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The Association of Direct Thrombin Inhibitor Anticoagulants With Cardiac Thromboses

Bruce L. Davidson, MD, MPH, FCCP

PODCAST

Direct thrombin inhibitor (anti-factor IIa) anticoagulants, now established for treatment and prevention of cardiac thromboembolism and VTE, have been repeatedly associated with a significantly increased frequency of thrombosis on abnormal cardiac endothelium when compared head-to-head with indirectly acting therapeutic anticoagulants in studies of sufficient patient number and duration. Although there is uncertainty as to the mechanism, the weight of evidence as a class effect warrants prescribing effective anticoagulants other than direct thrombin inhibitors.

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ABBREVIATIONS: HIT = heparin-induced thrombocytopenia; NNH = number needed to harm

Although no mechanism has been proven, the apparent paradoxical association of administering direct thrombin inhibitor anticoagulants with developing cardiac thromboses is being reported repeatedly. Their guilt appears undeniable.

The direct thrombin inhibitor anticoagulants bivalirudin, dabigatran, argatroban, desirudin, and lepirudin are indicated for therapeutic or prophylactic antithrombotic use. However, when clinical trials of substantial duration and patient number have compared a direct thrombin inhibitor to another active anticoagulant, there has been an unmistakable signal for increased myocardial infarction and/or ischemia, or coronary stent or cardiac valve thrombosis.

For bivalirudin, there are three such trials. Compared with IV unfractionated heparin usually given with a glycoprotein IIb/IIIa inhibitor, bivalirudin, administered for cardiac ischemia during transport to primary percutaneous coronary intervention,[1] was found to be associated with 6.1 times the risk of definite stent thrombosis in the first 24 h (95% CI, 1.4-27.2; $P = .007$; number needed to harm [NNH] = 111), despite continued administration of IV bivalirudin 4 h after the procedure ended and the coadministration of a potent oral platelet inhibitor to most of the patients. A previous trial[2] of bivalirudin found 5.3 times the risk of stent thrombosis in the first 24 h (95% CI, 1.80-15.3; $P = .001$; NNH = 100) compared with unfractionated heparin. Just published online[3] was the third randomized

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AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, Seattle WA.

CORRESPONDENCE TO: Bruce L. Davidson, MD, MPH, FCCP, 12209 Shorewood Dr SW, Burien WA 98146; e-mail: brucedavidson@pobox.com

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trial comparing bivalirudin with unfractionated heparin in primary percutaneous coronary intervention, in which the excess stent thrombosis rate with bivalirudin was 3.3 (95% CI, 1.3-8.1; $P = .007$; NNH = 50.)

A large database from many comparative clinical trials in several indications is available for assessing the cardiac thrombosis risk associated with dabigatran, compared with well-controlled warfarin treatment. It points in the same direction: Recipients of dabigatran had more cardiac ischemic and thrombotic events. In the > 18,000-patient trial comparing two dosage regimens of dabigatran with warfarin to prevent embolic complications in atrial fibrillation, dabigatran was associated with 1.38 and 1.35 times the risk of myocardial infarction compared with warfarin for the 150 mg bid and 110 mg bid dabigatran regimens ($P = .05$ and .07, NNH = 476 and 526, respectively).[4] The lower dosage is not approved in the United States. A correction[5] published later by the authors declaring they undercounted heart attacks (by 32) and also embolic events (by four) and major bleeds (by 68 or 69) edged the increased heart attack risk just into statistical insignificance. In acute VTE treatment, where acute coronary syndrome while taking active anticoagulant therapy was uncommon, the pooled odds for two clinical trials[6,7] of acute coronary syndrome for patients receiving dabigatran vs warfarin was 1.8 (95% CI, 0.6-6.2; NNH = 313) but nonsignificant, with only 747 patients receiving dabigatran and 692 receiving warfarin in the first, and 976 and 952, respectively, in the second, completing 6 months of anticoagulant therapy.

In a comprehensive review of individual patient data from atrial fibrillation and VTE clinical trials, scientists from dabigatran's sponsor, Boehringer-Ingelheim GmbH, concluded "the rate of myocardial infarction with well-controlled warfarin (for stroke prevention in patients with atrial fibrillation and acute VTE treatment or secondary VTE prevention) is lower than with dabigatran 150 mg twice daily"(OR, 1.4 [95% CI, 1.1-1.9] for 150 mg bid and OR, 1.3 [95% CI, 0.96-1.8] for 110 mg bid.[8]

Subsequent dabigatran clinical trials have provided more evidence of this direct thrombin inhibitor's association with thrombosis on abnormal cardiac endothelium. On-treatment myocardial infarction occurred in 13 patients receiving dabigatran vs three patients receiving warfarin, all receiving extended anticoagulant treatment after VTE (OR 4.3; 95% CI, 1.2-15.2; $P = .02$; NNH = 143).[9] This trial had > 1,400 patients per treatment group; these differences did not emerge in trials with fewer patients or when dabigatran was compared with placebo in a similar population.[9] A clinical trial[10] comparing dabigatran with warfarin for patients with mechanical heart valves was stopped prematurely because of a high rate of adverse events in those receiving dabigatran, including stroke presumably related to valve thrombosis (nine events vs zero events; $P = .03$; NNH = 20).

Argatroban, lepirudin, and desirudin are each direct thrombin inhibitors marketed in various venues for treatment of heparin-induced thrombocytopenia (HIT). Desirudin is also sold for thromboprophylaxis in hip replacement surgery. Because large numbers of patients with HIT cannot be accumulated for clinical trials, the treatment studies used historical control subjects. Of course, the patients with HIT were highly prothrombotic. Ruling in or out a small but significant increase in cardiac thrombosis associated with those drugs from those studies cannot be done.

Historically, from two clinical trials reported together[11] of the oral direct thrombin inhibitor ximelagatran compared with injected anticoagulant followed by warfarin for acute DVT with or without pulmonary embolism, there was an increased odds of acute coronary syndrome with ximelagatran treatment (OR, 10.1; 95% CI, 1.3-79; $P = .006$; NNH = 124). A meta-analysis that included ximelagatran and dabigatran (as well as other antithrombotic drugs) for atrial fibrillation suggested warfarin provided superior protection against myocardial infarction compared with the two oral direct thrombin inhibitors.[12]

Why should direct thrombin inhibitors be associated with higher cardiac thrombotic risk than warfarin or heparin? Authors of the heart valve study[10] speculated that the combination of tissue factor- and contact activation-generated thrombin might overwhelm a pharmacokinetically controlled dabigatran level. Ex vivo, plasma samples from warfarin-administered patients generated lower peak thrombin levels than those from dabigatran-administered patients.[13] What is known is that both vitamin K antagonists like warfarin as well as heparin indirectly inhibit thrombin but also inhibit other clotting factors. To date, no increase in cardiac thromboses for direct (eg, rivaroxaban, apixaban) and indirect (eg, fondaparinux) specific inhibitors of activated factor X is evident in their many published active-comparator-controlled clinical trials.

Physicians now have at least one sound alternative (injected unfractionated and low-molecular-weight heparins, oral vitamin K antagonists, and factor