they do not know who they help (they do not know whether a stroke is ever prevented in an individual patient). Because of this philosophy, there is a danger that the 110-mg dose would be over utilized, if approved.

For those who would like to see the 110-mg strength marketed, I am sympathetic. It is easy to envision some patients who would be excellent candidates for the 110-mg strength, i.e., patients with a history of GI bleeding, patients who are physically unstable and prone to falling, etc.

The Advisory Committee considered this issue at some length, and was split fairly evenly. The Division was unanimous in its opinion that only the 150-mg strength should be marketed, and Dr. Stockbridge was adamant about it.

My decision to approve only the 150-mg strength was a difficult one, based largely on the views of the Division, and my concern about loss of efficacy in many thousands of patients who would inappropriately opt for the lower dose, if available. If the applicant can make a stronger case for availability of the 110-mg strength, the Division can reconsider approval of the lower dose in a supplement.

Superiority to Warfarin:

Despite the apparent overall superiority of dabigatran to warfarin at the 150 mg BID dose in the population as a whole, the effect was driven entirely by patients in the warfarin group who were not as well controlled with respect to INR. Patients whose INRs were well-controlled with warfarin had the equivalent risk of having a stroke or fatal event as those treated with dabigatran 150 mg. Thus, the superiority is really conditional, and depends on how well warfarin is used. For "real world" warfarin use in a large population, dabigatran may be superior, but this may not be true for an individual patient. It is important, therefore, not to provide dabigatran with a superiority claim to warfarin, because it would imply that even those well-treated with warfarin should be switched to dabigatran. Clearly, that is not the case.

Non-valvular Atrial Fibrillation:

RE-LY was designed explicitly to study patients with non-valvular AF, and the enrollment criteria excluded patients with significant valvular disease. The indication will be restricted to patients with non-valvular atrial fibrillation. We recognize the potential for use in patients with significant native valvular disease, but such use would be off-label.

Renal Insufficiency:

In not approving the 110-mg strength, dosing options were limited for patients with severe renal insufficiency, but the Division concluded that it would be desirable to provide access to dabigatran for this patient population. Based on pharmacokinetic modeling, comparing pharmacokinetic data from RE-LY with data from a small study of subjects with compromised renal function, a dosing regimen of 75 mg bid appears appropriate for patients with estimated CrCL 15 to 30 mL/min. The 75-mg strength is already manufactured by the applicant (and marketed in the EU), and can be marketed in the US. Patients with CrCL $\geq$ 31 mL/min should receive 150 mg bid. Based on data from 1 subject who received hemodialysis, dabigatran appears dialyzable, but there are not sufficient data to make any dosing recommendation in the dialysis population.