Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: Resolving uncertainties in routine practice

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Summary

Dabigatran etexilate is a new oral anticoagulant recently approved in Europe for the prevention of stroke or systemic embolism in adult patients with non-valvular atrial fibrillation (AF) and at least one risk factor for stroke. With a fast onset of action and a predictable anticoagulant effect obviating the need for coagulation monitoring, dabigatran etexilate offers practical advantages over vitamin K antagonists in clinical practice. However, clinicians may have questions about practical aspects of dabigatran etexilate use including monitoring anticoagulant efficacy, interruption for surgical or invasive procedures and management of bleeding. This review article aims to address these concerns and provide guidance on the use of dabigatran etexilate in special situations, such as acute coronary syndromes and cardiac revascularisation. In addition, cut-off values for different coagulation assay results associated with an increased risk of bleeding are given.

Keywords

Dabigatran, atrial fibrillation, oral anticoagulant, bleeding

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia (1), which if untreated is a major risk factor for stroke. Extensive evidence from randomised trials supports the value of vitamin K antagonists (VKAs) in reducing the risk of stroke by about two thirds, even among elderly AF patients, who are at higher risk (2, 3). However, practical limitations may lead to wide variation in VKA use (4), as well as patient-related issues with adherence and convenience.

Dabigatran etexilate (hereafter referred to as dabigatran) is the first oral direct thrombin inhibitor approved for the prevention of stroke and systemic embolism in patients with non-valvular AF and one or more risk factors (Fig. 1) (5, 6). The efficacy and safety profile of dabigatran, demonstrated by the RE-LY trial (7, 8) (Table 1), together with practical advantages over VKAs (see Table 1), have led to its rapid uptake in clinical practice. However, there may be some areas of uncertainty in everyday clinical practice, which this article aims to address. We focus on dosing guidelines applicable to patients treated in Europe.

Dose selection

Dabigatran is administered as a prodrug (dabigatran etexilate), which is metabolised to the active form, dabigatran. Renal excretion of unchanged dabigatran is the predominant elimination pathway, with about 80% excreted unchanged in the urine (9). The recommended dose regimen is 150 mg twice daily (bid) with or without food. However, in certain regions including Europe a reduced dose of 110 mg bid is recommended or may be considered in certain patient groups (Fig. 1), including those with moderate renal impairment (creatinine clearance [CrCL] 30–50 ml/minute [min]) or treated concomitantly with verapamil, and the elderly at higher risk of bleeding (Table 2) (5). This dose is not approved in the US (6). In Europe, dabigatran is contraindicated in patients with severe renal impairment (CrCL <30 ml/min), active clinically significant bleeding, or if concomitantly treated with certain P-glycoprotein (P-gp)-inhibitors such as systemic ketoconazole, cyclosporine, itraconazole and tacrolimus (5). In the US, a 75 mg bid dose of dabigatran is approved for use in patients with CrCL 15–30 ml/min and can be considered in patients with moderate renal impairment who are also treated with dronedarone or systemic ketoconazole (6).

Prior to commencing treatment with dabigatran, renal function should be checked in all patients and CrCL calculated using

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the Cockcroft-Gault formula (10). This represents an obvious
cchange in clinical practice for patients commencing VKAs when
international normalised ratio (INR) monitoring only is perform-
ed.

Patients should be closely monitored for signs of bleeding
throughout treatment. This is especially important in patients
with multiple risk factors for the use of dabigatran, such as elderly
patients who may have low body weight, impaired renal function
and multiple relevant concomitant medications (11). During
treatment, CrCL should be rechecked periodically as clinically in-
dicated, or if a decline in renal function is suspected (e.g. hypovol-
amia, dehydration, certain comediations).

**Switching treatment**

A potential cause for concern among clinicians is in switching pa-
tients between different anticoagulant treatments. Suggested ap-
proaches are summarised in Table 3. If switching a patient from
a VKA to dabigatran, it is advisable to monitor the INR closely and
only initiate dabigatran when the INR is less than 2.0. When con-
verting from dabigatran to VKAs, the start time of the VKA is ad-
justed according to the CrCL. This is due to the prolonged anti-
coagulant effect of dabigatran in patients with impaired renal
function. Monitoring using the activated partial thromboplastin
time (aPTT) can be useful to assess when dabigatran anticoagulant
activity is excessively high (see below).

**Monitoring anticoagulant effect**

Anticoagulant monitoring is not necessary during routine dabig-
atran treatment. However, it may be indicated in certain situations,
such as suspected overdose, emergency situations, in the perioper-
ative setting, in the event of bleeding or to identify patients at in-
creased bleeding risk due to excessive dabigatran exposure, or in
patients with progressive or severe renal dysfunction. The anti-
coagulant tests can be broadly categorised as qualitative (i.e. suit-

![Figure 1: Clinical flowchart for the use of dabigatran for stroke pre-
vention in AF (as per European prescribing guidelines) (5).][3]

*Includes
- Previous stroke, transient ischemic attack, or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, NYHA Class 2
- Age ≥75 years
- Age ≥65 years and with one of the following: diabetes mellitus,
coronary artery disease, or hypertension

AF is also associated with a high risk of bleeding (1, 56). 110 mg bid
dose recommended in patients taking verapamil, irrespective of age or renal func-
tion. 110 mg bid dose can be considered in patients with associated gastri-
ts, oesophagitis or gastroesophageal reflux, irrespective of age or renal func-
tion. CrCL, Creatinine clearance; EU, European Union; NYHA, New York Heart
Association.

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able for detection of excess anticoagulant activity) or quantitative. Guidance for cut-off values for coagulation assays indicative of increased bleeding risk is summarised in Table 4. Clinicians should be aware that a blood sample taken 2 hours (h) after dabigatran dosage (∼peak level) will have a higher result in all clotting tests compared with samples taken at 10–12 h (trough level).

The INR test is not recommended for monitoring as it is insensitive to dabigatran (12). However, it is sometimes used despite these recommendations. Recent reports have noted falsely elevated INR levels for patients on dabigatran measured using the Hemochrom® point-of-care device compared with laboratory INR testing (13, 14). It is not known whether this artifactual effect also is also observed with other point-of-care devices. This problem is the subject of further study and highlights another reason not to use INR with dabigatran.

Detection or qualitative measurement

Both the aPTT and Thrombin Time (TT) test may be useful as qualitative measures to detect an excess of anticoagulant activity (5, 12). At a dose of 150 mg bid, the aPTT is approximately twice the baseline value although there is some variability due to differ-

| Table 1: Limitations of vitamin K antagonists (VKA) in comparison with dabigatran. |
|---------------------------------|---------------------------------|
| **VKA**                         | **Dabigatran**                  |
| Onset of action                 | Slow (36 to 72 hours)           |
| Offset of action                | Long (24 to 192 hours depending on type used) |
| Dosing                          | Individualised                  |
| Monitoring                      | Required; patient adherence and convenience can be problematic |
| Food and alcohol                | Interaction                     |
| Drug interactions               | Frequent                        |
| Relative Risk (Log scale)       |                                |
| 0.2 Favours Dabigatran          |                                |
| 1.0 Relative Risk                |                                |
| 2.0 Favours Warfarin            |                                |

Figure 2: Key findings from RE-LY (7, 8). a Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. bGastrointestinal bleeding could be life threatening or non-life threatening. CI, confidence interval; yr, year.
ent test reagents (15). A trough aPTT >80 seconds (s) (or 2- to 3-fold of baseline value) is associated with a higher risk of bleeding (5, 12). The TT is a more sensitive test and is significantly raised at therapeutic doses and thus a normal TT or aPTT measurement indicates no clinically relevant anticoagulant effect of dabigatran. Once again, there is some variability depending on the coagulometer and the thrombin reagent used for the measurement.

Quantitative measurement

The calibrated Hemoclot® Thrombin Inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France) and ecarin clotting time (ECT) are more sensitive tests suitable for use in monitoring anticoagulant activity (12, 16). However, in routine practice it is more likely that the former will be available. This laboratory-based assay generally takes a similar time to perform as an aPTT test. A trough Hemoclot® thrombin inhibitor assay value of 200 ng/ml (corresponding to a test result of >65 s) is associated with a higher risk of bleeding (17). The test can be especially useful when assessing plasma concentrations and anticoagulation activity in elderly fragile patients or those with impaired renal function although further studies are required to determine the normal test result range (11).

Interruption of dabigatran before and during surgery

Temporary discontinuation of dabigatran may be indicated in surgical patients, depending on the urgency of the procedure, level of bleeding risk and renal function. The decision to stop treatment in non-urgent or elective surgery depends on the risk of bleeding versus risk of thrombosis. Clinicians should take account of the patient’s renal function and the bleeding risk of the procedure in decisions regarding the timing of discontinuation (5) (Table 5). If possible, discontinue dabigatran 1–2 days (CrCL 50 ml/min or more) or 2–3 days (CrCL less than 50 ml/min) before invasive or surgical procedures. Longer delays may be needed for patients with a high bleeding risk including those undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port.

Semi-urgent and urgent surgery

In patients requiring semi-urgent surgery (within 2–12 h after the last dose of dabigatran), the risk of bleeding needs to be weighed against the clinical need for the procedure. Ideally, surgical pro-

Table 2: Factors identified in clinical trials which may increase the bleeding riska.

| Demographic | Age ≥75 years |
| Factors increasing dabigatran plasma levels | Major: Moderate renal impairment (CrCL 30–50 ml/min) P-gp inhibitor co-medication | Minor: Low body weight (<50 kg) |
| Pharmacodynamic interactions | ASA NSAID Clopidogrel |
| Diseases/procedures with special haemorrhagic risks | Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Active ulcerative GI disease Recent GI bleeding Recent biopsy or major trauma Recent ICH Brain, spinal, or ophthalmic surgery Bacterial endocarditis |

aFor special patient populations requiring a reduced 110 mg bid dose, see Figure 1. ASA, acetylsalicylic acid; CrCL, Creatinine clearance; P-gp, P-glycoprotein; GI, gastrointestinal; ICH, intracranial haemorrhage; NSAID, non-steroidal anti-inflammatory drug.

Table 3: Suggested approaches for switching to and from dabigatran (based on EU label) (5).

| Conversion | Start times recommended |
| From VKAs to dabigatran | Discontinue VKA and start dabigatran when INR <2 |
| From dabigatran to VKAsb | Start times for VKAs are based on renal function: − If CrCL ≥50 ml/min, start VKA 3 days before stopping dabigatran − If CrCL ≥30 to <50 ml/min, start VKA 2 days before stopping dabigatran − If CrCL 15–30 ml/min, start VKA 1 day before stopping dabigatranb |
| From dabigatran to parenteral | Start parenteral anticoagulant 12 h after last dose of dabigatran |
| From parenteral to dabigatran | Start dabigatran at the same time or up to 2 hours before the next parenteral drug dose. For continuous infusions of parenteral drugs, start dabigatran at the time of discontinuation of the continuous infusion. |

bBecause dabigatran may contribute to an elevated INR, the INR will better reflect the effect of the VKA after dabigatran has been stopped for at least 2 days; bApplies to patients treated in the US and for patients in whom the CrCL drops below 30 ml/min. CrCL, Creatinine clearance; h, hours; INR, International normalised ratio; VKA, vitamin K antagonists.
Table 4: Anticoagulation measurement for dabigatran in patients administered 150 mg twice-daily for AF.

<table>
<thead>
<tr>
<th>Test</th>
<th>Increased risk of bleeding</th>
<th>Expected value at peak concentration (2 h post dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>&gt;80 s at trough (2–3 x baseline value)</td>
<td>&gt; 2–3 x baseline value</td>
</tr>
<tr>
<td>Hemoclot (diluted TT)</td>
<td>&gt;65 s at trough</td>
<td>-</td>
</tr>
<tr>
<td>INR</td>
<td>Not applicable</td>
<td>-</td>
</tr>
<tr>
<td>ECT</td>
<td>3–4 x baseline value</td>
<td>3 x baseline value</td>
</tr>
</tbody>
</table>

*Evidence based on post-hoc review of pharmacokinetic samples collected from patients enrolled in RE-NOVATE II (57) (aPTT and Hemoclot) and RE-LY (aPTT and ECT) (7) trials. After administration of dabigatran 150 bid, the 90th percentile of trough plasma concentration to double the risk of bleeding was 215 ng/mL. Baseline aPTT range in RE-LY was 22–40 s. Baseline ECT range in healthy volunteer studies was 28–34 s (Boehringer Ingelheim, Data on file); INR is insensitive and unreliable for dabigatran. aPTT, activated partial thromboplastin time; ECT, ecarin clotting time; h, hours; INR, international normalised ratio; s, seconds.

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 mg 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 (18), may place the patient at risk of bleeding if given too close following surgery.

Managing bleeding and overdose

At present, there is no specific reversal or antidote agent available for dabigatran or other novel oral anticoagulants such as apixaban or rivaroxaban. Specific antidotes are in development, but it will take time before they are commercially available (19, 20). In the event of bleeding complications, dabigatran must be discontinued and the source of bleeding investigated. Since dabigatran is excreted predominantly by the renal route, an adequate diuresis must be maintained. Standard treatment, e.g. surgical haemostasis and blood volume replacement is recommended (5), and consideration may be given to the use of fresh whole blood or fresh-frozen plasma. There is some experimental evidence to support the role of general haemostatic agents such as prothrombin complex concentrates (e.g. non-activated or activated), recombinant factor VIIa or concentrates of coagulation factors II, IX or X in reversing the anticoagulant activity of dabigatran in cases of major/life-threatening bleeding (12, 21), although their usefulness in clinical settings has not yet been systematically evaluated. Eerenberg et al. reported that a single 50 IU/kg bolus of prothrombin complex concentrate (PCC, Cofact) did not reverse the aPTT, ECT and TT in a small number of healthy young volunteers (n=12) who received dabigatran 150 mg bid for two days (22). No assessment of bleeding time was performed and there was no correlation with bleeding events per se. The study findings were not unexpected as the aPTT and ECT can remain elevated despite PCC administration. The aPTT is generally more insensitive to PCCs, which predominantly influence the extrinsic pathway and are reflected in the PT or INR (23). In addition, using ECT or TT assays bypasses the additional prothrombin concentrates, since the stimulus for the assay activates thrombin or prothrombin independent of the prothrombinase complex. Thus, the lack of effect of dabigatran on anticoagu-

### Renal function (CrCL in ml/min) Estimated half-life (hours) Timing of discontinuation after last dose of dabigatran before elective surgery

<table>
<thead>
<tr>
<th>CrCL in ml/min</th>
<th>Estimated half-life (hours)</th>
<th>Standard bleeding risk</th>
<th>High bleeding risk&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80</td>
<td>13</td>
<td>24 h before</td>
<td>2 days before</td>
</tr>
<tr>
<td>≥50 to &lt;80</td>
<td>15</td>
<td>1–2 days before</td>
<td>2–3 days before</td>
</tr>
<tr>
<td>≥30 to &lt;50</td>
<td>18</td>
<td>2–3 days before (&gt;48 h)</td>
<td>4 days before</td>
</tr>
</tbody>
</table>

<sup>a</sup>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, h, hour.

Table 5: Discontinuation rules before elective invasive or surgical procedures.

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loration reversal may be due to the assays used to test this. Further support for this comes from preclinical models where it was shown that the lack of reversal of anticoagulation does not predict a lack of bleeding reversal (24).

The use of platelet concentrates may be considered where thrombocytopenia is present or long-acting antiplatelet drugs (e.g. aspirin, clopidogrel) have been used. The low plasma protein binding of dabigatran (∼35%), suggests that dialysis may be useful although there is only limited experience with this (12). If dialysis is not possible, constant haemoperfusion might also be applicable, although, once again, there is no clinical experience with this approach.

Managing overdose

In vitro studies show that dabigatran is adsorbed by activated charcoal therapy (12). Although this has not been tested in vivo, a reasonable approach would be to administer charcoal within 1–2 h of intake (overdose) to limit or prevent absorption in the gastrointestinal tract. Beyond 2 h use of charcoal is not useful. Haemoperfusion over a charcoal filter has also been suggested as a possible approach (25, 26), but has not been tested clinically.

Special situations

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 (27). 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 (28). The use of thrombolysis in patients receiving concurrent dabigatran has not been studied and may increase the risk of bleeding (5). 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 (29). Matute et al. (30) 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.

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 two 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 two weeks after a severe stroke (31).

Acute coronary events and coronary intervention

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 (three 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 (32). 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 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 x ULN, UFH can be started without a loading dose and LMWH can be initiated. If the aPTT is > 1.5 x ULN, this should be repeated every 4 h until < 1.5 x 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 (four weeks vs. 12 months) and
the associated lower potential risk of subsequent bleeding events
(33, 34). Triple therapy with aspirin, clopidogrel and dabigatran
after revascularisation can be given for a short period but requires
close observation for bleeding events (35).

Cardioversion and ablation

For patients with AF of >48 h duration, therapeutic anticoagula-
tion for at least three weeks before and four weeks after cardio-
version is recommended (1). VKAs have a number of disadvan-
tages in this setting, notably the delayed onset of action and diffi-
culties in achieving and maintaining an appropriate degree of
therapeutic anticoagulation before or following the procedure.
Evidence from RE-LY (36) suggests that dabigatran is a reasonable
alternative. Among 1,270 patients who underwent cardioversion,
stroke and systemic embolism rates within 30 days of this pro-
cedure were 0.8% and 0.3% for dabigatran 150 and 110 mg bid
doses, respectively, vs. 0.6% with warfarin. Major bleeding rates
were 1.7%, 0.6%, and 0.6%, respectively. It is therefore likely that
patients can stay on dabigatran while being cardioverted. Trans-
esophageal echocardiogram following a standard protocol may be
performed before the procedure according to local operating pro-
cedures.

At present, there are limited clinical data for the use of dabiga-
tran in catheter ablation in patients with symptomatic drug-resis-
tant AF (37). Current guidelines recommend the use of LMWH or
intravenous UFH post-ablation as a bridge to resumption of sys-
temic anticoagulation, which should be continued for a minimum
of three months (1). Some centres do not interrupt anticoagu-
lation for the ablation procedure. Whether anticoagulant therapy
should be continued post-ablation depends on the individual’s
risk factors for stroke. If there is sufficient risk to warrant oral anti-
coagulation for their AF preablation, oral anticoagulation therapy
should be continued indefinitely post-ablation regardless of ap-
parent procedural success (38, 39).

Mechanical heart valves

Currently, the use of dabigatran in patients with mechanical heart
valves cannot be recommended due to the lack of clinical evidence.
In vitro and pre-clinical studies have investigated the use of dabi-
gatran in conjunction with mechanical heart valves (40, 41). A
phase II study (the RE-ALIGN trial) to investigate the use of dabi-
gatran (150 mg, 220 mg and 300 mg bid) in patients with mechani-
cal heart valves (aortic or mitral) has just commenced (42). Data
from this trial will help to guide the development programme for
dabigatran in this setting.

Adverse effects and drug interactions

Other than bleeding, the most common adverse effect of dabigat-
ran is dyspepsia which typically affects ~5–10% of patients. In RE-
LY, about 2% of dabigatran-treated patients discontinued treatment
due to dyspepsia-like symptoms (classified in the trial as ab-
dominal pain upper, abdominal pain, abdominal discomfort, or
dyspepsia) compared with 0.6% on warfarin. Dyspepsia related to
dabigatran was mainly graded as mild or occasionally moderate in
severity by the investigators, appeared more likely to occur early
after starting treatment (43), and tended to be transient, often
spontaneously resolving with continued treatment (44) or after
cessation of treatment. One hypothesis for the dyspepsia is that it is
related to the capsule formulation. Each dabigatran capsule con-
tains hundreds of pellets of tartaric acid each coated with dabigat-
ran extelilate. Dissolution of these pellets produces a local acidic
environment resulting in an optimal pH for drug absorption. How-
ever, it is not known whether this is the cause of dyspepsia. This ef-
fect may be managed by giving dabigatran with a large glass of
water, with food or a proton-pump inhibitor (PPI) (26). Although
dyspepsia was not predictive for gastrointestinal (GI) bleeding, we
recommend the use of faecal occult blood testing (e.g. Haemocult)
to exclude this (see below). A prospective observational study is
planned to further evaluate the effect of food and PPIs given in
conjunction with dabigatran (Boehringer Ingelheim, data on file).

In RE-LY, a non-significant increase in risk for MI with both
doses of dabigatran (excess of two events/1,000 patients/year vs.
warfarin) was observed (Fig. 1). However, it should also noted
that the overall rate of MI in the trial was low, given that 30% of pa-
ients had objective evidence of coronary artery disease at baseline.
Other myocardial ischaemic events were not increased and the
treatment effects of dabigatran were consistent in patients at
higher and lower risk of myocardial ischaemic events (45). More-
over, there were also significantly fewer cardiovascular deaths (five
fewer events/1,000/year) and significantly fewer strokes (six fewer
events/1,000/year) with the higher dose of dabigatran (46). A re-
cent meta-analysis of seven trials (including RE-LY) reported an
absolute increase in MI or acute coronary syndrome events of
0.27% with dabigatran treatment versus control (warfarin, enox-
aparin or placebo) (47). Of note, this analysis included patients
from different clinical indications who had differing risks of MI
and were treated with different comparators. Overall mortality re-
mained in favour of dabigatran. Thus, any possible increase in risk
of MI with dabigatran is unlikely to outweigh the clinical benefits
of dabigatran in most patients. If appropriate, co-administration
of low-dose aspirin (≤100 mg daily) with dabigatran may be con-
sidered for patients with a history of coronary artery disease.

In RE-LY, there was a significantly higher risk of gastrointestinal
bleeding with dabigatran 150 mg bid compared with warfarin (ex-
cess of five events/1,000/year). Therefore we recommend that pa-
tients should be monitored clinically for evidence of lower GI tract
bleeding. Faecal occult blood testing (e.g. Haemocult) within the
first month of initiating treatment is a reasonable option to detect
early signs of bleeding possibly associated with anticoagulant use
(48).
Dabigatran has a low potential for drug interactions. 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 (5), 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 (49). 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. However, in the European Union, when co-administered with verapamil, a reduced dose of dabigatran 110 mg bid is recommended. 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 (50). Further, 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 mg, 150 mg or warfarin (51). Data are lacking concerning the use of dabigatran in conjunction with other drugs based on the European prescribing guidelines (5).

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 mg, 150 mg or warfarin (51). Data are lacking concerning the use of dabigatran in conjunction with new antiplatelet treatments such as prasugrel and ticagrelor.

### Practical aspects

Dabigatran etexilate capsules should be swallowed whole as breaking, chewing or emptying the contents can increase oral bioavailability and exposure by up to 75% (5). Once the medication bottle has been opened, the capsules must be used within 120 days as they are susceptible to humidity (6).

Compliance with twice-daily dosing is important and should be addressed by patient education. Patients who miss a dose of dabigatran can take the dose up to 6 h before the next scheduled dose. If this is not possible, the missed dose should be omitted. Patients should not take a double dose to compensate for missed individual doses. Clinicians should advise their patients about how to look for signs of abnormal bleeding (such as epistaxis, gingival haemorrhage, subcutaneous haemorrhage, haematuria, or bloody stools) and to call them immediately if such episodes develop.

### Table 6: Guidance for use of dabigatran with other drugs (as per EU label) (5).

<table>
<thead>
<tr>
<th>Drug interactions and dosing recommendation</th>
<th>Effect on dabigatran exposure due to drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No adjustment required</strong></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↓ 18%</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>No effect</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>↓ 30%b</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>↑ 30–40%c</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Use lower dose (110 mg bid)</strong></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>↑ 20–150%ab</td>
</tr>
<tr>
<td><strong>Use with caution and assess bleeding risk</strong></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>↑ 50% a</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>↑ 60% a</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>↑ 19% a</td>
</tr>
<tr>
<td><strong>Not recommended</strong></td>
<td></td>
</tr>
<tr>
<td>Dronedarone</td>
<td>↑ 100%a (58)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>↓ 67%c</td>
</tr>
<tr>
<td>Carbamazepine, phenytoin</td>
<td>↓ (% not reported)</td>
</tr>
<tr>
<td>Protease inhibitors (e.g. ritonavir, tipranavir, nelfinavir and saquinavir)</td>
<td>Exposure not reportedd</td>
</tr>
<tr>
<td><strong>Contraindicated</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic ketoconazole</td>
<td>↑ 150%a</td>
</tr>
<tr>
<td>Itraconazole, taclorimus and cyclosporin</td>
<td>↑ (% not reported but likely to be similar to ketoconazole based on in vitro data)</td>
</tr>
</tbody>
</table>

Exposure refers to reported area under the plasma concentration curve.

*aBased on data in healthy volunteers. Depend on timing of administration of and formulation of verapamil. Dabigatran exposure is 150% higher if the first dose of immediate release formulation verapamil is given 1 hour before dabigatran; lower if given as extended release formulation (70% higher) or with multiple doses of verapamil (50% increase); and negligible if given 2 hours after dabigatran (20% increase). Both medications should be taken at the same time. *Protease inhibitors including ritonavir and its combinations with other protease inhibitors affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with dabigatran.

### Conclusions

Very clearly, many questions remain, and the present review article nicely complements a recent position document from the Italian Federation of Thrombosis Centers (FCSA) dealing with the use of the new oral anticoagulants (52). The latter have clearly changed our approach to thromboprophylaxis (53), so that in AF, effective stroke prevention with new oral anticoagulants such as dabigatran can be offered to patients with one or more stroke risk factors (54, 55).
Conflicts of interest

Menno Huisman has received honoraria for presentations as well as research grants of Boehringer Ingelheim, Bayer HealthCare, Pfizer, GSK and Actelion. Gregory Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers’ bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. Hans-Christoph Diener has received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Daichii-Sankyo, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Jansen Cilag, Knoll, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parkes-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Thrombogenics, Wyeth and Yamanouchi. Financial support for research projects was provided by Astra Zeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Jansen-Cilag, Sanofi-Aventis, Syngis and Talecris. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, National Institute of Health, Bertelsmann Foundation and Heinz-Nixdorf Foundation. Hans-Christoph Diener has no ownership interest and does not own stocks of any pharmaceutical company. Martina Brueckmann, Joanne van Ryn, and Andreas Clemens are employees of Boehringer Ingelheim.

References