Two new analyses link dabigatran to MI risk

Toronto, ON - The question of whether treatment with dabigatran etexilate (Pradaxa, Boehringer Ingelheim) increases the risk of MI is once again being raised, this time in two unrelated analyses. Both showed an increased risk of MI ranging from 38% to 70% vs comparator drugs and placebo.

In the first, Dr Ilke Sipahi (University Hospitals and Case Medical Center, Cleveland, OH), Dr Seden Celik (Acibadem University Medical School, Istanbul, Turkey), and Dr Ahmet Akyol (Acibadem University Medical School) report that treatment with dabigatran resulted in a statistically significant 48% increased risk of MI compared with controls [1]. When the original Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial is removed from the analysis, the results are still statistically significant, say Sipahi et al.

In the analysis, published online June 26, 2013 as a letter in the Journal of the American College of Cardiology, the researchers looked at all randomized controlled studies, including from the pivotal RE-LY trial, studies on the use of dabigatran in patients with venous thromboembolism and acute coronary syndrome, as well as data presented by Boehringer Ingelheim to the Food and Drug Administration.

The new analysis challenges an earlier assessment published online April 1, 2013 in the Journal of the American College of Cardiology by Dr Torben Bjerregaard Larsen (Aalborg University Hospital, Denmark) that gave a completely opposite interpretation of the MI risks with the drug [2]. In that report, which was an analysis of the Danish Registry of Medicinal Product Statistics and other nationwide records, dabigatran performed at least as well against warfarin in atrial fibrillation in a prospective "real-world" setting. In fact, the 110-mg and 150-mg doses reduced the risk of MI by 70% and 60%, respectively.

"We think that the imperfect nature of observational studies mostly stemming from residual confounding despite propensity matching may explain the discrepancy between the current observational study and previous randomized trials," write Sipahi, Celik, and Akyol.

Meta-analysis presented at ISHT

The risk of MI with dabigatran was also highlighted at the recent 2013 Congress of the International Society on Thrombosis and Haemostasis meeting in Amsterdam, the Netherlands. Jonathan Douxfils (University of Namur, Belgium), along with senior author Dr Jean-Michel Dogné (University of Namur), presented data from a dose-response meta-analysis of randomized, controlled trials (RCTs) with outcome data from MI and cardiac events [3].

Ten studies were included in the meta-analysis. Among the 23 839 dabigatran-treated patients, there were 292 MIs. Overall, the risk of MI was increased 32% compared with the comparator arm, an increase that was statistically significant. Among patients treated with the 150-mg dose, the risk of MI was 41% to 45% higher in the dabigatran arm. The risk of MI only trended toward statistical significance among those treated with the 110-mg dose (p=0.057).

Compared with warfarin, the risk of MI was increased 38%, while the risk of MI was 70% higher among dabigatran-treated patients compared with placebo-treated patients.

"This meta-analysis of RCTs provides robust evidence that dabigatran etexilate is associated with a significantly increased risk of MI, especially at high dose (150 mg bid)," concluded Douxfils and colleagues. "No firm conclusion can be taken with the lower dabigatran etexilate dose (110 mg bid) because of the limited number of studies included in this meta-analysis."

Dr Gregory Lip (University of Birmingham, UK), who was the senior author on the analysis by Larsen, told heartwire that he believes the increased risk of MI observed in RE-LY and by Sipahi et al is simply the play of chance. In RE-LY, the risk of MI trended higher for low-dose dabigatran, with an odds ratio (OR) of 1.35 (p=0.07), and was significantly higher for the high-dose group (OR 1.38; p=0.048). As reported by heartwire at the time, the MI finding was unexpected, but Lip said the issue has been studied since the trial was published in 2009.
"Our observational data, however, showed things the other way around," said Lip. "But they are real-world data, and we tried to adjust for that. We used propensity-matching and we accept that our published paper includes patients at a lower risk compared with the main RE-LY trial. We tried to adjust for the potential for confounding, but you can't exclude the possibility of residual confounding. We are up front about this."

Lip, who along with Larsen wrote a response Sipahi et al in JACC [4], pointed out that there were numerically more MIs in patients treated with aspirin and clopidogrel in Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) study, but that hasn't stopped patients from receiving this drug combination.

"I think we have to put the nonsignificant difference in myocardial infarction [in RE-LY] into perspective against the overall magnitude of reduction in stroke and cardiovascular mortality," said Lip. "The MI aspect in RE-LY has been examined very carefully. If the numerical difference in MI with dabigatran is important it would translate into more downstream revascularizations and more new angina hospitalizations. But it didn't. If you look at cardiovascular mortality, it's actually significantly less with dabigatran 150 mg compared with warfarin. So we need to put this into perspective."

Lip reports serving as a consultant to Bayer, Astellas, Merck, AstraZeneca, Sanofi, Bristol-Myers Squibb/Pfizer, and Boehringer Ingelheim. He has also participated as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, and Sanofi. Disclosures for the coauthors are listed in the response letter. Larsen has served on the speaker's bureau for Bayer, Bristol-Myers Squibb/Pfizer, and Boehringer Ingelheim. Sipahi et al reports no conflicts of interest. Disclosures were not available in the abstract by Douxfils and colleagues.

Sources


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- FDA: Bleeding risk with dabigatran similar to warfarin [heartwire > Medscape Medical News; Nov 02, 2012]
- Dabigatran use climbing in US, on- and off-label [Clinical Conditions > Arrhythmia/EP; Sep 28, 2012]
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