Association between statin use and ischemic stroke or major hemorrhage in patients taking dabigatran for atrial fibrillation

Antoniou and colleagues[1] reported that dabigatran etexilate was associated with increased major hemorrhage risk, when coadministered with simvastatin or lovastatin, relative to other statins. Although we appreciate the efforts of the authors, several points deserve attention.

Evidence that simvastatin or lovastatin inhibit P-glycoprotein (P-gp) is based on in-vitro findings and requires confirmation in clinical pharmacology studies. P-glycoprotein inhibitors are expected to increase plasma levels of the P-gp probe, digoxin.[2] Upon coadministration, simvastatin and atorvastatin are associated with slight increases in plasma digoxin concentration;[3] these marginal effects are consistent with those observed in an atorvastatin and dabigatran etexilate drug–drug interaction study.[4] Lovastatin had no effect on digoxin.[5]

Using data from the RE-LY(R) study, Liesenfeld and colleagues[6] showed that the prototypic P-gp inhibitors (verapamil, amiodarone, diltiazem) resulted in ≤ 23% increases in dabigatran steady state exposure.[6] No difference in hemorrhagic events was observed between patients with/without statin comedication in an unpublished analysis from the RE-LY(R) study (Paul Reilly, et al., Boehringer Ingelheim Pharmaceuticals Inc.: unpublished data, 2011).

It is unclear whether, for their comparisons, the authors focused on patients initiating treatment and assessed baseline characteristics at that time point. Another approach would be inappropriate.[7–10] The authors adjusted for variables showing imbalance between cases and controls, but do not seem to have considered baseline stroke and bleeding risk. The authors used a random index date for the controls, and dabigatran exposure is likely different between patients on simvastatin/lovastatin and patients on other statins. The definition of statin exposure (one prescription within 60 days from index date) makes assessment of concomitant exposure to dabigatran and statins difficult.

Published pharmacokinetic and clinical data provide no evidence that coadministration of dabigatran etexilate and statins, including simvastatin and lovastatin, results in an increase in dabigatran exposure or bleeding rates. Open questions regarding the study design may lead to some uncertainty over the conclusions drawn by Antoniou and colleagues.[1]

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