interaction, described by ex vivo testing, has a clinically significant effect on thrombosis rates.

This retrospective cohort study of 9205 patients who were prescribed clopidogrel after discharge has prompted serious discussion on the potential effects of PPIs in modulating the clinical effectiveness of the thienopyridine clopidogrel in patients with ACS. The key findings of this analysis include a 25% increased risk of the composite endpoint of death and rehospitalization for ACS among patients receiving a PPI and clopidogrel compared with those patients receiving only clopidogrel. There was no statistically significant difference in mortality rates, although there was an 86% increased risk of rehospitalization for ACS and a 49% increased risk in the need to undergo a revascularization procedure. There were significant differences in the 2 populations of patients studied: patients in the clopidogrel plus PPI group had a greater prevalence of diabetes, prior MI, heart failure, peripheral vascular disease, renal disease, and dementia, and were less likely to be taking aspirin, factors that could have had an effect on outcomes.

Unfortunately, only ischemic-type complications were considered in this assessment of the safety of combination therapy, and there was no analysis of the impact on bleeding episodes. We know that the combination of clopidogrel and aspirin was associated with a 37% increase in major bleeding and 112% increase in minor bleeding compared with aspirin alone in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.[7] Therefore, the benefits and risks of clopidogrel use with a PPI need to also take into account any reduction in bleeding risk associated with combination use.

Unfortunately, patients with a history of gastrointestinal bleeding or any bleeding event during the index hospitalization or after discharge were excluded from this analysis, as were patients who filled a prescription for an H_2-antagonist, which precludes the ability to obtain a true assessment of safety in the widest population of patients presenting with ACS.

Although PPIs have been shown to reduce the antiplatelet effects of clopidogrel in ex vivo assessments of platelet activity, there are no clear data showing that this effect is clinically relevant. That being said, it seems prudent to withhold the use of PPIs in patients who are prescribed clopidogrel unless there is a compelling indication. If possible, other options, including H_2-antagonists, should be considered. ■

Statin Therapy

Avoiding Statin-Related Muscle Side Effects

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Efficacy and Tolerability of Fluvastatin XL 80 mg Alone, Ezetimibe Alone, and the Combination of Fluvastatin XL 80 mg With Ezetimibe in Patients With a History of Muscle-Related Side Effects With Other Statins

Stein EA, Ballantyne CM, Windler E, et al.

Am J Cardiol. 2008;101:490-496.

Muscle-related side effects (MRSE) are the most common side effect of statin therapy that leads to cessation of therapy. Because statin-based therapy plays a key role in the prevention of cardiovascular events, an approach that enables patients who experience MRSE to remain on therapy would be useful. Stein and colleagues[8] evaluated the efficacy and tolerance of fluvastatin XL 80 mg alone, ezetimibe alone, and combination therapy with fluvastatin plus ezetimibe in 199 patients who had MRSE.

Low-density lipoprotein cholesterol (LDL-C) reduction and incidence of MRSE was 33% and 17% in the fluvastatin-alone group, 16% and 24% in the ezetimibe-alone group, and 46% and 14% in the combination-therapy group. More than 80% of patients in the combination therapy group met the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C goals (Figure 3). This is good news for patients who have experienced MRSE from previous statin therapy and who might have required an alternative to statins. ■

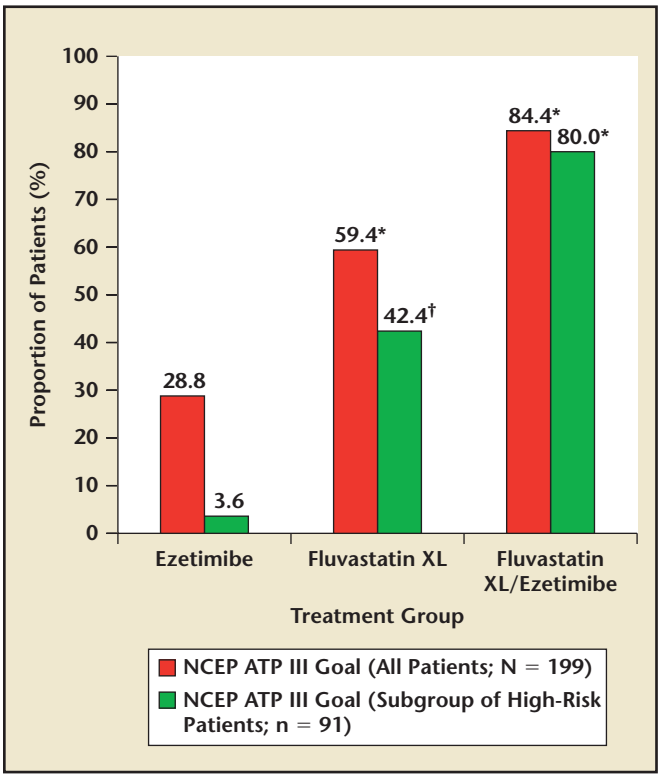

Figure 3. *Proportion of patients achieving their National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) low-density lipoprotein cholesterol goals (< 100 mg/dL for high-risk patients, < 130 mg/dL for moderate-risk patients, and < 160 mg/dL for low-risk patients) at week 12. *P < .001; †P = .002 vs ezetimibe monotherapy. Reprinted from* Journal of the American College of Cardiology. *Volume 101, Stein EA et al. Managing dyslipidemia in chronic kidney disease. Pages 490-496.*[8] *Copyright © 2008, with permission from the American College of Cardiology.*

Diabetes Mellitus

Detection of Ischemia

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Cardiac Outcomes After Screening for Asymptomatic Coronary Artery Disease in Patients With Type 2 Diabetes: The DIAD Study: A Randomized Controlled Trial

Young LH, Wackers FJ, Chyun DA, et al.

JAMA. 2009;301:1547-1555.

The Detection of Ischemia in Asymptomatic Patients With Diabetes (DIAD) study was a randomized trial of 1123 patients with type 2 diabetes mellitus (T2DM) with no symptoms of or previously recognized coronary artery disease, who were assigned to undergo screening with adenosine-stress myocardial perfusion imaging or to not undergo screening.[9] The primary endpoint of the study was the incidence of cardiac death or nonfatal MI. The mean follow-up period was 4.8 years. Patients were excluded if they had angina, a stress evaluation or coronary angiogram within the last 3 years, abnormal resting electrocardiogram, or any clinical indication for a stress test. The mean age of the patients enrolled in the study was 61 years, and the average duration of diabetes was just over 8 years. This was a low-risk population of T2DM; only 6% of patients had large or medium-sized perfusion defects, 10% had small perfusion defects, and 6% had nonperfusion defects (eg, abnormal stress electrocardiogram, transient ischemic dilation). A cardiac event was reported in 12% of patients with moderate to large perfusion defects, in only 2% of patients with normal or small defects, and in 6.7% of patients with nonperfusion defects. During the follow-up period, 30% of patients underwent a nonprotocol stress test due to a clinical indication.

The results of this evaluation are not surprising in the least. The only way a screening examination will lead to a reduction of cardiac risk is if it leads to initiation of life-saving therapy. In this clinical trial, there was no difference in the use of lipid-lowering drugs, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aspirin either at the initiation of the clinical trial or at completion. Abnormal stress tests may have led to revascularization procedures, which, in this low-risk, asymptomatic, stable T2DM patient population, have not been shown to be life-saving.

Is a screening nuclear perfusion examination the correct test to perform in this low-risk patient cohort? Instead, should we be assessing coronary risk by using coronary calcium screening, carotid intimal media thickening (cIMT), or carotid artery assessments with magnetic resonance imaging, which do a much better job of identifying those patients who have subclinical coronary artery disease? Or should we not be screening at all? Only if screening were to impact the selection or intensity of life-saving therapies should it be performed because it is not the screening examination that saves lives but the actions that result from it. A good example would be the 40-year-old woman with T2DM who has an LDL-C of 125 mg/dL, who is not on any prevention therapies, and who then has an abnormal cIMT. Or the 45-year-old man