Figure 1 shows that the majority of the studies had a point estimate to the right of 0. The 2-sided p value from the sign test is 0.023. In Study 9, the treatment effect in the United States seemed to be substantially better than outside the United States, but in Studies 5, 12, 13, 17, and 21, the treatment effect appeared to be substantially worse in the United States than outside of the United States.

In the random effects meta-analysis, the estimate of the between-trial variability was 0. The estimate of the mean log-hazard ratio was 0.103 with a standard error of 0.035. Thus, the approximate confidence interval is (0.031 to 0.175) and the 2-sided p value for the test of mean zero difference is p = 0.007. Because the estimate of the between-trial variability was zero, the point estimate and estimated standard error from the fixed effect model are identical to those from the random effect model described.

It seems that there may be systematic differences between the treatment effects observed in the United States and non-U.S. regions, with the U.S.-specific treatment effect usually being smaller. Some factors that might contribute to differences in treatment effects between regions include differences in compliance, follow-up, and concomitant medications. There are other possible explanations, and in any particular trial the factors that may attenuate the treatment effect may not be anticipated or even measured. In future trials, if there is a concern that there may be a difference in the treatment effect in the United States versus other countries and the U.S.-specific treatment effect is of interest, there are both issues of design and analysis to consider. An analysis could be planned in the protocol to deal with this possible difference. This could include formal tests for interaction or examination of differences in baseline characteristics or background therapy between regions. Planning for a test for qualitative or quantitative interaction is helpful in some cases, but both tests are known to have low power when the differences are moderate, and this situation may not be totally satisfactory for this purpose. In studies in which a goal of the study is to confirm a global treatment effect and a country-specific treatment effect, there should be a plan to obtain a sufficient amount of information in the country or region of interest, and an analysis should be pre-planned to do so.

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Letters to the Editor

Safety of Dabigatran Versus Warfarin for Periprocedural Anticoagulation in Patients Undergoing Ablation for Atrial Fibrillation

We read with interest the recent report by Lakkireddy et al. (1) regarding periprocedural dabigatran in patients undergoing atrial fibrillation (AF) ablation. This multicenter study noted a significant increase in bleeding and thromboembolic complications with essentially uninterrupted dabigatran versus uninterrupted warfarin. Their findings emphasize the importance of fully understanding the pharmacokinetics of pharmacologic agents, particularly anticoagulants, which can cause serious complications. Dabigatran possesses several pharmacokinetic properties that are important to safe periprocedural use. These properties predict the potential for increased complications when used in an uninterrupted manner for ablations.

1. There is an in vitro heparin-dabigatran interaction (2). Dabigatran potentiates heparin’s antithrombotic properties with quantitatively doubled anticoagulant effect. The increased bleeding complications noted by Lakkireddy et al. (1) suggest that this in vitro interaction very likely occurs in vivo. This interaction is much less apparent with rivaroxaban and apixaban (2).
2. Immediately following hip surgery, dabigatran absorption can be both delayed and reduced (3). Thus, oral dabigatran immediately after an AF ablation may not provide anticoagulation during the immediate post-procedural period. Enoxaparin immediately post-ablation will avoid this anticoagulant lapse until oral absorption of dabigatran occurs.
3. Dabigatran has no direct antidote, so when bleeding complications occur they may be more difficult to treat than those with warfarin.

Based on these pharmacokinetic considerations, we agree it is not appropriate to use dabigatran in a nearly uninterrupted manner. This does not diminish dabigatran’s utility when used in an interrupted manner. We have reported the safety of interrupted dabigatran in 123 patients (4) and have subsequently extended our experience to more than 500 patients (40% of whom were on dabigatran pre-ablation) without a single hemorrhagic or thromboembolic complication. As emphasized by Lakkireddy et al. (1),

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there were significant differences in our use of dabigatran that likely account for the safety and efficacy demonstrated in our series. Heparin administration to patients in whom dabigatran has not been fully interrupted might be expected to lead to increased bleeding complications due to a probable drug-drug interaction and poor absorption post-ablation might lead to increased thromboembolic events. The convenience of standardized oral dosing and elimination of INR monitoring makes dabigatran and other new oral anticoagulants attractive alternates to warfarin for AF ablation patients.

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Please note: Dr. Winkle has reported that he has no relationships relevant to the contents of this letter to disclose. Dr. Mead is a consultant and director to i3Rhythm and Voyage Medical, an advisor to Medtronic and Proteus Biomedical, and a stockholder in i3Rhythm and Proteus Biomedical. Dr. Engel is a speaker and advisor to Medtronic. Dr. Kong is a member of the Medtronic Advisory Board. Dr. Patrawala is a consultant to and stockholder in Voyage Medical.

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Reply

We appreciate the interest of Dr. Winkle and colleagues in our recent study on the safety of periprocedural dabigatran during atrial fibrillation (AF) ablation (1). We do concur with some of the comments made by Dr. Winkle and colleagues and would like to add some more information to help us all better understand this important aspect of periprocedural anticoagulation during AF ablation.

1. The in vitro interaction of simultaneously administered dabigatran and heparin is well known and is probably an extension of their pharmacodynamic properties. However, starting parenteral heparin 12 h after the last dose of dabigatran is considered reasonably safe for bridging anticoagulation before any invasive procedure, as supported by the safety profile in more than 600 patients who were bridged in the Re-Ly trial, and is currently recommended (2). The approximate mean time from the last dose of dabigatran to intravenous administration of heparin was 16 h. As mentioned in our paper, the reason for the increased bleeding outcomes in our study may still partly be explained by the interaction between unfractionated heparin and the residual dabigatran effect at the time of the procedure.
2. The absorption of dabigatran after hip surgery can be delayed and potentially reduced in a minority of patients as shown by an increase in the time to peak and a decrease in the peak plasma levels (3). However, the therapeutic effect of the drug can be seen at 50% of the peak plasma level. These differences in the plasma levels after a hip surgery are probably not clinically significant as evidenced by multiple trials showing either noninferiority or superiority of dabigatran when compared with heparin in preventing venous thromboembolism in postoperative settings (4).
3. We do recognize that the lack of a direct antidote to dabigatran could make the management of bleeding episodes difficult. However, the same is true for subcutaneous enoxaparin, which was the primary anticoagulant used for bridging patients to dabigatran by Dr. Winkle and colleagues.

There is overwhelming data to support much better outcomes when AF ablation is done on therapeutic warfarin when compared to the interrupted approach (5,6). When enoxaparin is used for bridging, the bleeding complications normally occur after discharge and might not be captured unless an appropriate data collection system is in place and the thromboembolic complications (in 1% to 5% of patients) tend to be clustered in nonparoxysmal AF cases (5). Therefore, the lack of thromboembolic complications in Dr. Winkle and colleagues series could be due to either a different patient selection or a limited ablation lesion set, which may be inadequate to achieve freedom from atrial arrhythmias in the nonparoxysmal group.

We do hope that the newer anticoagulants (rivaroxaban and apixaban), with their slightly different pharmacokinetic and pharmacodynamic profile, would be safer than dabigatran in this setting. Future studies evaluating these drugs as periprocedural anticoagulants for AF ablation are urgently needed.

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