Response to Letter by Stöllberger et al
Regarding Article, “Stroke Risk and Antithrombotic Strategies in Atrial Fibrillation”

Response:
We thank Dr Stöllberger and colleagues for their interest in our recent review article, “Stroke Risk and Antithrombotic Strategies in Atrial Fibrillation,” and we concur with the sentiments they have expressed.

1. We agree that good international normalized ratio control is crucial for the effectiveness of vitamin K antagonists and that there are several potential strategies to optimize international normalized ratio control, which may include self-monitoring. As noted in our article, we agree that time-in-therapeutic-range is of paramount importance with warfarin therapy, and it also has prognostic implications. The time-in-therapeutic-range is in part caused by differences in health systems as Stöllberger et al suggest; however, there may also be the possibility that those with a better prognosis have a greater time-in-therapeutic-range, rather than the reverse. In addition, there are many patients not on oral anticoagulant because of difficulties with control and compliance, and the alternative anticoagulants, such as the newer antithrombins and anti-Xa agents, have a role in filling this gap.

2. We agree that the new oral anticoagulants are substrates of the intestinal P-glycoprotein transport system and that many hospitalized atrial fibrillation patients are prescribed drugs that may affect the P-glycoprotein system; the latter would influence blood concentrations of the new oral anticoagulants. Although this did not appear to be a problem in the RE-LY² trial, where patients were rigorously assessed, followed, and managed, the potential interaction of P-glycoprotein inhibitors and novel oral anticoagulants outside the clinical trial setting, in general clinical practice, is uncertain. However, with dabigatran, when taking the higher dose, lower serum levels caused by concurrent effects of other drugs that affect the P-glycoprotein system are still likely to have a salutary effect, and the therapeutic window for dabigatran may not be as narrow as for oral anticoagulant.

We also agree that the long-term effects of inhibiting thrombin generation with the new oral anticoagulants are uncertain. It is therefore important that the long-term safety of inhibiting thrombin generation with dabigatran is being evaluated in an ongoing, long-term, follow-up study of RE-LY patients (RELYABLE, NCT00808067).³

The long-term effects of all the new alternative anticoagulants are obviously of great importance. In RE-LY, there was a higher overall rate of myocardial infarction of borderline significance if both doses of dabigatran are considered together compared with warfarin (1.6% versus 1.2%; P=0.055), but not for each dose considered alone (each dabigatran dose had a myocardial infarction rate of 0.81% to 0.82%/year versus 0.64%/year for warfarin, with relative risk of 1.29 and 1.27, and 95% CI for each dose crossing unity, although survival analysis for both doses combined was not presented).³ If these small differences are real, given the well-demonstrated efficacy of warfarin for prevention of recurrent myocardial infarction in the WARIS studies, it could mean that warfarin is superior to dabigatran for the prevention of myocardial infarction.⁵

3. Stöllberger et al have reiterated the statements in our review on the caution required with left atrial appendage occlusion devices caused by high procedural events and the absence of long-term outcome data.

Disclosures
C.M. has nothing to disclose. G.J.H. has received honoraria for serving as a member of the executive committees of the ROCKET-AF (Johnson and Johnson), AMADEUS (Sanofi-Aventis), and BOREALIS (Sanofi-Aventis) trials; the stroke outcome adjudication committees of the RELY and AVERROES trials; the steering committee of the TRA-2P TIMI 50 trial (Schering Plough); and the Australian Pradaxa (dabigatran) advisory board (Boehringer Ingelheim). S.B.F. has received travel support to attend a meeting (Boehringer Ingelheim).

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