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dabigatran (PRADAXA°): deep vein thrombosis and pulmonary embolism

Warfarin remains the standard drug

● **Not more effective than warfarin in three "non-inferiority" trials. Less bleeding but more acute coronary events with *dabigatran*, and still no antidote.**

Initial treatment for deep vein thrombosis or pulmonary embolism usually consists of a low-molecular-weight heparin (LMWH) injected subcutaneously, although an unfractionated heparin is preferable for patients with severe renal impairment (1). To prevent recurrence of thromboembolic events, treatment for at least 3 months with an LMWH or switching to adjusted-dose warfarin has a similar harm-benefit balance. Prolongation of anticoagulant therapy beyond 3 months should be considered for patients with no identified triggering factor, thrombophilia, or recurrent deep vein thrombosis, provided the bleeding risk remains low (1).

Dabigatran (Pradaxa°, Boehringer Ingelheim), an oral anticoagulant that acts by inhibiting thrombin, has been approved for the treatment of deep vein thrombosis and pulmonary embolism, and for the prevention of recurrences. Clinical evaluation of *rivaroxaban*, an oral anticoagulant that acts by inhibiting factor Xa, has shown no advantages over standard treatment in these situations (1). What about *dabigatran*?

Not better than warfarin. Clinical evaluation of *dabigatran* in these settings is mainly based on three randomised, double-blind, "non-inferiority" trials versus *warfarin* (**a**)(2-5).

Re-cover I and II, two trials with similar protocols, compared *dabigatran* versus *warfarin* during a 6-month period after initial heparin therapy lasting at least 5 days, in a total of about 5100 patients (2-4). Overall mortality was similar, about 2% (2). The recurrence rate did not differ significantly between the *dabigatran* and *warfarin* groups: pulmonary embolism occurred in respectively 1.1% and 1.0% of patients, and symptomatic deep vein thrombosis in 1.8% and 1.5% of patients (2).

The Re-medy trial compared long-term (6 months to 3 years) *dabigatran* and *warfarin* prophylaxis in 2856 patients following initial anticoagulant therapy lasting 3 to 12 months (2,5). Overall mortality was similar, about 1.2% (2). Similarly, the recurrence rates were not significantly different: pulmonary embolism occurred in respectively 0.7% and 0.4% of patients receiving *dabigatran* and *warfarin*, and symptomatic deep vein thrombosis occurred in 1.2% and 0.9% of patients (2).

Slightly fewer major bleeding events but more acute coronary events. In randomised double-blind trials comparing *dabigatran* versus *warfarin*, adverse events were similarly frequent with the two anticoagulants (affecting about 70% of patients), as were serious adverse events (about 14% of patients) (2).

Bleeding occurred in respectively 14% and 20% of patients treated with *dabigatran* and *warfarin* in the Re-cover I and II trials, and in respectively 19% and 26% of patients in the Re-medy trial (2). Gastrointestinal bleeding tended to be more frequent with *dabigatran* than with *warfarin* (2.9% versus 2.2% in Re-cover I and II, 3.1% versus 2.2% in Re-medy), but major bleeding events were less frequent with *dabigatran* (1% versus 1.6% in Re-cover I and II, a statistically significant difference; 0.9% versus 1.8% in Re-medy, a non-significant difference) (2,5).

Dabigatran was associated with an increase in myocardial infarction and unstable angina (0.4% versus 0.2% in Re-cover I and II; 1% versus 0.2% in Re-medy; no statistical analysis) (2). A similar increase in acute coronary events was reported in a trial of *dabigatran* in atrial fibrillation (2).

No antidote and no routine clotting test in early 2015. In early 2015, there is still no antidote for *dabigatran* nor a routine clotting test for dose adjustment (6,7). Various situations can lead to *dabigatran* overdose and thus increase the risk of bleeding, including even mild renal failure, old age, extremes of body weight, opening the capsules, and drug interactions (2,6).

In practice. Compared with adjusted-dose *warfarin*, *dabigatran* provides no tangible advantages for patients with pulmonary embolism or deep vein thrombosis.

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dabigatran capsules

PRADAXA°

- **110 mg** or **150 mg** of *dabigatran* per capsule

anticoagulant; thrombin inhibitor

■ **New indications:** *"(…) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults".*
[EU centralised procedure]

a- The Re-Sonate trial compared 6 months of treatment with dabigatran versus placebo in 1343 patients initially treated with an oral anticoagulant for several months. Dabigatran reduced the risk of recurrent deep vein thrombosis (0.3% versus 3.5% with placebo) and pulmonary embolism (0.1% versus 2.1%), but did not significantly reduce mortality (0% versus 0.3%) (refs 2,5).

Selected references from Prescrire's literature search.

In response to our request for information, Boehringer Ingelheim provided us with administrative documents and published articles.

1- Prescrire Editorial Staff "Deep venous thrombosis and pulmonary embolism. Part 2 - prevention of recurrences: warfarin or low-molecular-weight heparin for at least 3 months" *Prescrire Int* 2013; 22 (138): 129-133.
2- EMA - CHMP "Assessment report for Pradaxa-EMEA/H/C/829/II/48/G" 25 April 2014: 148 pages.
3- Schulman S et al. "Dabigatran versus warfarin in the treatment of acute venous thromboembolism" *N Engl J Med* 2009; 361 (**24**): 2342-2352.
4- Schulman S et al. "Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis" *Circulation* 2014; **129** (7): 764-772.
5- Schulman S et al. "Extended use of dabigatran, warfarin, or placebo in venous thromboembolism" *N Engl J Med* 2013; 368 (**8**): 709-718.
6- Prescrire Editorial Staff "Bleeding with dabigatran, rivaroxaban and apixaban. No antidote, and little clinical experience" *Prescrire Int* 2013; **22** (139): 155-159.
7- Prescrire Rédaction "2-5-4. Patients sous dabigatran" *Rev Prescrire* 2014; **34** (374 suppl. interactions médicamenteuses).

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