completely occlude the ostium. The shape mismatch between the LAA ostium and the device is clearly evidenced in the three-dimensional transesophageal echocardiographic images, such as the one included in our paper (1).

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New Oral Anticoagulants: Good but Not Good Enough!

In the recent article by the European Society of Cardiology Working Group on anticoagulants in heart disease (1), the authors describe in great clarity the emerging data regarding new anticoagulants for the treatment of nonvalvular atrial fibrillation. In the closing segment of conclusions and implications, the authors list their concerns regarding "scientific knowledge gaps" and the lack of clinical tools (like reversal agents or pharmacodynamic monitoring objectives and means). Regrettably, in the name of simplicity (i.e., no pharmacodynamic monitoring or dose adjustment and rigid dose regimens with a one-size-fits-all strategy), we have taken potentially great drugs and made them good, but truly not good enough for some of our individual patients.

Why should we bother with pharmacodynamic studies of these agents? Numerous known factors (body weight, age, renal function, liver function, Cyp 3A4, and P-glycoprotein inhibitors and inducers) and probably many unknown factors interact with these agents to create heterogeneous effect on plasma levels and coagulation profile. Because these agents are meant to be lifelong prescriptions, they probably command the effort of knowing how the individual patient responds to the prescribed agent and dose. This is especially true because we have the option of prescribing alternative drugs and doses to suit the individual patient best.

Major bleeding is the most common complication of these agents in patients with nonvalvular atrial fibrillation (exceeding in most current studies the rate of clinical thromboembolism) and probably can be reduced by individualized drug prescribing and dosing based on individual pharmacokinetic and pharmacodynamic studies. Further, thromboembolism and stroke possibly related to therapeutic failure potentially can be reduced by monitoring and dose adjustments to enhance efficacy.

Should we decide to extend the use of these agents to other patient subsets (valvular atrial fibrillation, mechanical valves, hypercoagulable states), establishing monitoring protocols and delineating the therapeutic targets may facilitate the design of future clinical trials and may optimize both efficacy and safety. As an example, in the PETRO (Prevention of Embolic and ThROmbotic events study) among patients receiving dabigatran 150 mg twice daily, there was an approximately 7-fold difference in between the fifth and 95th percentile in both peak (95% confidence interval: 64 to 443 ng/ml) and trough (95% confidence interval: 31 to 225 ng/ml) plasma levels (2). This 7-fold difference translates into significantly higher exposure, thrombin time, and bleeding risk. On the other end of the spectrum, approximately 15% of the patients had peak activated partial thromboplastin time of <40 s.

Future research should attempt to delineate: 1) the best pharmacodynamic monitoring tools for dabigatran (2) and Xa inhibitors (3,4); 2) the best monitoring protocol (5) (including timing relative to dosing and frequency); and 3) the best therapeutic targets. It is very likely that by using these strategies, we could enhance further the efficacy and safety of these agents and could extend their use to new indications.

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Reply

We thank Dr. Kaluski and colleagues for their thoughts on the possibility of individualizing dosing strategies for the new oral anticoagulants. From a theoretical perspective, the one-size-fits-all strategy seems not to be ideal, because of the potential pharmacokinetic interactions, the variability in drug metabolism during lifelong administration, and the inherent risks of thrombosis in the case of underdosing or of bleeding in the case of overdosing. For this reason, we favored the European