Dabigatran for stroke prevention in atrial fibrillation

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Keywords
Atrial fibrillation, anticoagulation, stroke, dabigatran, warfarin

Summary
Dabigatran is a novel direct thrombin inhibitor that has recently been approved for primary and secondary stroke prevention and prevention of systemic embolism in patients with atrial fibrillation. In the pivotal RE-LY study, dabigatran 110 mg BID was demonstrated to be associated with a stroke rate similar to that observed with warfarin (INR target 2.0 to 3.0), but with a lower rate of major haemorrhage. Dabigatran administered at a dose of 150 mg BID was significantly more effective in stroke prevention than warfarin and showed a similar rate of major hemorrhages. Of note, both dosages resulted in an approximately 60–70% relative risk reduction of haemorrhagic stroke. The dosage of 110 mg BID should be preferably used in patients aged 75–80 years or older as the rate of extracranial bleeding events tends to increase with dabigatran 150 mg BID above this age limit. In RE-LY, myocardial infarcts occurred at a very low incidence. There were numerically more myocardial infarcts in dabigatran-treated patients than in warfarin patients; however, other myocardial ischaemic events were similar in the three treatment arms.

Schlüsselwörter
Vorhofflimmern, Antikoagulation, Schlaganfall, Dabigatran, Warfarin

Zusammenfassung

Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia with a continuously increasing prevalence in Western societies due to the increasing age of the populations. AF is associated with significant morbidity and mortality, predominantly due to thromboembolic complications and heart failure.

Ischaemic stroke is the most serious and devastating complication of the arrhythmia.

Compared with sinus rhythm, AF is associated with a five-fold increased risk of ischaemic stroke which is independent of the type of AF (paroxysmal, persistent, permanent) (1, 2). Even short subclinical AF episodes carry a significantly increased risk of stroke as recently demonstrated in a large prospective trial in 2580 patients with implanted pacemakers (3).

Dose-adjusted oral anticoagulation with vitamin K antagonists is highly efficacious in reducing the risk of ischaemic stroke in AF patients (4) and was – up to recently – considered the mainstay of therapy in AF patients. However, in clinical practice only about 70% of AF patients with the indication receive stroke prevention with vitamin K antagonists (5). Reasons for this important under-use include the narrow therapeutic window with a need for regular INR monitoring, interactions with multiple drugs and diets as well as a considerable bleeding risk.

Therefore, several new thrombin antagonists and factor Xa inhibitors have been developed to improve stroke prevention strategies in AF patients. All of these novel agents can be orally administered at a fixed dose and do not require regular coagulation checks. The direct thrombin inhibitor dabigatran represents the first licensed drug in this indication. This review summarizes the present knowledge on the...
The use of dabigatran for stroke prevention in AF.

**RE-LY, the pivotal phase III dabigatran trial**

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial included 18,113 patients with AF and at least one vascular risk factor (6–8). Patients were randomized into one of three groups and treated over a median follow-up of two years with either

- warfarin (target INR 2.0–3.0),
- dabigatran 110 mg bid or
- dabigatran 150 mg bid.

Doses of dabigatran were blinded while warfarin was given open label. The primary outcome in this non-inferiority trial was a composite of stroke and systemic embolism with adjudication blinded to treatment.

The primary outcome occurred in 1.71% of patients per year in the warfarin group, compared with 1.54% per year in the 110 mg bid dabigatran group (HR 0.90, 95% CI 0.84–1.00; p = 0.03 for non-inferiority) and 1.11% in the 150 mg bid dabigatran group (HR 0.65, 95% CI 0.52–0.81; p = 0.004 for superiority) (Fig. 1a) (7, 8). Blinded adjudication of types of stroke revealed a rate of haemorrhagic stroke of 0.38% per year in the warfarin group, as compared to 0.12% and 0.10% in the 110 and 150 mg bid dabigatran groups corresponding to a relative risk reduction of 69% to 74% for dabigatran versus warfarin (p < 0.001 for both comparisons) (Fig. 1b).

Patients who were previously treated with vitamin K antagonists and anticoagulation-naive patients had a consistent benefit from dabigatran (9).

Mortality rates were 4.13% per year in the warfarin group, 3.75% per year with dabigatran 110 mg (RR 0.91, 95% CI 0.80–1.03; p = 0.13) and 3.64% per year with dabigatran 150 mg (RR 0.88, 95% CI 0.77–1.00; p = 0.05).

The primary safety outcome – major bleeding – occurred in 3.57% per year in warfarin-treated patients, in 2.87% in the 110 mg bid dabigatran group (p = 0.03 compared to warfarin) and in 3.32% per year in 150 mg bid dabigatran group (p = 0.03 compared to warfarin). Of note, intracranial bleeding rates (intracerebral, subarchnoidal and subdural haematomas) for all patients were lower in the dabigatran groups than in the warfarin group (110 mg bid dose: RR 0.30, 95% CI 0.19–0.45; 150 mg bid dose: RR 0.41, 95% CI 0.28–0.60, p < 0.001 superior to warfarin for both dabigatran doses) (7, 8). The rate of study drug discontinuation at two years was higher in both dabigatran groups (21%) compared to warfarin (17%) mainly due to dyspepsia, nausea or diarrhea.

**RE-LY subgroup analyses**

Dabigatran treatment effects according to warfarin time in therapeutic range

The therapeutic effects of warfarin strongly depend on INR-based time in therapeutic range (TTR). Hence, the RE-LY trial results were analyzed according to center-based TTR. This subgroup analysis confirmed a correlation between the quality of oral anticoagulation with warfarin and the primary endpoint. Patients under warfarin whose INR was well maintained within the therapeutic window (INR 2.0–3.0) had similar stroke rates compared with patients under dabigatran but fewer intracranial bleeds. Patients with a lower time in therapeutic range showed a larger difference in outcomes between dabigatran and warfarin (10).

Dabigatran treatment effects in patients with prior stroke/TIA

An important secondary analysis concerned the subgroup of patients with a history of prior stroke or TIA who were enrolled in RE-LY (11). Regarding stroke or...
systemic embolism, a finding consistent with that seen in the main RE-LY study was found in these 3623 patients (RR, 0.84; 95% CI 0.58–1.20; for dabigatran 110 mg vs warfarin; RR, 0.75; 0.52–1.08; for dabigatran 150 mg vs warfarin).

In this subgroup, there was also an 89% and 73% relative risk reduction in the incidence of haemorrhagic stroke in the dabigatran 110 mg and dabigatran 150 mg groups, respectively, compared with warfarin. With one exception (vascular death) all interaction P values were non-significant, indicating that the results in the subgroup of patients with TIA or stroke were comparable to those in the main study. Intracranial bleeding rates were also lower in patients with prior stroke or TIA compared with warfarin (p = 0.001 for dabigatran 110 mg; p = 0.007 for dabigatran 150 mg).

Thus, the main trial findings were replicated indicating the effectiveness and safety of dabigatran in secondary stroke prevention (11).

Dabigatran-associated bleeding risk

Major bleedings occurred at similar incidences with warfarin and dabigatran 150 mg (p = 0.032) but at lower rates with dabigatran 110 mg (p = 0.002). A detailed analysis of all bleeding events in RE-LY (12) revealed a significant treatment-by-age interaction, such that dabigatran 110 mg BID compared with warfarin was associated with a lower risk of major bleeds in patients aged <75 years (1.89% versus 3.04%; p < 0.001) and a similar risk in those aged ≥75 years 4.43% versus 4.37%; p = 0.89; P for interaction < 0.001). The higher dabigatran dose compared with warfarin was associated with a lower risk of major bleeds in individuals aged <75 years (2.12% versus 3.04%; p < 0.001) and a trend towards higher risk in patients ≥75 years (5.10% versus 4.37%; p = 0.07; P for interaction < 0.001).

Importantly, this interaction with age was evident for extracranial bleeding but not for intracranial bleeding. The risk of the latter was consistently reduced with dabigatran compared with warfarin irrespective of age.

The increased extracranial bleeding rate with dabigatran 150 mg bid was predominately due to more lower gastrointestinal tract bleeding events. Based on these data, it is recommended that patients above the age of 75–80 years should be treated with the lower dose of dabigatran.

Dabigatran and myocardial ischaemic events

In studies with ximelagatran, another direct thrombin antagonist, a trend for an increased rate of myocardial infarctions was observed compared with warfarin (13, 14). In the initial publication of the RE-LY results, 86 myocardial infarctions were reported in patients on dabigatran 110 mg bid, 89 in dabigatran 150 mg bid and 63 in warfarin patients (7), which was significant (p = 0.048) only for the higher dose of dabigatran.

In a subsequent analysis performed upon request of the FDA for silent myocardial infarctions, 98 myocardial infarctions were reported under dabigatran 110 mg bid, 97 under dabigatran 150 mg bid and 75 under warfarin, which was no longer significant and corresponds to a relative risk of 1.29 or 1.27, respectively (8). However, one needs to keep in mind that the absolute risk of myocardial infarctions (like in other AF studies) was very low which is the reason why a more comprehensive analysis of all myocardial ischaemic events in RE-LY was carried out (15). Annual rates of a composite of MI, unstable angina, cardiac arrest, and cardiac death were 3.16%/year on dabigatran 110 mg, 3.33%/year on dabigatran 150 mg, and 3.41%/year on warfarin (HR versus warfarin 0.93 (95% CI 0.80–1.06; p = 0.28) for dabigatran 110 mg and 0.98 (95% CI 0.85–1.12; p = 0.77) for dabigatran 150 mg.

Events pre-specified as “net clinical benefit” (all strokes, systemic embolism, MI, PE, major bleeding, all-cause death) occurred 7.34%/year on dabigatran 110 mg, 7.11%/year on dabigatran 150 mg, and 7.91%/year on warfarin (HR 0.92 (95% CI 0.81–1.01; p = 0.09) for dabigatran 110 mg and 0.90 (95% CI 0.82–0.99; p = 0.02 for dabigatran 150 mg). Finally, the relative effects of dabigatran versus warfarin on myocardial ischaemic events were consistent in patients with or without a baseline history of MI/CAD. The conclusion from this secondary analysis was that there was a non-significant increase in MI with dabigatran compared to warfarin in RE-LY, but other myocardial ischaemic events were not increased.

In addition serious adverse events have to be put in perspective. The number of MIs (75) and intracranial bleeds (87) were almost identical in the warfarin treated groups. The absolute number of fatal MIs was increased by one in the high dose and 4 in the low dose dabigatran groups compared to warfarin. Fatal intracranial bleeds were reduced by 19 and 17 cases for the two doses of dabigatran compared to warfarin.

Dabigatran in patients with renal impairment

Approximately 75% of dabigatran is excreted via the kidneys. In RE-LY, patients with a creatinine clearance of < 30 ml/min were excluded. When the trial results were analyzed according to various levels of kidney dysfunction, there was consistency as to the efficacy and safety of dabigatran therapy across all subgroups (all p-values for interaction negative). However, close monitoring of kidney function is mandatory particularly in elderly patients.

In patients with compromised renal function (i.e. creatinine clearance 30–50 ml/min), it seems prudent to use the lower dose of dabigatran particularly when intercurrent comorbidities such as infections or loss of fluids occur.

If in this situation the aPTT rises > 80 s, dabigatran should be temporarily discontinued. Dabigatran in a dose of 110 mg or 150 mg is contraindicated in renal failure with a creatinine clearance < 30 ml/min.

Practical aspects of the use of dabigatran

Drug-drug interactions

There is an interaction of dabigatran with P-glycoprotein-inhibitors such as
• amiodarone,
• verapamil,
• cholinesterase inhibitors such as carbamazepine, decrease the bioavailability of dabigatran and therefore should be avoided.

Additionally, strong P-glycoprotein-inductors such as rifampicin or carbamazepine increase the risk of bleeding. If two antiplatelet agents are combined with oral anticoagulation ("triple therapy") the bleeding risk is further increased.

In RE-LY, there was also a significant increase in bleeding rates in patients who received warfarin plus aspirin or even warfarin plus dual antiplatelet therapy. The same pattern was observed in the dabigatran treatment arms; however, bleeding rates were lower with dabigatran plus mono- or dual antiplatelet therapy than those observed in the warfarin arm. If AF patients need to undergo coronary stenting, preferably bare metal stents should be used where a triple therapy with aspirin, clopidogrel and dabigatran is required for only 4 weeks and thereafter dual therapy with dabigatran and one antiplatelet agent for another 6–12 months (16).

Treatment of bleeding complications under dabigatran

If a major or intracranial bleeding occurs, treatment with dabigatran needs to be stopped immediately.

Due to its short half-life, the anticoagulation effects of dabigatran vanish within 24 to 48 hours, depending on kidney function.
Obviously, this is an important advantage over vitamin K antagonists and allows for elective surgical procedures within short time intervals. At present, there is no specific antidote for dabigatran. Its manufacturer is currently developing a specific neutralizing antibody but it will take some time until it will be available for clinical use.

So far, only limited experience exists in dabigatran-treated patients with a major bleeding event. A preliminary analysis of the risk of peri-operative bleeding in RE-LY demonstrated that there was no significant difference in the risk of major peri-operative major bleeding or other bleeding outcomes between patients receiving either dose of dabigatran compared to warfarin (17). Emergency treatment therefore should be performed according to local clinical practices with

- prothrombin complex concentrate,
- fresh frozen plasma or
- possibly with recombinant factor VIIa.

Factor IIa, however, is not effective in the treatment of brain haemorrhage. Dabigatran can be removed by dialysis in case of an urgent operation or surgical procedure.

Side effects

The only relevant side effects of dabigatran in the RE-LY trial were gastrointestinal complaints. Two percent of patients discontinued dabigatran due to vomiting, abdominal pain, diarrhea, or dyspepsia (18). Whether this rate can be reduced by a combination with proton pump inhibitors is currently unknown. Patients should be advised to take dabigatran together with food.

Conclusions

Dabigatran is the first of several novel anticoagulant drugs indicated for stroke prevention in AF. The RE-LY study showed that dabigatran is either more effective or safer compared with warfarin. Both doses of dabigatran are associated with large reductions in intracerebral bleeding events compared with therapy with vitamin K antagonists. Use of dabigatran is largely facilitated by its

- short half-life,
- the absence of need for coagulation monitoring, drug–drug or food interactions, and
- an acceptable side effect profile.

The drug is effective for both, primary and secondary prophylaxis of stroke in patients with AF. Patients with severely impaired renal function cannot be treated with dabigatran.

Conflict of interest

S. H. Hohnloser has received honoraria and/or grant support from companies that develop and market new antithrombotic therapies for stroke prevention in AF including Bayer, BI, BMS, Merck, Sanofi aventis, Pfizer

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