Dr. de Boer brings up some important design considerations regarding our analysis of the TREAT-AF (Retrospective Evaluation and Assessment of Therapies in AF) study (1). He correctly argues that there can be misclassification of digoxin exposure in our design. Our observational study was designed as an intention-to-treat analysis, comparing the strategies of use and nonuse of digoxin as initial or early therapy in patients with newly diagnosed atrial fibrillation (AF) (1). Although we found that 80% of patients in the digoxin arm were still on therapy at 1 year, there is a strong possibility of digoxin exposure in the control arm after 90 days. However, we believe this would not represent “misclassification” in an intention-to-treat design but rather crossover of therapy. Generally, crossover would bias toward the null and therefore would not likely account for the observed difference in outcomes.

Therapy crossover is common in management of AF and complicates analysis and interpretation of randomized trials. Crossover may be motivated by observed and unobserved confounders, which can further complicate analysis and may in part explain the seemingly incongruent results of 2 secondary analyses of digoxin using the same AFFIRM (AF Follow-Up Investigation of Rhythm Management) trial data set (2,3). Separating patients into exposed and unexposed blocks of person-time without adjusting for time-varying confounders could exaggerate treatment effect (or harm) (4). On the other hand, contemporary approaches such as marginal structural models that incorporate time-varying data can bias toward the null from overadjustment or model misspecification (5).

For these reasons, we elected to study a new disease cohort using an intention-to-treat design that evaluated digoxin as an initial treatment strategy. Our decision to adjust for adherence rather than to stratify was to account for variation in adherence in the overall point estimate. We agree that further work to explore the heterogeneity of treatment effects across strata of adherence and time course of therapy would be valuable and complementary.

REFERENCES

Patent Foramen Ovale and Paradoxical Systemic Embolism
Can We Determine High-Risk Characteristics by Echocardiography?

We read with interest the review paper on paradoxical embolism by Windecker et al. (1). It was suggested, on the basis of available evidence from published reports, that device closure of patent foramen ovale (PFO) should be considered in patients with first-timecryptogenic stroke, particularly in those with high-risk criteria, such as presence of an atrial septal aneurysm (ASA), large PFO, Eustachian valve, or Chiari network. The viewpoints of
Windecker et al. on those with high-risk criteria should be discussed and clarified.

With routine clinical application of intracardiac echocardiography (ICE) in more than 3,000 cases of left heart ablation, it has been proven that ICE is an excellent ultrasound modality that can be used for diagnosis of an ASA, PFO, variant Eustachian valve, or Chiari network (2). A statistical analysis of 938 consecutive cases with left heart ablation from 2012 to August 2014 showed that the incidence of ASA was 6.9% and the incidence of PFO was 6.4%. A variant Eustachian valve or Chiari network in the right atrium is more commonly detected by routine ICE. Generally speaking, ASA without a septal defect and probe PFO should not be considered forms of an atrial septal defect and are benign. By themselves, they cause no hemodynamic abnormalities. A previous case report (3) showed a small PFO (diameter of <4 mm) with left to right shunting (Figure 2E in the review by Windecker et al. [1]) and a transseptal sheath for hemodynamic support with a left ventricular assist device (the TandemHeart) (3). An iatrogenic PFO with large sheath placement at the interatrial septum is commonly detected with ICE monitoring (Figures 1A and 1B). In the case report (3), the conclusion of “death by PFO” remains questionable. Iatrogenic PFO (<4 mm) might not be excluded, even in Figure 3 in the case report (3), with a small/weak right-to-left shunt flow (not mosaic color pattern) accompanying the transseptal sheath. A small PFO could not explain that particular case, in which deep left femoral vein thrombosis and bilateral subsegmental pulmonary embolism advanced to myocardial embolic infarction.

We disagree with the viewpoints of Windecker et al. (1) on device closure in those with high-risk criteria, including an ASA, PFO, Eustachian valve, or Chiari network. We particularly dispute the idea that a prominent Eustachian valve would direct blood from the inferior vena cava toward the PFO; our figure (Figures 1C and 1D) suggests that this is not the case. ICE color Doppler flow imaging is superior to transient imaging with injected bubbles. The same applies to the Chiari network in the right atrium with chaotic motion (Figure 1E). Therefore, device closure should not necessarily be considered in patients with first-time cryptogenic stroke who have these benign variant anatomic abnormalities.

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