

# EDITORIALS

## The trouble with dabigatran

Doctors and patients must tread carefully through emerging risks

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Options for stroke prevention in high risk non-valvular atrial fibrillation have recently broadened with the addition of new oral anticoagulants as an alternative to warfarin, the traditional and effective treatment. The new class of drug promised safety and effectiveness without the monitoring and dose adjustment needed for warfarin. However, recent insights into the development and approval of dabigatran—the first new oral anticoagulant brought to market—have raised serious questions about its risks.<sup>1</sup> New analysis published in *The BMJ* today illuminates a lack of transparency about the safety of unmonitored dabigatran, compounded by the drug's fickle pharmacokinetics, which can cause a fivefold variation of plasma concentration.<sup>2,3</sup>

Equally unsettling are data integrity issues, which prompted the US Food and Drug Administration initially to refuse to review dabigatran. The investigators reviewed the data and identified 81 new events, including one stroke, one systemic embolism, and 69 major haemorrhages.<sup>4</sup> An accelerated FDA review process also contributed to a less robust evaluation of risks and benefits. In effect, the current situation leaves clinicians and patients the choice between the devil they know and the one they don't.

The single pivotal study for dabigatran was the RE-LY trial (Randomised Evaluation of Long-Term Anticoagulation Therapy).<sup>5</sup> Boehringer Ingelheim applied for “fast track” approval premised on the novelty of fixed dose anticoagulation. This meant that the FDA decision was based on a review before the completion of RE-LY rather than an assessment after the completion of two randomised clinical trials as required under standard approval procedures. The FDA originally refused the dabigatran application because of data irregularities<sup>1</sup> but reconsidered after additional review and revision of the data. Despite the reservations of at least one advisory panel member about the drug's widely variable plasma levels,<sup>3</sup> the FDA approved fixed dose dabigatran without clinical monitoring. A year later, the European Medicines Agency (EMA) also approved fixed dose dabigatran but required physician education, monitoring of renal function, publication of therapeutic drug levels, and availability of a test to evaluate anticoagulation.

Dabigatran achieved blockbuster status, with sales of over \$1bn (£580m; €740m) globally by April 2012<sup>1</sup> and \$2bn in the US

by 2014 despite increasing concerns about safety.<sup>2</sup> By December 2011 adverse drug event databases in Europe, Japan, and the US showed thousands of serious and fatal haemorrhages in patients taking dabigatran, particularly older patients.<sup>4</sup>

The FDA issued a reassuring “drug safety communication” after data from its pilot electronic surveillance programme (Mini-Sentinel, [www.mini-sentinel.org](http://www.mini-sentinel.org)) indicated that dabigatran's risks were less than warfarin's.<sup>6</sup> However, a recent meta-analysis of randomised controlled trials examining risk of gastrointestinal bleeding with warfarin and dabigatran reached the opposite conclusion.<sup>7</sup>

In addition to bleeding risks identified in RE-LY, other methodological concerns include the fact that dabigatran was blinded while warfarin was non-blinded and that RE-LY used an intention to treat analysis, which may bias it toward non-inferiority. These concerns, taken together with the observed incidence of major haemorrhage show the risk data are evolving and that the risks of dabigatran could be larger than previously reported.

Additional data from recent US lawsuits alleges that Boehringer did not adequately warn patients of the bleeding risks of dabigatran. Litigation revealed internal documentation that the company failed to disclose that monitoring might reduce risk of stroke and bleeding, which conflicted with the drug's “novel” no monitoring required status.<sup>2</sup> A recent RE-LY sub-trial concludes that a subset of patients “may improve their benefit-risk” balance with an adjusted dose.<sup>8</sup>

There is also uncertainty about the efficacy of the FDA approved 75 mg twice daily regimen, which has not been tested in a randomised trial. The EMA has approved the 150 mg and 110 mg doses studied in the RE-LY trial and published therapeutic plasma levels.

In summary, clinical concerns regarding dabigatran include potentially higher than reported bleeding risk; the possibility of undertreating or overtreating with fixed doses, especially in older patients and patients with changing renal function; the unknown value of monitoring dabigatran levels and adjusting the dose; and the lack of a specific reversal agent.

How then should clinicians advise patients with non-valvular atrial fibrillation at risk of stroke? We suggest a shared decision

that balances patients' tolerance of unknown risks, their tolerance of routine laboratory monitoring and dose adjustment, and their risk of stroke. It would be helpful to quantify the risk of stroke without treatment by using the CHADSVasc score<sup>9</sup> and the risk of bleeding with warfarin using the HASBLED score.<sup>9 10</sup> We are not aware of any validated tool for quantifying the risk of bleeding with dabigatran. Patients and doctors tolerant of unknown risk and close monitoring will have to choose which drives them more strongly, with the more conservative option being warfarin. Patients intolerant of frequent monitoring and unknown risk will find themselves with no appealing options. In such situations, framing the discussion in terms of tolerance may help patients and clinicians identify the personal values that would underlie any decision.

Society must consider the trade-offs of accelerated drug approval in terms of assurance of safety and effectiveness. A more transparent process of data collection and review would make important clinical data available without waiting for litigation and subpoenas, which is what it took to unearth some of Boehringer's early concerns with dabigatran.<sup>2</sup> Without doubt, society benefits when there is an expeditious pathway to bring novel treatments to market, particularly in diseases with no alternative treatments. However, as we are learning from dabigatran, more methodological rigour before regulatory approval and careful and accessible postmarketing surveillance can better inform patient care and allow us to recognise a truly novel treatment.

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