Dabigatran and Myocardial Infarction

To the Editor:

In a recent issue of CHEST (January 2015), Davidson commented on the association between direct thrombin inhibitors, including bivalirudin, ximelagatran, and dabigatran, and cardiac thrombosis. He concludes that the guilt of these substances in causing cardiac thrombosis appears undeniable and that clinicians should avoid prescribing direct thrombin inhibitors. This statement is based on a rather one-sided thought process and warrants a more balanced view based on a careful review of the current knowledge, particularly with respect to the use of dabigatran. The major indication for this drug is stroke prevention in atrial fibrillation (AF) for which it has been approved since 2009. Hence, our response focuses on dabigatran in patients with AF.

In the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, there were numerically more myocardial infarctions (MIs) in patients taking dabigatran (0.8%/y) than in those taking warfarin (0.6%/y), but this finding was nonsignificant. The absolute difference in rates of new MIs was extremely low (0.2%/y), limiting statistical power for any comparison. In a post hoc analysis of the RE-LY trial, a variety of other ischemia-related outcomes were similar between treatment groups. An estimation of the net clinical benefit indicated a significant difference in favor of dabigatran.

Several real-world datasets have been published evaluating the benefits and risks of dabigatran. In a nationwide Danish registry study, 4,978 incident dabigatran users were propensity matched to 8,936 users of warfarin. Rates for stroke, peripheral embolism, and major bleeding were similar for dabigatran and warfarin. However, mortality, intracranial bleeding, and MI events were lower with dabigatran. The unadjusted hazard ratio (HR) for MI for dabigatran 110 mg bid vs warfarin was 0.60 (95% CI, 0.33-1.02) and for dabigatran 150 mg bid vs warfarin, 0.62 (95% CI, 0.30-1.14). The largest study on dabigatran 150 mg was published by the US Food and Drug Administration, which collected data from >134,000 Medicare patients treated with dabigatran for stroke prevention in AF. Dabigatran compared with warfarin significantly reduced the risk of stroke (HR, 0.80; 95% CI, 0.67-0.96), intracranial bleeding (HR, 0.34; 95% CI, 0.26-0.46), and mortality (HR, 0.86; 95% CI, 0.77-0.96). Of particular note, there were numerically fewer MIs in patients taking dabigatran than in those taking warfarin (HR, 0.92; 95% CI, 0.78-1.08).

Warfarin offers good protection against cardiac events. In recent thromboprophylaxis trials with oral factor Xa inhibitors (eg, rivaroxaban, edoxaban) compared with well-managed warfarin (as reviewed in a recent European consensus document), numerically higher MI rates were actually seen with oral factor Xa inhibitors compared with warfarin.

Thus, the commentary by Davidson needs to be put into perspective. Absolute MI rates are small and nonsignificant and may reflect better cardioprotection with warfarin rather than an adverse effect of direct thrombin inhibitors or oral factor Xa inhibitors.

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Financial/Nonfinancial Disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Hohnloser has been a consultant and advisor to Bayer HealthCare AG; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Pfizer, Inc; Johnson & Johnson Services, Inc; sanofi-aventis; Gilead; and Les Laboratoires Servier and has participated in speaker activities for Bayer HealthCare AG; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Pfizer, Inc; Johnson & Johnson Services, Inc; and sanofi-aventis. Dr Lip has served as a consultant for Bayer HealthCare AG; Astellas Pharma Inc; Merck Sharp & Dohme Corp; sanofi SA; Bristol-Myers Squibb Company/Pfizer, Inc; Daiichi Sankyo Company Limited; Biotronik SE & Co.KG, Medtronic, Inc; Portola Pharmaceuticals, Inc; and Boehringer Ingelheim GmbH and has been on the speakers bureau for Bayer HealthCare AG; Bristol-Myers Squibb Company/Pfizer, Inc; Boehringer Ingelheim GmbH; Daiichi Sankyo Company Limited; and Medtronic, Inc.

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DOI: 10.1378/chest.14-2534

References


Response

To the Editor:

Drs Hohnloser and Lip do not dispute that direct thrombin inhibitors are statistically significantly associated with cardiac thromboses in patients with cardiac devices (bivalirudin and coronary stents, dabigatran and mechanical heart valves) or that dabigatran is similarly associated with excess myocardial infarctions (MIs) in patients with VTE. They misquote me as attributing cause, rather than what I wrote, association. Their defense of dabigatran for atrial fibrillation, ie, that increased MIs do not matter in the big picture, uses questionable observations from large registries to refute hard evidence from patients under surveillance in randomized studies. The Danish registry study1 of Dr Lip and colleagues cannot support their claim. Their report states that MI was not predefined as either a primary or secondary outcome; they studied only new users; their patients were far less sick than those in the clinical trials; they followed patients for <18 months; few patients with moderate/severe renal or liver disease received dabigatran; and so forth.

The bias in the US Food and Drug Administration Medicare dataset2 is that US patients using dabigatran are, on average, likely to be wealthier, hence less sick, than patients taking warfarin. The patients taking dabigatran in the Medicare dataset mostly pay extra for Medicare-plus insurance and still afford about $40/mo more just for dabigatran; poorer Medicare-only patients pay $4/mo (or less) for warfarin (international normalized ratios and clinic visits are free). The groups are socioeconomically dissimilar, and MIs are not diligently looked for as they were in the clinical trials that led the sponsor of dabigatran to conclude that dabigatran is associated with more MIs than well-controlled warfarin, as cited in my commentary3 and in the US Food and Drug Administration-approved dabigatran drug label.

The dabigatran Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study is an unfortunate example of clinical research gone awry. After the initial publication found significantly increased MIs in the patients taking dabigatran, a published revision discarded the RE-LY study's previously published diagnostic criteria for MI4 and chose to include silent MIs, thereby nudging the finding into insignificance. Dr Hohnloser's analysis5 also used cardiac causes of death assigned without autopsies and does not include results from an astonishing second revision (a third reporting) of the count of primary outcome events, unveiled in October 2014, nearly 5 years after the original publication. It is difficult to consider any of these revised series of event numbers as robust.6,7

The doctors' comment about statistically insignificant higher numerical rates of MI associated with different oral anti-Xa anticoagulants pertains to subsets of patients receiving a low dose and populations from selected continents. Unlike the repeatedly confirmed, significantly higher rate of MIs associated with direct thrombin inhibitors compared with warfarin, there is still not the first piece of randomized trial evidence for such an association with anti-Xa anticoagulants. To reiterate: Other than in exceptional circumstances, clinicians should prescribe effective anticoagulants other than direct thrombin inhibitors.

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FINANCIAL/NONFINANCIAL DISCLOSURES: The author has reported to CHEST the following conflicts of interest: Dr Davidson has received consultant payments for serving on steering committees for venous thromboembolism trials of rivaroxaban (Bayer Pharmaceuticals Corp/ Janssen Pharmaceuticals Inc) and edoxaban (Daiichi Sankyo Co Ltd) and on advisory boards for both drugs.

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DOI: 10.1378/chest.14-2600

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