We thank Drs. Almeda and Scher for their interesting comments. We have previously reported that ostial in-stent restenotic lesions treated with intracoronary radiation have equivalent clinical outcomes to nonostial irradiated in-stent restenotic lesions and have significantly reduced recurrent restenosis compared to in-stent restenotic ostial lesions treated with conventional percutaneous intervention alone (1). We did not find that postprocedural minimal luminal diameter correlated with subsequent failure, although smaller vessels (based on reference vessel diameter) have higher restenosis rates. Intracoronary radiation therapy reduces angiographic restenosis in all sized vessels, with the effect seen predominantly in small vessels (<2.5 mm) (2). In the current analysis, these factors did not influence clinical outcomes.

The initial enthusiasm for the cutting balloon as an Interventional strategy for in-stent restenosis has not been supported by reduced event rates in clinical trials. There is no evidence showing the cutting balloon to be superior over conventional angioplasty with adjunctive intracoronary radiation.

Our ongoing analysis suggests the time to first target vessel revascularization in the majority of patients is between 6 to 12 months, suggesting there is a “delay” in recurrent restenosis compared to conventional angioplasty. Recurrent restenosis beyond 12 months has been infrequent in the majority of published Washington Radiation for In-stent Restenosis Trial (WRIST) series.

The overall use of glycoprotein (GP) IIb/IIIa inhibitors in the current analysis was 22% and did not influence clinical outcomes. Integritin WRIST was a randomized trial addressing whether the treatment of epitifibatide (small-molecule competitive GPIIb/IIIa inhibitor) would improve both the procedural and the long-term outcomes in patients undergoing treatment for in-stent restenosis with intracoronary radiation therapy. That study (submitted for publication) did not detect differences in major clinical events with use of GPIIb/IIIa inhibitors. However, at any end point of the study there was nonsignificant reduction of creatine phosphokinase release in the epitifibatide group when compared to control, and these findings may stimulate a larger study to detect benefit of GPIIb/IIIa inhibitors in the setting of intracoronary radiation therapy.

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Clinical Decision Making on Statin Drug Interactions

Recent comments by Dr. Hansten (1) regarding drug-drug interactions and myopathy risk with statins provide important additional information to guidelines issued last year on the use of these agents (2). The metabolism of statins is complex, with extensive conversion between the lactone, open-acid, and glucuronidated forms as well as other less common metabolites (3,4). As Dr. Hansten noted, pravastatin undergoes the least cytochrome P450 (CYP)-mediated metabolism and is therefore the least susceptible to interactions with drugs that inhibit this system (5–7). Also, simvastatin and lovastatin are more prone to interactions with CYP inhibitors, owing in part to the fact that these agents are administered as the more lipophilic lactone form, whereas all other agents (including cerivastatin) are administered as the open-acid form (3,8). And though these findings are important, I believe they should be incorporated into clinical practice with several important caveats in mind.

First, the kinetics of statins is more complex than just their hepatic handling. The 5-fold increase in pravastatin area under the curve (AUC) induced by cyclosporine is now widely recognized to be the result of inhibition of the adenosine triphosphate-binding cassette transporter P-glycoprotein (Pgp) in the gut wall (9,10). Inhibition of Pgp allows greater absorption of pravastatin, thereby increasing its systemic bioavailability, which is already four-fold higher than lovastatin and simvastatin (3,8). Other inhibitors of Pgp include erythromycin, quinidine, amiodyarone, and verapamil (11–13).

Second, the greatest risk of myopathy with statins occurs when they are used with other lipid-lowering agents and is the result of pharmacodynamic, as well as pharmacokinetic, interactions (3,8,10,14). In this regard, pravastatin carries an increased risk similar to the other agents (5,15,16). And though case reports of myopathy are more common with lovastatin and simvastatin, four published studies of 39,285 patients and over 160,000 patient-years of therapy have failed to find a greater risk for these agents compared to placebo (14,17,18).

Finally, the primary aim of statins is to reduce cardiovascular (CV) events. The recent failure of 40 mg of pravastatin to significantly reduce CV events in the ALLHAT–LLT trial (19) stands in contrast to the recent findings of a robust benefit of 40 mg of simvastatin in the HPS trial (17). It is also notable that while a lower threshold low density lipoprotein (LDL) of 125 mg/dl was found for the beneficial effects of pravastatin in both the CARE and LIPID trials (20,21), no such threshold finding for simvastatin was found in the 4S trial (18). In fact, in the HPS trial, CV events were significantly reduced by simvastatin in the 3,500 participants with a baseline LDL below 100 mg/dl (mean 97 mg/dl) (17).

Thus, though interactions should always be considered when prescribing multiple medications, until clearer mechanisms of both benefit and risk are elucidated for statins, outcomes data remain

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