Troponin elevations in this analysis were associated with the number of diseased arteries, the number of narrowings treated, the number of stents implanted, the increased complexity of the stenosis treated, the stent length, and the use of rotational atherectomy. There was no relationship between troponin elevations and the probability of death or Q wave MI within 1 year. Therefore, it would seem that the use of troponin elevation post elective PCI as an independent marker of a future major cardiac adverse event is not supported by clinical data. It does seem to be associated with the treatment of more complex coronary artery disease. Therefore, the use of troponin assessment after elective PCI as a quality indicator is not founded and should not be considered a PCI quality benchmark.

Long-Term Outcomes in Patients Undergoing Coronary Stenting on Dual Oral Antiplatelet Treatment Requiring Oral Anticoagulant Therapy

Rossini R, Musumeci G, Lettieri C, et al.

Am J Cardiol. 2008;102:1618-1623.

A common clinical conundrum is the management of patients who present with an acute coronary syndrome and/or who undergo coronary stent placement with a need for dual antiplatelet therapy, who also receive oral anticoagulant therapy for conditions such as atrial fibrillation, deep venous thrombosis, or mechanical valve prosthesis. The major concern in these patients is the risk of hemorrhagic complications.[4] In this single-center study, Rossini and colleagues[5] studied bleeding risk in 102 patients undergoing PCI who were placed on dual antiplatelet therapy on top of background use of warfarin to achieve a goal international normalized ratio (INR) of 2.0 to 2.5 in comparison with a control group of 102 patients who received dual antiplatelet therapy and did not require warfarin. Patients requiring warfarin for a prosthetic valve were excluded from this study. The mean duration of triple therapy was 157 days, with follow-up for 18 months.

At 18 months, there was a strong trend toward an increase in bleeding risk in those patients receiving triple therapy versus those receiving dual antiplatelet therapy (10.8% vs 4.9%; $P = .1$). Interestingly, in those patients who had INRs in the targeted range, the risk of bleeding was much lower than in those with an INR exceeding 2.5 (4.9% vs 33%; $P = .00019$). There was no significant difference in major cardiac adverse events.

In summary, this analysis suggests that in patients who require triple therapy (exclusive of those with prosthetic heart valves), targeting a lower INR in the range of 2.0 to 2.5 may be prudent to reduce hemorrhagic complications without compromising clinical efficacy. Before this goal can be considered an official recommendation, it must be studied in a randomized, multicenter clinical trial. ■

Acute Coronary Syndromes

The Interaction of Proton Pump Inhibitors and Clopidogrel

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Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome

Ho PM, Maddox TM, Wang L, et al.

JAMA. 2009;301:937-944.

Ho and colleagues[6] reported on a relationship between the use of proton pump inhibitors (PPI) plus clopidogrel and the risk of rehospitalization and recurrent coronary revascularization in patients presenting with acute coronary syndromes (ACS). Data from this study are important because PPIs are known to reduce the platelet inhibitory effects of clopidogrel. The interaction between the PPI omeprazole and clopidogrel is based on competitive and noncompetitive inhibitory mechanisms on cytochrome P450 2C19 (CYP2C19). This pathway is responsible for the metabolism of clopidogrel, which is a prodrug, to its active form. No prospective randomized clinical trial data have confirmed that this

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. ■