in any of the dabigatran groups.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)¹⁶

RE-LY trial is the randomized, double-blind phase III trial evaluated the efficacy and safety profile of

dabigatran (110 or 150 mg twice a day) on 18113 patients, compared to warfarin. The median length of the follow-up period was 2 years. The primary efficacy outcome was stroke or systemic embolism. The primary safety outcome was a major haemorrhage. Stroke or systemic embolism had a rate of 1.53% per year in the group of dabigatran 110 mg twice a day, and 1.11% per year in the group of dabigatran 150 mg twice a day (Figure 1). Both doses of dabigatran were non-inferior to warfarin ($p < 0.001$). For the prevention of thrombotic events, the dose of 150 mg was superior to warfarin (relative risk 0.66, 95% CI, 0.53-0.82, $p < 0.001$), whereas the dose of 110 mg was not (relative risk 0.91, 95% CI, 0.74-1.11, $p = 0.34$) (Figure 2). In contrast, the rate of major bleeding was 3.36% per year in the warfarin group, while it was 3.11% per year in the 150 mg dabigatran group (relative risk of 0.93, CI 95%, 0.81-1.07, $p = 0.31$) and 2.71% per year in the 110 mg dabigatran group (relative risk of 0.8, CI 95%, 0.69-0.93, $p = 0.003$). Incidence

of Dyspepsia with Dabigatran 110mg was 11.8% and with 150mg it is 11.3% as compared to warfarin which was 5.8%. The mean proportion of time in which the INR was within the therapeutic range was 64%.

RELY-ABLE Extension Study

RELY-ABLE (Long Term Multi-Center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) was designed to provide additional information on the long-term effects of the two doses of dabigatran etexilate in patients who had completed RE-LY.

In RELYABLE study, 5851 patients continued to receive the same dosage of dabigatran etexilate during more than 28 months of additional treatment (total mean follow-up 4.3 years). The rate of stroke and systemic embolism was 1.46% per year with dabigatran etexilate 150 mg twice daily and 1.60% per year with dabigatran etexilate 110 mg twice daily [hazard ratio (HR) 0.91; 95% CI 0.69-1.20]. Rates of other ischaemic and thrombotic outcomes, including net clinical benefit, were also not significantly different between the two dabigatran groups.¹⁷

Guidelines Recommendations¹⁸

Current ESC 2016 guidelines on AF says when oral anticoagulation is initiated in patients with AF who is eligible for NOAC (Dabigatran, apixaban, rivaroxaban), a NOAC is recommended in preference to VKAs(warfarin, acenocoumarol) – it has class I level A evidence.

Dabigatran Vs acenocoumarol¹⁹

Observational study done by Jennie Korenstra et al. In total, 920 consecutive AF patients were enrolled (478 acenocoumarol, 442 dabigatran), of which 2×383 were available for analysis after propensity score matching. Mean follow-up duration was 1.5+0.56 year. The mean calculated stroke risk according to the CHA2DS2-VASc score was 3.5%/year in dabigatran vs. 3.7%/year acenocoumarol-treated patients. The actual incidence rate of stroke or systemic embolism was 0.8%/year [95% confidence interval (CI): 0.2-2.1] vs. 1.0%/year (95% CI: 0.4-2.1), respectively. Multivariable analysis confirmed this lower but non-significant risk in dabigatran vs. acenocoumarol after adjustment for

Table 1: Selected patient features and results from pivotal phase 3 trials of 3 new anticoagulants²⁶

Features and results	Dabigatran 110 mg	Dabigatran 150 mg	Rivaroxaban 20 mg	Apixaban 5 mg
Patients, N	6015	6076	7131	9120
Age, years	71.4 (Mean)	71.5 (Mean)	73 (Median)	70 (Median)
CHADS2 score, mean	2.1	2.2	3.5	2.1
Median follow-up, years	2	2	1.9	1.8
TTR (%), mean	64	64	55	62
Primary end point	Non-inferior	Superior	Non-inferior	Superior
Ischemic stroke	Non-inferior	Superior	Non-inferior	Non-inferior
Hemorrhagic stroke	Superior	Superior	Superior	Superior
Intracranial bleeding	Superior	Superior	Superior	Superior
Any bleeding	Superior	Superior	Non-inferior	Superior

To date, a direct comparison of commercially available NOACs in a prospective head-to-head trial has not been performed. Results refer to doses compared head-to-head with warfarin in each trial. All trials had stroke or systemic embolism as a primary end point. TTR time in therapeutic range (for warfarin arms of corresponding trial)

the CHA2DS2-VASc score [hazard ratio (HR) dabigatran ¼ 0.72, 95% CI: 0.20–2.63, P ¼ 0.61]. According to the HAS-BLED score, the mean calculated bleeding risk was 1.7%/year in both groups. Actual incidence rate of major bleeding was 2.1%/year (95% CI: 1.0–3.8) in the dabigatran vs. 4.3%/year (95% CI: 2.9–6.2) in acenocoumarol. This over 50% reduction remained significant after adjustment for the HAS-BLED score (HR dabigatran ¼ 0.45, 95% CI: 0.22–0.93, P ¼ 0.031). Authors concluded that in ‘real-world’ patients with AF, dabigatran appears to be as effective, but significantly safer than acenocoumarol.

A retrospective observational study of patients prescribed dabigatran between 2010 and 2013 conducted by Yap LB et. al. Data was available for 510 patients: median age 68 years (range 20–91) This showed that patients frequently preferred the dabigatran due to convenience when given a choice to switch from warfarin. Reassuringly, they found that there cohort had a low rate of rate of ischaemic stroke, low rates of side effects and bleeding with the drug.²⁰

The major advantages of dabigatran over vitamin K antagonists (VKA) like acenocoumarol and warfarin are: the absence of periodic laboratory analysis i.e. PT/INR monitoring, the low extent of dietary and drug interactions and the favourable efficacy and safety profile, which may decrease the rate of clinical complications because of vitamin K inhibitors in selected patients.²¹

Comparison with other NOACs

Large scale head to head randomized comparative studies among available NOACs are not available till date. In all

the trials NOACs had been compared with warfarin (Table 1). In ROCKET AF trial Rivaroxaban did not demonstrate superiority of rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism, with a similar rate of major bleeding and a substantial reduction in intracranial haemorrhage.²² In ARISTOTLE, apixaban reduced the risk of stroke or systemic embolism by 21% compared with warfarin (1.27% vs 1.60% per year; hazard ratio, 0.79; 95% confidence interval, 0.66–0.95). The reduction was significant and demonstrated the superiority of apixaban over warfarin for the primary outcome of preventing stroke or systemic embolism (P = 0.01 for superiority). Apixaban also reduced all-cause mortality by 11% (P = 0.047) and major bleeding by 31% (P < 0.001) compared with warfarin.²³ In the RE-LY trial, dabigatran was shown to have superior safety with equivalent efficacy (when it was administered at a dose of 110 mg twice daily) or superior efficacy with similar safety (when it was administered at a dose of 150 mg twice daily) for stroke and systemic embolism.²⁴ Stroke or systemic embolism had a rate of 1.53% per year in the group of dabigatran 110 mg twice a day, and 1.11% per year in the group of dabigatran 150 mg twice a day. Dabigatran etexilate 150 mg twice daily was significantly (p < 0.001) more effective at preventing stroke and systemic embolism than warfarin (relative risk reduction of 35%) (Figure 2).²⁵

Summary

Dabigatran, is a potent, competitive and reversible direct thrombin inhibitor.

It is the first of the oral anti-thrombin agents; hence it has the largest and longest experience. The Patients with NVAf, dabigatran etexilate 150 mg twice daily is more effective than warfarin for the prevention of stroke and systemic embolism, without an increase in the risk of major bleeding. Dabigatran etexilate has a rapid onset of action, relatively few drug interactions and no requirement for routine laboratory monitoring. In addition, an approved specific reversal agent is available. Dabigatran can be a useful alternative in patients who have had challenges with vitamin K antagonists (ischaemic strokes or bleeding complications), fluctuant INR, and who have difficulty in regular monitoring and to avoid chances of drug-drug and drug-food interactions. Dosing schedule is dabigatran 150mg BID patients with normal renal function 110 mg BID is specifically for elderly patients above 80 years and over, as well as for patients at an increased risk of bleeding and in renal impairment CrCL 15–30 mL/min dosing is 75mg twice daily. Dabigatran 150 mg twice daily was significantly (p < 0.001) more effective at preventing stroke and systemic embolism than warfarin (relative risk reduction of 35%). dabigatran etexilate 150 mg twice daily was significantly (p = 0.004) more effective than dabigatran 110 mg twice daily at preventing stroke and systemic embolism (relative risk reduction of 28%). It is more expensive than warfarin, but is more cost effective.

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