Ximelagatran Versus Warfarin in the Prevention of Atrial Fibrillation–Related Stroke: Both Sides of the Story

To the Editor:

We have carefully read the interesting article by Akins et al1 focusing on a pivotal issue in the prevention of atrial fibrillation-related stroke. The authors pooled the data from high-risk (previous stroke/TIA) versus nonhigh-risk (no previous stroke/TIA) patients included in SPORTIF III and SPORTIF V trials in which the direct thrombin inhibitor ximelagatran was compared with warfarin in the primary and secondary prevention of thromboembolic stroke. The authors concluded stating that ximelagatran was at least as effective as warfarin.

In our opinion, some points deserve attention and a deeper examination. Our group recently published nonfunded/nonbiased meta-analytic data about the comparison of ximelagatran versus conventional anticoagulant therapy in different clinical settings (ie, prophylaxis of deep vein thrombosis after total knee or hip replacement; treatment of deep vein thrombosis, and primary prevention of thromboembolic stroke in patients with nonvalvular atrial fibrillation) showing that ximelagatran/melagatran was comparable to conventional anticoagulant therapy in terms of risk of major adverse events. The overall risk of major bleeds was also comparable between the 2 treatment modes, although in the management of deep vein thrombosis and in the prevention of atrial fibrillation-related stroke, prolonged ximelagatran/melagatran was associated with a significantly lower risk of bleeds (in absolute terms, the risk was reduced from 3.3% to 2.2%, with a number needed to harm by causing one major bleed in the conventional anticoagulant arm of 100).5,6 However, the risk of hepatic toxicity, measured as the rate of alanine aminotransferase elevation ≥3 above the upper normal limit was prohibitive with ximelagatran. In particular, for treatments of ≥3 months the odds of hepatotoxicity was 6.73 (5.01 to 9.05; P < 0.001). In absolute terms, for prolonged treatments, the incidence of hepatotoxicity increased from 1.1% to 7.1%, with a number needed to harm of 17.

This point is crucial because, although ximelagatran was promising for some attractive features and was associated with a lower risk of hemorrhages, in the era of evidence-based medicine one of the duties of the research is the completeness and, in our opinion, 2 points in the discussion could be misleading. The first is the statement that the results in the group of high-risk patient (ie, a 0.5 increase in the percentage of patients free of stroke per year for the ximelagatran group) are “quite encouraging,” and the second is that the manufacturer “voluntarily” decided to withdraw the product from the European market. Serious liver injury and related mortality have persuaded the Food and Drug Administration to deny approval of ximelagatran/melagatran in the United States7 and the European Agency for the Evaluation of Medicinal Products to approve only ximelagatran/melagatran against conventional anticoagulation: a meta-analysis of 13 randomised controlled trials enrolling 22639 patients. Int J Cardiol. 2007 (in press).


Disclosures
None.

Luca Testa, MD, PhD
Institute of Cardiology
John Radcliffe Hospital
Oxford, UK

Pierfrancesco Agostoni, MD
Antwerp Cardiovascular Institute Middelheim
Antwerp, Belgium

Antonio Abbate, MD
Department of Medicine
Virginia Commonwealth University
Richmond, VA

Graziana Trotta, MD
Institute of Cardiology
Catholic University
Rome, Italy

Giuseppe G.L. Biondi-Zoccai, MD
Division of Cardiology
University of Turin
Turin, Italy

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Luca Testa, William Van Gaal, Pierfrancesco Agostoni, Antonio Abbate, Graziana Trotta and Giuseppe G.L. Biondi-Zoccai

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