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Intervention & Prevention: Keeping Current with ACUTE CORONARY SYNDROME

JOURNAL CLUB

Clopidogrel with or without omeprazole in coronary artery disease.

Bhatt DL, Cryer BL, Contant CF, et al; for the COGENT Investigators.
***N Engl J Med.* 2010;363:1909-1917.**

ABSTRACT

Background Gastrointestinal complications are an important problem of antithrombotic therapy. Proton-pump inhibitors (PPIs) are believed to decrease the risk of such complications, though no randomized trial has proved this in patients receiving dual antiplatelet therapy. Recently, concerns have been raised about the potential for PPIs to blunt the efficacy of clopidogrel.

Methods We randomly assigned patients with an indication for dual antiplatelet therapy to receive clopidogrel in combination with either omeprazole or placebo, in addition to aspirin. The primary gastrointestinal end point was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, or stroke. The trial was terminated prematurely when the sponsor lost financing.

Results We planned to enroll about 5000 patients; a total of 3873 were randomly assigned and 3761 were included in analyses. In all, 51 patients had a gastrointestinal event; the event rate was 1.1% with omeprazole and 2.9% with placebo at 180 days (hazard ratio with omeprazole, 0.34, 95% confidence interval [CI], 0.18 to 0.63; P<0.001). The rate of overt upper gastrointestinal bleeding was also reduced with omeprazole as compared with placebo (hazard ratio, 0.13; 95% CI, 0.03 to 0.56; P=0.001). A total of 109 patients had a cardiovascular event, with event rates of 4.9% with omeprazole and 5.7% with placebo (hazard ratio with omeprazole, 0.99; 95% CI, 0.68 to 1.44; P=0.96); high-risk subgroups did not show significant heterogeneity. The two groups did not differ significantly in the rate of serious adverse events, though the risk of diarrhea was increased with omeprazole.

Conclusions Among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper gastrointestinal bleeding. There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but our results do not rule out a clinically meaningful difference in cardiovascular events due to use of a PPI.

SYNOPSIS

Omeprazole Prophylaxis Reduces Upper Gastrointestinal Bleeding in Patients on Dual Antiplatelet Therapy

Gastrointestinal (GI) bleeding is a potentially serious complication of long-term dual antiplatelet therapy. Previous studies have shown that proton pump inhibitors (PPIs) reduce aspirin-related acidity and decrease GI complications in patients on antiplatelet therapy as well as reduce the rate of recurrent GI bleeding in patients taking aspirin. There have been some reports, however, of a possible interaction between clopidogrel and PPIs, most notably omeprazole, which may inhibit the antiplatelet effect of clopidogrel.

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NEEDS ASSESSMENT

Although there have been advances in treatment, the incidence, morbidity, and mortality associated with acute coronary syndrome (ACS) remain significant. Therapy for ACS utilizes a combination of surgical interventions (including percutaneous coronary interventions [PCI]) and pharmacotherapy, with antiplatelet agents playing an essential role. There may be significant risks with these interventions, during the procedure itself and in the months and years following. Ischemic events can continue to occur, despite the use of either standard antiplatelet therapy or variations in dosages and combinations of agents. Further complicating the choice of treatment is emerging evidence that not all patients respond comparably to antiplatelet drugs, the so-called "resistance" to aspirin and clopidogrel.[1,2] Because of the recognized limitations of current therapy, improvements in antiplatelet therapy continue to be the focus of much research and development.[3,4] Early evidence from clinical trials suggests that these newer agents offer faster, higher, and more consistent inhibition of platelet aggregation, with better overall bioavailability and an improved pharmacokinetic profile.

According to an editorial published in the *Journal of the American Medical Association*, a physician would need to read nearly 20 articles per day, 365 days a year, to maintain current knowledge in general internal medicine.[5] The value of the Acute Coronary Syndrome Journal Club resides in its ability to summarize and synthesize key scientific advances and clinical lessons from the literature, and offer commentary and insight from recognized experts in the field of treating ACS, who can explain the implications of the latest research findings and clinical trials for day-to-day patient care.

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LEARNING OBJECTIVES

After taking part in this educational activity, participants should be better able to:

- Discuss current approaches to the management of patients with acute coronary syndrome (ACS), particularly those undergoing percutaneous coronary intervention (PCI)
- Review the current guidelines of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions regarding use of dual antiplatelet therapy to prevent myocardial infarction (MI) and death in patients following PCI
- Describe the concept of thienopyridine "resistance" and explain its potential implications for secondary prevention in patients post-ACS
- Evaluate emerging options for antiplatelet therapy post-ACS, including new thienopyridines, non-thienopyridines, and other agents, taking into consideration their safety, efficacy, and mechanisms of action

INTENDED AUDIENCE

Cardiologists and Primary Care Physicians

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James A. de Lemos, MD, has received speakers' honoraria from sanofi-aventis—Bristol-Myers Squibb partnership; consulting fees from AstraZeneca; and research grants from Roche Diagnostics.

Robert P. Giugliano, MD, SM, has received research support from Daiichi-Sankyo and Merck; and lecture honoraria from Bristol-Myers Squibb, Merck, and sanofi-aventis. He is a consultant for Daiichi-Sankyo, Merck, Ortho-McNeil, Regeneron, and sanofi-aventis. Dr. Giugliano is on the data safety monitoring board for Angel Med and on the clinical end point committee for Novo Nordisk.

Anand Rohatgi, MD, has no relevant relationships to disclose.

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Other studies have not substantiated such an interaction. Still, other researchers have identified genetic polymorphisms in the cytochrome P450 pathway that not only may affect the response to clopidogrel but increase the potential for drug-drug interactions.

The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) by Bhatt et al. is the first prospective, randomized study to evaluate the efficacy and safety of concomitant treatment with clopidogrel and omeprazole in patients with coronary artery disease (CAD) on dual antiplatelet therapy. Unfortunately, COGENT was terminated prematurely due to withdrawal of funding and before the target population of 5000 patients was enrolled.

The study population included in the analysis comprised 1876 patients at increased risk for death from cardiovascular (CV) causes. More than 25% of the patients had a history of myocardial infarction (MI). The patients were randomized to daily treatment with fixed-dose clopidogrel/omeprazole (75 mg/20 mg) or clopidogrel 75 mg/placebo for a maximum of 341 days (median, 106 days). The rate of compliance was 84.5% in the clopidogrel/omeprazole group and 83.3% in the clopidogrel/placebo group.

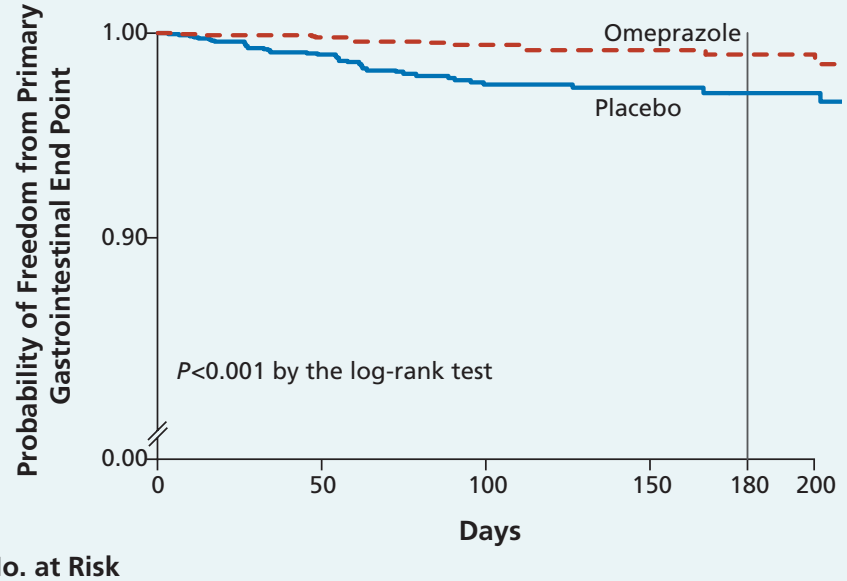
The event rate for the primary GI end point—a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation—at 180 days was reduced from 2.9% in the clopidogrel/placebo group to 1.1% in the clopidogrel/omeprazole group ($P<0.001$) (***Figure***). Significantly lower event rates for the clopidogrel/omeprazole group compared with the clopidogrel/placebo group were seen in individual components of the primary GI end point, including overt gastroduodenal bleeding and overt upper GI bleeding of unknown origin (0.1% vs. 0.6%, $P=0.03$ for each component), as well as the composite of these two components (0.2% vs. 1.2%, $P<0.001$).

Symptomatic GI reflux disease occurred in 0.2% of patients in the clopidogrel/omeprazole group and 1.2% in the clopidogrel/placebo group ($P=0.01$). There was one case of GI obstruction in each group and no reports of GI perforation. Rates of non-GI bleeding events in the clopidogrel/omeprazole and clopidogrel/placebo groups were 0.5% and 0.1%, respectively, and not significantly different.

For the primary composite CV end point (CV death, nonfatal MI, revascularization, or stroke), the event rate at 180 days was not significantly different between the groups: 4.9% in the clopidogrel/omeprazole group and 5.7% in the clopidogrel/placebo group ($P=0.96$). Furthermore, there were no significant differences between the groups in the rates of individual components of the primary CV end point, nor was there significant heterogeneity in the analysis of subgroups of patients with various forms of vascular disease. There also was no difference between the groups in the composite CV end point based on NSAID use or serologic data for *Helicobacter pylori*.

The clopidogrel/omeprazole and clopidogrel/placebo groups had similar rates of overall adverse events (41.3% and 42.8%, $P=0.33$) and serious adverse events (10.1%

Figure. Kaplan-Meier Estimates of the Probability of Remaining Free of Primary Gastrointestinal Events, According to Study Group.



No. at Risk

Placebo	1885	1455	951	523	260	231
Omeprazole	1876	1500	987	553	250	215

The event rate for the primary gastrointestinal end point at day 180 was 1.1% in the omeprazole group and 2.9% in the placebo group.

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and 9.4%, *P*=0.48). For specific adverse events, only diarrhea occurred at a higher rate in the clopidogrel/omeprazole group than in the clopidogrel/placebo group (3.0% vs 1.8%, *P*=0.01), but no case of diarrhea was caused by *Clostridium difficile*.

In COGENT, the addition of omeprazole to the dual antiplatelet regimen of clopidogrel and aspirin significantly reduced the risk for GI clinical events, including upper GI bleeding, and was not associated with a significantly increased risk for adverse CV events, even in high-risk subgroups and for individual CV end points. Although the findings in COGENT do not rule out clinically meaningful differences in CV-event rates associated with PPI prophylaxis, PPI as an adjunct to dual antiplatelet therapy shows promise for reducing the risk for adverse GI events.

COMMENTARY

Is There a "COGENT" Argument For or Against PPI Use in Patients Treated With Clopidogrel?

Among patients with acute coronary syndrome (ACS), few topics have generated more recent controversy than the possible interaction between PPIs and clopidogrel. As a prodrug, clopidogrel must undergo conversion in the liver to its active metabolite, which binds to the P_2Y_{12} receptor on the platelet surface and inhibits platelet activation. Clopidogrel conversion is complex, involving serial activation by cytochrome P450 2C19 isoenzymes. Certain PPIs—most notably omeprazole—compete for *CYP 2C19* and may block the conversion of clopidogrel to its active metabolite.

In vitro pharmacokinetic studies, as well as observational studies,[1] suggested that the clopidogrel/PPI interaction was biologically and clinically relevant; however, more recent observational studies performed in well-characterized clinical trial populations have failed to confirm these findings.[2] Because approximately 50% of patients with ACS who are treated with clopidogrel are also discharged with a PPI,[1] it is critical for practitioners to have a clear assessment of the risks and benefits of concomitant treatment with these two agents.

It is in many ways ironic that the COGENT trial was designed before concern was raised about potential hazards of PPI and clopidogrel co-administration, to evaluate whether the addition of a PPI *improved* outcomes in clopidogrel-treated patients. This study, which intended to randomize 5000 patients with coronary artery disease to either clopidogrel alone or a fixed-dose combination of clopidogrel + PPI, was unfortunately stopped prematurely due to the sponsor's financial collapse, with 3761 patients available for analysis with a mean follow-up of only 106 days.

> "COGENT was designed to evaluate the effects of omeprazole on GI bleeding outcomes and not to definitively exclude an increased risk for ischemic complications."

Although only 51 of the intended 143 GI adverse events were accrued, the authors still found a significantly lower rate of GI events in the omeprazole arm compared with the placebo arm (HR 0.34; 95% CI 0.18-0.63; *P*<0.001). Additionally, overt upper GI bleeding was significantly reduced (HR 0.13; 95% CI 0.03-0.56; *P*=0.001). No differences were observed in rates of adverse CV events.[3]

Does this study allow us to put our concerns about an interaction between PPIs and clopidogrel behind us? Indeed, should we actually consider broader use of prophylactic PPI therapy to reduce the risk of GI bleeding events, an important complication of clopidogrel therapy?

Unfortunately, the limitations of the study preclude definitive conclusions being drawn regarding these important questions. First, COGENT was designed to evaluate the effects of omeprazole on GI bleeding outcomes and not to definitively exclude an increased risk for ischemic complications. In particular, the study was far too small to evaluate the impact of a PPI/clopidogrel interaction on the risk for stent thrombosis, which although uncommon, would be the most feared outcome from a PPI/clopidogrel interaction.

Moreover, with only 109 ischemic events, the study cannot exclude a clinically meaningful difference in ischemic-event rates between the two arms. The implications of early termination of the trial also need to be considered. The length of follow-up was much shorter than planned, which may bias the study toward detection of early bleeding events as opposed to later ischemic events and stent thrombosis.

Finally, it should be recognized that even if the study conclusions are taken as valid, the absolute reduction in overt upper GI bleeding was only 0.5%. This means that 200 patients would have to be treated to prevent one GI bleed. Because GI bleeding is rarely fatal, if PPI co-treatment resulted in even a small increase in the risk for stent thrombosis or recurrent ischemic events, it would have an unfavorable risk/benefit and cost/benefit profile.

The COGENT trial, when taken in the context of recent observational data, suggests that initial concerns about a clinically important PPI/clopidogrel interaction were overblown. However, given the plausibility of the mechanistic data, the inconsistency of the observational data, and the weaknesses of the COGENT trial, this issue is not yet resolved.

Therefore, although clinicians should feel comfortable using PPIs together with clopidogrel when indicated for patients with GI symptoms or those at high risk for GI bleeding, they should not use them indiscriminately for prophylaxis of GI bleeding in low-risk individuals. When a PPI is used, selecting an agent other than omeprazole seems to be prudent whenever possible.

– James A. de Lemos, MD

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Increased platelet inhibition after switching from maintenance clopidogrel to prasugrel in patients with acute coronary syndromes: results of the SWAP (SWitching Anti Platelet) study.

Angiolillo DJ, Saucedo JF, DeRaad R, et al. *J Am Coll Cardiol*. 2010;56:1017-1023.

ABSTRACT

Objectives The objective was to evaluate the pharmacodynamic response of switching patients on maintenance phase clopidogrel therapy after an acute coronary syndrome (ACS) to prasugrel.

Background Prasugrel $P2Y_{12}$ receptor blockade is associated with greater pharmacodynamic platelet inhibition and reduction of ischemic complications compared with that of clopidogrel in ACS patients undergoing percutaneous coronary intervention. The pharmacodynamic effects of switching patients during maintenance phase clopidogrel therapy after an ACS event to prasugrel are unknown.

Methods The SWAP (SWitching Anti Platelet) study was a phase 2, multicenter, randomized, double-blind, double-dummy, active-control trial. After a run-in of daily open-label clopidogrel 75 mg with aspirin therapy for 10 to 14 days, patients were randomly assigned to 1 of the following 3 treatments: placebo loading dose (LD)/clopidogrel 75 mg maintenance dose (MD), placebo LD/prasugrel 10 mg MD, or prasugrel 60 mg LD/10 mg MD. Platelet function was evaluated at 2 h, 24 h, 7 days, and 14 days using light transmittance aggregometry, VerifyNow $P2Y_{12}$ assay, and vasodilator-stimulated phosphoprotein phosphorylation.

Results A total of 139 patients were randomized, of whom 100 were eligible for analysis. Maximum adenosine diphosphate-induced platelet aggregation (20 μM) by light transmittance aggregometry at 1 week (primary end point) was lower after prasugrel MD compared with clopidogrel MD (41.1% vs. 55.0%, $p < 0.0001$), and was also lower in the prasugrel LD+MD group compared with clopidogrel MD (41.0% vs. 55.0%, $p < 0.0001$). At 2 h, a prasugrel LD resulted in higher platelet inhibition compared with the other regimens. Similar results were found using light transmittance aggregometry with 5 μM adenosine diphosphate, VerifyNow $P2Y_{12}$, and vasodilator-stimulated phosphoprotein phosphorylation assays.

Conclusions For patients receiving maintenance clopidogrel therapy after an ACS event, switching from clopidogrel to prasugrel is associated with a further reduction in platelet function by 1 week using prasugrel MD or within 2 h with the administration of a prasugrel LD.

SYNOPSIS

Switching Maintenance Therapy from Clopidogrel to Prasugrel Increases Platelet Inhibition in Patients With Acute Coronary Syndromes

Combination therapy with aspirin and a thienopyridine is a standard of care to prevent recurrent cardiovascular (CV) events in patients with acute coronary syndrome (ACS) following percutaneous coronary intervention (PCI). Both clopidogrel and prasugrel inhibit platelet activation through $P2Y_{12}$ receptor blockade; however, a variable response to clopidogrel may leave patients at risk for ischemic complications and recurrent events.

Angiolillo et al. hypothesized that switching from clopidogrel to prasugrel may be a treatment option for patients who have a poor response to clopidogrel or are at risk for drug-drug interactions that may diminish the effect of clopidogrel. They evaluated the pharmacodynamic response of this switch in the SWitching Anti Platelet (SWAP) study. After 2 weeks of a daily open-label maintenance dose (MD) clopidogrel 75 mg, 100 patients were randomized to a placebo loading dose (LD) and clopidogrel 75 mg (MD), placebo LD and prasugrel 10 mg MD, or prasugrel 60 mg LD and 10 mg MD for 14 days.

Platelet function was assessed after stimulation with 20 μM adenosine diphosphate (ADP) using light transmittance aggregometry (LTA). Reduced platelet aggregation was seen as early as 2 h after the switch. Mean maximum platelet aggregation (MPA) was significantly lower with prasugrel LD/prasugrel MD compared with placebo LD/prasugrel ($P<0.0001$) or placebo LD/clopidogrel MD ($P<0.0001$) and persisted through 24 h ($P<0.0001$ for both) (***Figure [A]***).

By day 7 after the switch, MPA with both prasugrel LD/prasugrel MD (41.1%) and prasugrel LD/prasugrel MD (41.0%) was significantly lower than with placebo LD/clopidogrel MD (55.0%) ($P<0.0001$ for both) and remained significantly lower through day 14 ($P<0.0001$) (***Figure [A]***). Furthermore, there were greater decreases in MPA with prasugrel LD/prasugrel MD than with placebo LD/clopidogrel MD at all time points from 2 h to 14 days ($P<0.0001$ at all time points).

Similar changes in platelet aggregation were observed after stimulation with 5 μM ADP at 2 and 24 h and at 7 and 14 days (***Figure [B]***). However, there was no significant reduction in MPA between placebo LD/prasugrel MD and placebo LD/clopidogrel MD at 2 h (49.5% vs. 48.1%) or 24 h (52.3% vs. 53.8%). Results of the VerifyNow $P2Y_{12}$ and vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) assays were consistent with the LTA results.

Bleeding by Thrombolysis in Myocardial Infarction (TIMI) criteria was reported for 12%, 8.5%, and 13.6% of patients in the placebo LD/clopidogrel MD, placebo LD/prasugrel MD, and prasugrel LD/prasugrel MD groups, respectively. All of the events

were considered mild, and none required medical or surgical intervention.

The results of the SWAP study indicated that switching from a clopidogrel 75 MD to a prasugrel 10 mg MD, with or without a prasugrel LD, can significantly reduce platelet aggregation after 7 days, with no loss in existing platelet inhibition from the clopidogrel MD. Furthermore, administration of a prasugrel 60 mg LD can rapidly and significantly reduce platelet aggregation as early as 2 h.

COMMENTARY

A Yankee Swap of Oral Antiplatelet Therapy

In the time-honored New England Christmas tradition known as a Yankee Swap, wrapped gifts are selected one at a time with the option to upgrade to another individual's gift that had been opened, or to retain the gift selected. In the SWAP (SWitching Anti Platelet) study, Angiolillo et al. evaluated the pharmacodynamic response of switching patients from clopidogrel to prasugrel following an acute coronary syndrome (ACS).

The major finding was that switching patients from 75 mg MD clopidogrel to 10 mg MD prasugrel resulted in significantly decreased platelet function after 1 week using 3 different assays. Other important findings:

- Use of a prasugrel 60 mg LD resulted in greater platelet inhibition after 2 hours that was well-tolerated compared to placebo LD
- Omission of an LD of prasugrel did *not* result in a loss of platelet inhibition during the first 24 hours after a swap.

Strengths of this study include the study design (randomized, double-blind, double-dummy) that minimized bias and use of multiple modalities to assess platelet function. In addition, the relatively large number of patients for a pharmacodynamic study permitted greater confidence in the precision of the results.

An important limitation in the data presented is the emphasis on mean values, whereas there is considerable inter- (and sometimes intra-) patient variability in the measurements of platelet function, particularly with clopidogrel.[1] Furthermore, studies exploring the relationship between the degree of platelet inhibition and clinical outcomes demonstrate the presence of a threshold (non-linear) effect—insufficient platelet inhibition below a "critical level" leads to a dramatic increase in thrombotic risk.

What is the relevance to the practitioner? A growing body of data supports the use of more intensive long-term antiplatelet therapy in patients at high risk for stent thrombosis or recurrent ischemia to reduce the rate of future stent thrombosis, myocardial infarction, and cardiovascular death.

In addition, we have learned that certain patient profiles (eg, patients with diabetes, increased body weight, older age, bifurcation lesions)[2] or genetic polymorphisms that result in decreased *2CYP19* function place patients at increased risk for thrombotic events. Therefore, in patients who have had a stent thrombosis on clopidogrel or those who are at high risk for ischemic complications, providers should consider swapping over to prasugrel, provided no absolute contraindications exist.

– Robert P. Giugliano, MD, SM

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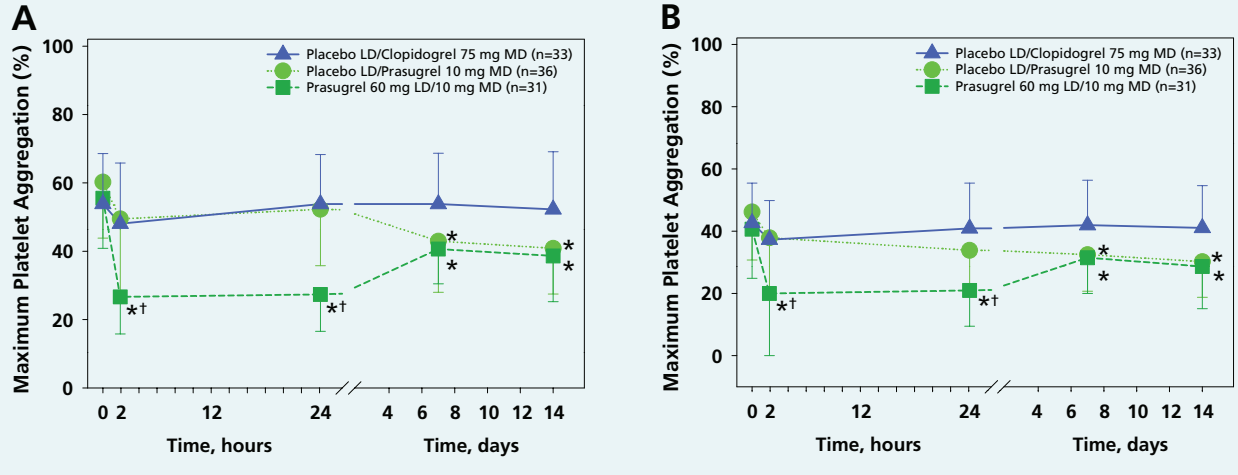
Figure. Maximum Platelet Aggregation.



(A) Mean maximum platelet aggregation (MPA) to 20 µM adenosine diphosphate (ADP) ± SD. **(B)** Mean MPA to 5 µM ADP ±SD. Time 0 is baseline value obtained after 2-week open-label clopidogrel and before administration of first dose of study drug. *P<0.0001 versus clopidogrel 75 mg maintenance dose (MD).†P<0.0001 versus prasugrel 10 mg MD. Blue triangles indicate placebo loading dose (LD)/clopidogrel 75 mg MD (n=33); green circles indicate placebo LD/prasugrel 10 mg MD (n=36); and green squares indicate prasugrel 60 mg LD/10 mg MD (n=31).

A prospective natural-history study of coronary atherosclerosis.

Stone GW, Maehara A, Lansky AJ, et al; for the PROSPECT Investigators.
***N Engl J Med*. 2011;364:226-235.**

ABSTRACT

Background Atherosclerotic plaques that lead to acute coronary syndromes often occur at sites of angiographically mild coronary-artery stenosis. Lesion-related risk factors for such events are poorly understood.

Methods In a prospective study, 697 patients with acute coronary syndromes underwent three-vessel coronary angiography and gray-scale and radiofrequency intravascular ultrasonographic imaging after percutaneous coronary intervention. Subsequent major adverse cardiovascular events (death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization due to unstable or progressive angina) were adjudicated to be related to either originally treated (culprit) lesions or untreated (nonculprit) lesions. The median follow-up period was 3.4 years.

Results The 3-year cumulative rate of major adverse cardiovascular events was 20.4%. Events were adjudicated to be related to culprit lesions in 12.9% of patients and to nonculprit lesions in 11.6%. Most nonculprit lesions responsible for follow-up events were angiographically mild at baseline (mean [±SD] diameter stenosis, 32.3±20.6%). However, on multivariate analysis, nonculprit lesions associated with recurrent events were more likely than those not associated with recurrent events to be characterized by a plaque burden of 70% or greater (hazard ratio, 5.03; 95% confidence interval [CI], 2.51 to 10.11; P<0.001) or a minimal luminal area of 4.0 mm^2 or less (hazard ratio, 3.21; 95% CI, 1.61 to 6.42; P=0.001) or to be classified on the basis of radiofrequency intravascular ultrasonography as thin-cap fibroatheromas (hazard ratio, 3.35; 95% CI, 1.77 to 6.36; P<0.001).

Conclusions In patients who presented with an acute coronary syndrome and underwent percutaneous coronary intervention, major adverse cardiovascular events occurring during follow-up were equally attributable to recurrence at the site of culprit lesions and to nonculprit lesions. Although nonculprit lesions that were responsible for unanticipated events were frequently angiographically mild, most were thin-cap fibroatheromas or were characterized by a large plaque burden, a small luminal area, or some combination of these characteristics, as determined by gray-scale and radiofrequency intravascular ultrasonography.

SYNOPSIS

Multimodality Intravascular Imaging Characterizes Nonculprit Coronary Lesions Responsible for Nearly Half of Recurrent Events in Patients With Acute Coronary Syndrome

Despite successful treatment with percutaneous coronary intervention (PCI) and appropriate medical therapy, a substantial number of patients with acute coronary syndrome (ACS) experience recurrent major adverse cardiovascular events (MACE).

In the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study, Stone and colleagues prospectively evaluated the clinical- and lesion-related factors that increase the risk for recurrent MACE. They performed three-vessel angiography, gray-scale intravascular ultrasound (IVUS), and radiofrequency IVUS to evaluate vessel characteristics at baseline and during the median 3.4 years of follow-up in 697 patients with ACS previously treated successfully with PCI.

About one in five patients (20.4%) experienced MACE over 3 years after PCI, and the events were nearly equally attributable to the originally treated culprit lesion (118 lesions, 12.9%) and nonculprit lesions (106 lesions, 11.6%). Most of these events were rehospitalizations for angina; only 4.9% were attributed to cardiac death, cardiac arrest, or MI.

Many of the nonculprit lesions (32 of 106 lesions, 30.2%) causing recurrent events were considered mild on baseline angiography (<30% stenosis by visual assessment), whereas follow-up angiography revealed stenosis ≥50% but ≤70% in 30 lesions (28.3%) and stenosis ≥70% in 5 (4.7%). Of the 55 lesions imaged by IVUS, all had a baseline plaque burden ≥40%.

Insulin-requiring diabetes mellitus was the strongest patient-related predictor of recurrent MACE due to a nonculprit lesion. Independent lesion-related factors were plaque burden ≥70% (P<0.001), minimal luminal area ≤4.0 mm^2 (P=0.001), and the presence of thin-cap fibroatheromas (P<0.001). The proportion of recurrent events increased with the number of these variables present in nonculprit lesions, from none (0.3%), one (4.8%), two (10.5%), to all three (18.2%).

Although routine multimodality imaging to detect potentially harmful lesions is not feasible, the PROSPECT findings confirmed the hypothesis that MACE arise from thin-cap fibroatheromas with specific histopathologic characteristics not necessarily associated with the degree of angiographic stenosis at the same site.

COMMENTARY

Confirming Old Wisdom: Both Obstructive and Nonobstructive Coronary Plaques Lead to Cardiovascular Events

Angina, defined as chest discomfort with exertion, is usually due to significantly obstructed (>75%) epicardial coronary arteries, causing a myocardial oxygen supply-demand mismatch and resultant ischemia during states of increased myocardial stress. However, autopsy studies have shown that coronary plaque rupture leading to ACS can arise from nonobstructive as well as obstructive plaques, depending more on plaque composition than simply

the amount of luminal narrowing.

This study by Stone et al. uses advanced intracoronary imaging modalities in patients with ACS undergoing percutaneous coronary revascularization to document whether the observations from autopsy studies are consistent in living individuals with symptomatic coronary disease.

The study's main findings confirm that recurrent cardiovascular events arise equally from revascularized culprit lesions as well as from nonrevascularized nonculprit lesions. The major strengths of this study include the extensive phenotyping of coronary plaque composition in vivo and long-term follow-up. However, multiple weaknesses limit the authors' conclusions and dampen any clinical utility of their findings.

Although almost 700 patients were enrolled and 149 cardiovascular events were recorded, only 31 (21%) were hard coronary end points including cardiovascular death, cardiac arrest, or MI. Most of the deaths and cardiac arrests could not be attributed to either the culprit or nonculprit lesions, leaving MI (n=21) as the only hard end point.

About twice as many recurrent MIs occurred from initially revascularized lesions (culprit) than from nonrevascularized lesions, inconsistent with the overall observations. Furthermore, an additional 11 cardiovascular events (coronary dissections and perforation) resulted from the invasive imaging catheters, leading to an additional 10% nonfatal MIs.

Though the investigators' findings that increased percent plaque burden, decreased minimal luminal area, and the presence of thin-cap fibroatheromas predicted recurrent cardiovascular events, only 18% of those with all three worrisome plaque characteristics developed recurrent events. Further analysis of plaque composition and recurrent MI alone would have been potentially instructive despite the low numbers of MIs.

The message remains the same: patients at high risk for coronary events, especially those surviving ACS, require aggressive medical treatment, specifically antiplatelet therapy and high-potency statins, regardless of their coronary plaque anatomy. There is no current indication to invasively determine coronary plaque composition at the time of coronary angiogram to guide mechanical or pharmacologic therapy.

– Anand Rohatgi, MD

Multiple testing, cumulative radiation dose, and clinical indications in patients undergoing myocardial perfusion imaging.

Einstein AJ, Weiner SD, Bernheim A, et al. *JAMA*. 2010;304:2137-2144.

ABSTRACT

Context Myocardial perfusion imaging (MPI) is the single medical test with the highest radiation burden to the US population. Although many patients undergoing MPI receive repeat MPI testing, or additional procedures involving ionizing radiation, no data are available characterizing their total longitudinal radiation burden and relating radiation burden with reasons for testing.

Objectives To characterize procedure counts, cumulative estimated effective doses of radiation, and clinical indications for patients undergoing MPI.

Design, Setting, and Patients A retrospective cohort study of 1097 consecutive patients undergoing index MPI during the first 100 days of 2006 (January 1-April 10) at Columbia University Medical Center, New York, New York, that evaluated all preceding medical imaging procedures involving ionizing radiation undergone beginning October 1988, and all subsequent procedures through June 2008, at the center.

Main Outcome Measures Cumulative estimated effective dose of radiation, number of procedures involving radiation, and indications for testing.

Results Patients underwent a median of 15 (interquartile range [IQR], 6-32; mean, 23.9) procedures involving radiation exposure; of which 4 (IQR, 2-8; mean, 6.5) were high-dose procedures (≥3 mSv; ie, 1 year's background radiation), including 1 (IQR, 1-2; mean, 1.8) MPI study per patient. A total of 344 patients (31.4%) received cumulative estimated effective dose from all medical sources of more than 100 mSv. Multiple MPIs were performed in 424 patients (38.6%), for whom cumulative estimated effective dose was 121 mSv (IQR, 81-189; mean, 149 mSv). Men and white patients had higher cumulative estimated effective doses. More than 80% of initial and 90% of repeat MPI examinations were performed in patients with known cardiac disease or symptoms consistent with it.

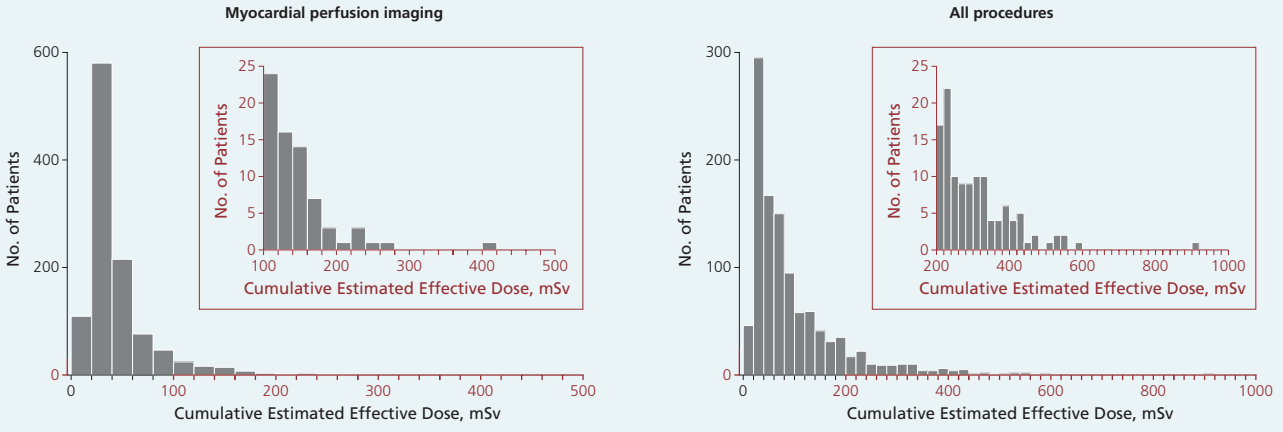
Conclusion In this institution, multiple testing with MPI was common and in many patients associated with high cumulative estimated doses of radiation.

SYNOPSIS

Repeated Myocardial Perfusion Imaging Exposes Patients to High Cumulative Doses of Radiation

Myocardial perfusion imaging (MPI) represents the single medical imaging test with the highest radiation burden. MPI currently accounts for approximately 10% of the entire cumulative effective dose (CED) from all sources in the US, with the exception of radiotherapy. Increasing numbers of MPI procedures prompted Einstein et al. to conduct a retrospective cohort study to estimate the CED from all medical imaging procedures performed

Figure. Cumulative Estimated Effective Doses for Myocardial Perfusion Imaging and All Procedures



The inset is the expanded y-axis from x=100 mSv to x=500 mSv for myocardial perfusion imaging and from x=200 mSv to x=1000 mSv for all procedures. All bins are of width 20 mSv.

on 1097 patients undergoing index MPI in the first 100 days of 2006. All procedures involving radiation exposure performed on those patients from October 1988 to June 2008 were evaluated, including radiography, mammography, computed tomography, fluoroscopy, cardiac catheterization, other nuclear medicine procedures, and percutaneous coronary intervention.

The patients underwent a median of 15 procedures, and of these, a median of 4 were high-dose procedures; that is, they delivered an effective dose >3 millisievert (mSv), or the equivalent of 1 year's natural background radiation. These procedures included at least 1 MPI per patient.

For all procedures involving radiation exposure, the median CED was 64.0 mSv; 344 patients (31.4%) received CEDs >100 mSv (***Figure***), including 120 patients (10.9%) with a CED of ≥200 mSv. The median number of procedures was significantly higher in women than men (18 vs. 12, $P<0.001$), even when mammography was excluded (14 vs. 12, $P=0.04$). However, the median CED was higher in men (60 vs. 69 mSv, $P<0.001$), primarily due to more cardiac catheterizations ($P=0.006$) and fluoroscopy ($P<0.001$).

For MPI examinations alone, the median CED was 28.9 mSv (range, 6.5 to 406.9 mSv), and 71 patients (6.5%) had a CED ≥100 mSv (***Figure***). A total of 424 patients (38.6%) underwent multiple MPIs that exposed them to a median CED of 121 mSv. Of these patients, 56% and 28% had two examinations within 2 years and 1 year of each other, respectively.

This single-center study indicates that the high CEDs of radiation associated with multiple MPIs warrant careful consideration of the clinical benefits of medical imaging and the potential risks for cancer in patients with known or suspected cardiac disease.

COMMENTARY

The Case for Caution in Repeat Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI) accounts for nearly one-quarter of the cumulative effective radiation exposure from medical sources. In 2010, the US FDA unveiled an initiative to reduce unnecessary radiation exposure from medical imaging, thus the analysis by Einstein et al. of the utilization, cumulative estimated effective dose of radiation, and clinical indications for MPI is timely.

The major contributing factor to high levels of exposure was repeat MPI studies, which occurred in 39% of patients. Although the reason that an MPI was performed in most cases (>80% for first MPI, >90% for repeat testing) was appropriate (ie, for patients with known cardiac disease or symptoms consistent with cardiac disease), the use of multiple MPIs within one year, particularly if the prior study had been normal, exposed patients to high doses of ionizing radiation and appeared to be of little to no benefit.

As can be seen from the "all procedures" figure, an individual patient's use of the healthcare system can lead to concerning radiation exposures due to multiple high radiation diagnostic tests and test types. Such "outliers" face a particular risk from such exposures, especially if they are of a young age.

Strengths of this study include the identification of a large, well-defined cohort with data collection spanning more than a decade. Limitations of this paper include the use of estimated radiation exposure in this single-center experience and lack of information regarding the suitability of patients to undergo alternative studies with less radiation exposure.

The major lesson here is that while it is convenient, easy, non-invasive, and relatively inexpensive to obtain an MPI study—compared with conventional angiography—greater appreciation of the radiation exposure is needed, particularly in patients undergoing repeat MPI studies. Use of diagnostic tests that do not utilize radiation (eg, exercise ECG, stress-echocardiography, pharmacologic stress MRI) or more definitive tests (eg, angiography) that could, if results were unambiguous, put an end to further testing should be strongly considered in patients who have had multiple exposures to ionizing radiation.

– Robert P. Giugliano, MD, SM

Pilot study of the antiplatelet effect of increased clopidogrel maintenance dosing and its relationship to *CYP2C19* genotype in patients with high on-treatment reactivity.

Barker CM, Murray SS, Teirstein PS, et al. *J Am Coll Cardiol Intv.* 2010;3:1001-1007.

ABSTRACT

Objectives The objective of this study was to evaluate the antiplatelet effect of clopidogrel 150 mg/day in patients with high on-treatment reactivity (OTR) and to further assess this effect according to *CYP2C19* genotype.

Background High OTR is associated with ischemic events in clopidogrel-treated patients after percutaneous coronary intervention. Alternative dosing regimens might enhance platelet inhibition.

Methods Patients with high OTR receiving a standard clopidogrel regimen were identified with the VerifyNow P2Y12 assay and administered clopidogrel 150 mg daily for 7 days, after which OTR was reassessed. Comprehensive *CYP2C19* genotyping was performed with the BeadXpress platform (Illumina, San Diego, California) for the *2, *3, *4, *5, *6, *7, *8, and *17 variants.

Results A total of 41 subjects were enrolled, 20 of whom were carriers of a *CYP2C19* loss-of-function (LoF) allele. High-dose clopidogrel significantly reduced OTR from 285 ± 47 $P2Y_{12}$ reaction units (PRU) to 220 ± 91 PRU ($p < 0.001$). There were no significant differences in antiplatelet effect according to *CYP2C19* status, although the reduction in reactivity was minimal in the small number of patients homozygous for LoF alleles (n = 3, 28 ± 31 PRU, p = NS). Increasing body mass index was independently and negatively associated with the reduction in OTR ($p = 0.009$).

Conclusions In patients with high OTR, clopidogrel 150 mg/day results in a significant reduction in platelet reactivity. Carriage of an LoF *CYP2C19* polymorphism does not seem to have a major influence on dose effect. The observed lack of effect in patients with 2 copies of a *CYP2C19* LoF allele must be confirmed by larger studies.

SYNOPSIS

High-dose Clopidogrel Reduces Platelet Reactivity in PCI Patients With High On-Treatment Reactivity to Adenosine Diphosphate

Dual antiplatelet therapy with clopidogrel and aspirin reduces cardiovascular events following percutaneous coronary intervention (PCI). However, patients who exhibit high on-treatment reactivity (OTR) to adenosine diphosphate are at increased risk for these events. Furthermore, clopidogrel may have a diminished antiplatelet effect in patients with genetic variants of *CYP2C19*, an enzyme involved in the hepatic metabolism of clopidogrel.

Barker et al. conducted the first study to evaluate the antiplatelet effect of an increased maintenance dose (MD) of clopidogrel according to polymorphisms of *CYP2C19*. Using the VerifyNow $P2Y_{12}$ assay, the investigators identified 41 subjects currently on a standard clopidogrel 75 mg/day MD with high OTR (≥235 $P2Y_{12}$ reaction units [PRU]), of which 20 were carriers of at least one loss of function (LOF) *CYP2C19* allele.

The mean baseline OTR (while on standard clopidogrel MD) for all subjects was 284 PRU. Increasing the clopidogrel MD to 150 mg/day significantly reduced mean OTR by 24% to 220 PRU ($P<0.0001$) after 8 days. There was no difference in either baseline OTR or the reduction of OTR after high-dose clopidogrel MD between carriers of at least one *CYP2C19* LOF allele and noncarriers. Multivariate analysis revealed a significant correlation between increased body mass index (BMI) and the reduction in OTR ($P=0.009$), but no other clinical characteristic was independently associated with the change in OTR.

The OTR reverted to normal (PRU <235) in 23 subjects (56%). Subjects with persistently high OTR were more likely to have diabetes ($P=0.02$) and a higher baseline OTR ($P=0.02$), and tended to have a higher BMI ($P=0.09$). Furthermore, the OTR for these subjects on high-dose clopidogrel MD correlated with their OTR on a standard MD ($P=0.001$).

These findings suggest that systematic *CYP2C19* genotyping may be useful to identify patients with high OTR and selecting an appropriate type and/or dose of a $P2Y_{12}$ inhibitor. However, the improved antiplatelet effect observed with higher-dose clopidogrel MD may not translate to obese patients or patients with a very high OTR.

COMMENTARY

Genes vs. Environment: Relationship Among CYP2C19 *Genotype, Clopidogrel Dose, and Platelet Reactivity*

Loss of function (LOF) genetic variants of *CYP2C19*, the key hepatic enzyme involved in the biotransformation of clopidogrel for a prodrug to its active metabolism, are associated with increased risk for cardiovascular ischemic complications. Insufficient platelet inhibition, or high platelet reactivity, in patients treated with aspirin and clopidogrel following ACS or stenting is also associated with increased ischemic risk. Finally, doubling the dose of clopidogrel reduces the rate of clopidogrel hyporesponsiveness. How these three factors inter-relate is not clearly understood.

A pilot study by Barker et al. evaluated the effect on platelet reactivity of higher maintenance dose clopidogrel in patients with and without *CYP2C19* LOF polymorphisms. Patients (20/41 of whom had an LOF allele) on clopidogrel 75 mg daily with high on-treatment platelet reactivity (OTR) assessed using the VerifyNow $P2Y_{12}$ assay, had reassessment of OTR after doubling the dose of clopidogrel to 150 mg daily. The key findings were:

1. Doubling the dose of clopidogrel reduces OTR in the overall population compared with 75 mg daily.
2. The change in OTR was similar whether the patient had a single LOF allele or normal functioning alleles.
3. The strongest predictor of persistently high OTR after doubling the dose of clopidogrel was having a high OTR on standard dose (75 mg) clopidogrel, although increased body mass was also an important factor.

While the study was the first of its kind to explore the relationship between various *CYP2C19* polymorphisms, different maintenance doses of clopidogrel, and platelet function, 8 different alleles of varying effect on clopidogrel metabolism were represented in this modest-sized population of 41 patients, of whom only 3 were homozygotes. Thus, the possibility of substantial type II error must be considered (ie, the absence of proof does not equal the proof of absence of effect).

For practicing clinicians, this study does not provide much insight regarding the utility (or disutility) of genetic testing to assess clopidogrel metabolism. Larger pharmacogenomic studies are needed, preferably embedded in a clinical outcomes study, to guide the practitioner regarding the optimal use of genetic testing, patient characteristics, and dosing of clopidogrel to ensure the desired antiplatelet effect is achieved in our patients.

– Robert P. Giugliano, MD, SM

Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults.

deFilippi CR, de Lemos JA, Christenson RH, et al. *JAMA*. 2010;304:2494-2502.

ABSTRACT

Context Older adults comprise the majority of new-onset heart failure (HF) diagnoses, but traditional risk-factor prediction models have limited accuracy in this population to identify those at highest risk for hospitalization or death.

Objectives To determine if cardiac troponin T (cTnT) measured by a highly sensitive assay would be detectable in the majority of community-dwelling older adults, and if serial measures were associated with risk of HF hospitalization and cardiovascular death.

Design, Setting, and Participants A longitudinal nationwide cohort study (Cardiovascular Health Study) of 4221 community-dwelling adults aged 65 years or older without prior HF who had cTnT measured using a highly sensitive assay at baseline (1989-1990) and repeated after 2 to 3 years (n = 2918).

Main Outcome Measures New-onset HF and cardiovascular death were examined through June 2008 with respect to cTnT concentrations, accounting for clinical risk predictors.

Results Cardiac troponin T was detectable (≥3.00 pg/mL) in 2794 participants (66.2%). During a median follow-up of 11.8 years, 1279 participants experienced new-onset HF and 1103 cardiovascular deaths occurred, with a greater risk of both end points associated with higher cTnT concentrations. Among those participants with the highest cTnT concentrations (>12.94 pg/mL), there was an incidence rate per 100 person-years of 6.4 (95% confidence interval [CI], 5.8-7.2; adjusted hazard ratio [aHR], 2.48; 95% CI, 2.04-3.00) for HF and an incidence rate of 4.8 (95% CI, 4.3-5.4; aHR, 2.91; 95% CI, 2.37-3.58) for cardiovascular death compared with participants with undetectable cTnT levels (incidence rate, 1.6; 95% CI, 1.4-1.8 and 1.1; 95% CI, 0.9-1.2 for HF and cardiovascular death, respectively). Among individuals with initially detectable cTnT, a subsequent increase of more than 50% (n = 393, 22%) was associated with a greater risk for HF (aHR, 1.61; 95% CI, 1.32-1.97) and cardiovascular death (aHR, 1.65; 95% CI, 1.35-2.03) and a decrease of more than 50% (n = 247, 14%) was associated with a lower risk for HF (aHR, 0.73; 95% CI, 0.54-0.97) and cardiovascular death (aHR, 0.71; 95% CI, 0.52-0.97) compared with participants with 50% or less change. Addition of baseline cTnT measurements to clinical risk factors was associated with only modest improvement in discrimination, with change in C statistic of 0.015 for HF and 0.013 for cardiovascular death.

Conclusion In this cohort of older adults without known HF, baseline cTnT levels and changes in cTnT levels measured with a highly sensitive assay were significantly associated with incident HF and cardiovascular death.

SYNOPSIS

Highly Sensitive Cardiac Troponin Assay Identifies Older Adults at Risk for Heart Failure and Cardiovascular Death

The elderly account for 80% of the more than 1.1 million hospital admissions for heart failure (HF) in the United States each year. Until recently, using traditional cardiovascular (CV) risk factors and blood-based biomarkers have not been reliable or consistent for identifying elderly individuals at risk for HF hospitalization or death.

The development of a highly sensitive cardiac troponin T (cTnT) assay has made it possible to obtain prognostic information specific for hospital admission and CV death in patients with chronic HF. deFilippi et al. evaluated the ability of the cTnT assay to predict the risk for new-onset HF and CV death, independent of

traditional risk factors, in individuals ≥65 years of age and without a prior diagnosis of HF.

The investigators used data from 2918 participants in the Cardiovascular Health Study (CHS) who had baseline and follow-up (2 to 3 years) cTnT levels. Of these, 2794 (66.2%) had detectable cTnT levels (≥3.00 pg/mL). Higher baseline cTnT levels were significantly associated with known coronary heart disease, abnormal left ventricular ejection fraction, and increased left ventricular mass (P<0.001 for each).

During the median 11.8 years of follow-up, new-onset HF occurred in 1279 participants, and 1103 died of CV causes. Among participants with a baseline cTnT level <3.00 pg/mL, the incidence rates for new-onset HF and CV death were 1.6 and 6.4 per 100 person-years, respectively. In comparison, the respective incidence rates were 6.4 and 4.8 per 100 person-years among participants with the highest baseline cTnT levels (>12.94 pg/mL).

Risk for both clinical end points was further defined according to the change from baseline in cTnT level. For participants with a detectable cTnT level at baseline, the risk for HF and CV death was highest for those with a >50% increase in cTnT level and lowest for those with a change <50% from baseline (***Table***).

In this population of community-dwelling elderly, the cTnT assay demonstrated that even low troponin levels increase the risk for new-onset HF and CV death. In addition, changes in cTnT concentrations over time reflect the dynamic nature of CV disease in older adults.

COMMENTARY

Changing Roles of Troponin Testing: From Diagnosing Acute Coronary Syndrome to Screening for Cardiovascular Disease

Cardiac troponins T and I are released from myocardial cells during cellular injury and death, and detectable circulating levels using standard assays are the hallmarks of an acute myocardial infarction. Detectable levels in the general population are rare (<1%) and are associated with prevalent heart failure, left ventricular hypertrophy, diabetes, and chronic kidney disease.[1]

Recently, a highly sensitive cTnT assay was developed and found to detect circulating levels in almost all patients with chronic heart failure and coronary artery disease. deFilippi et al. set out to determine the prognostic relevance of single and serial cTnT measurements using the highly sensitive assay in ambulatory elderly individuals free of HF at baseline using the well-characterized CHS cohort. They discovered that 66% of ambulatory individuals over the age of 65 had detectable cTnT and that both single measurement and serial measurements independently predicted incident HF and CV death.

A novel finding in the serial-measurement arm of the study showed that among those with detectable cTnT levels at baseline, those with a >50% decrease in cTnT levels on serial measurement had similarly low rates of HF and CV death as those with undetectable cTnT levels at baseline. Unfortunately, metrics of biomarker performance did not reveal any significant clinical utility in measuring cTnT either as a single measurement or serially in addition to standard risk-prediction algorithms for predicting HF or CV death.

The study's strengths include an extremely large number of events (>1000 HF events and >1000 CV deaths) and analyses of not only associations with events but clinical utility beyond standard risk-prediction algorithms. Weaknesses include restriction to age ≥65 and lack of adjustment for baseline left ventricular systolic function, which is a powerful predictor of incident HF and CV death.

Circulating levels of cTnT using the highly sensitive assay have now been measured in two other large, ethnically diverse cohorts with similar findings. In the Atherosclerosis Risk in Communities (ARIC) study of approximately 10,000 subjects (mean age 63) without prevalent coronary disease, 61% had detectable levels of cTnT and increasing levels were independently associated with risk of death and HF.[2]

In a younger cohort of more than 3500 subjects in the Dallas Heart Study (mean age 44), 25% of the general population had detectable cTnT levels with similar associations with all-cause mortality.[3] Combining these findings using the highly sensitive cTnT assay with similarly robust associations between elevated levels of circulating natriuretic peptides (BNP and NT-proBNP) and death and HF, the time has come to formally evaluate these markers currently used for diagnosis of acute myocardial infarction (troponins) and HF (BNP and NT-proBNP) for screening the general population for prevalent cardiac structural disease and consideration of earlier intervention and prevention.

– Anand Rohatgi, MD

Table. Association of Change in cTnT Concentration With Subsequent Heart Failure and Cardiovascular Death Among Participants With Detectable cTnT Levels at Baseline (n=1797)

	>50% Increase (n=393)	Change ≤50% (n=1157)	>50% Decrease (n=247)
Heart failure			
Incidence rate per 100 person-years	(n=155) 5.3	(n=366) 3.5	(n=56) 2.0
Hazard ratio*	1.61	1 [reference]	0.73
Cardiovascular death			
Incidence rate per 100 person-years	(n=140) 4.1	(n=321) 2.6	(n=48) 1.6
Hazard ratio*	1.65	1 [reference]	0.71

cTnT = cardiac troponin T
*Adjusted for demographic and traditional risk factors.

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Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis.

Khera AV, Cuchel M, de la Llera-Moya M, et al. *N Engl J Med*. 2011;364:127-135.

ABSTRACT

Background High-density lipoprotein (HDL) may provide cardiovascular protection by promoting reverse cholesterol transport from macrophages. We hypothesized that the capacity of HDL to accept cholesterol from macrophages would serve as a predictor of atherosclerotic burden.

Methods We measured cholesterol efflux capacity in 203 healthy volunteers who underwent assessment of carotid artery intima-media thickness, 442 patients with angiographically confirmed coronary artery disease, and 351 patients without such angiographically confirmed disease. We quantified efflux capacity by using a validated ex vivo system that involved incubation of macrophages with apolipoprotein B-depleted serum from the study participants.

Results The levels of HDL cholesterol and apolipoprotein A-I were significant determinants of cholesterol efflux capacity but accounted for less than 40% of the observed variation. An inverse relationship was noted between efflux capacity and carotid intima-media thickness both before and after adjustment for the HDL cholesterol level. Furthermore, efflux capacity was a strong inverse predictor of coronary disease status (adjusted odds ratio for coronary disease per 1-SD increase in efflux capacity, 0.70; 95% confidence interval [CI], 0.59 to 0.83; P<0.001). This relationship was attenuated, but remained significant, after additional adjustment for the HDL cholesterol level (odds ratio per 1-SD increase, 0.75; 95% CI, 0.63 to 0.90; P=0.002) or apolipoprotein A-I level (odds ratio per 1-SD increase, 0.74; 95% CI, 0.61 to 0.89; P=0.002). Additional studies showed enhanced efflux capacity in patients with the metabolic syndrome and low HDL cholesterol levels who were treated with pioglitazone, but not in patients with hypercholesterolemia who were treated with statins.

Conclusions Cholesterol efflux capacity from macrophages, a metric of HDL function, has a strong inverse association with both carotid intima-media thickness and the likelihood of angiographic coronary artery disease, independently of the HDL cholesterol level.

SYNOPSIS

Cholesterol Efflux Capacity Predicts Carotid Artery Media Thickness and Coronary Artery Disease Status

Cholesterol efflux capacity—the ability of high-density lipoprotein cholesterol (HDL-C) to accept cholesterol from lipid-rich macrophages in the reverse cholesterol transport pathway—is thought to play a key role in atheroprotection. A study designed by Khera et al. examined the relationship between cholesterol efflux capacity, HDL-C level, and two surrogate measures of atherosclerosis, carotid artery intima-media thickness and angiographically confirmed coronary artery disease (CAD).

Using an assay that quantifies total cholesterol efflux by incubating macrophages with apolipoprotein B-depleted serum, the investigators first established that cholesterol efflux capacity correlated with both HDL-C and apolipoprotein A-I (apo A-I) levels in 203 healthy volunteers. In addition, carotid artery intima-media thickness correlated with age, systolic blood pressure, and glycated hemoglobin level (A1C) ($P<0.05$ for each), but not with HDL-C level. However, increased carotid artery intima-media thickness was associated with reduced cholesterol efflux capacity ($P=0.02$), even after adjustment for HDL-C and apo A-I levels ($P=0.003$ and $P=0.005$, respectively).

Khera et al. then compared cholesterol efflux capacity in 442 patients with CAD and 351 case controls. The CAD patients not only had lower levels of HDL-C and apo A-I than the controls ($P<0.001$ for each), but also lower cholesterol efflux capacity ($P<0.001$). Reduced cholesterol efflux capacity correlated with male sex ($P<0.001$) and current smoking ($P=0.003$), and the association with current smoking persisted even after adjustment for HDL-C level ($P=0.004$).

In this case-control cohort, the adjusted risk for CAD decreased with increasing cholesterol efflux capacity ($P<0.001$) and remained robust after further adjustment for HDL-C and apo A-I levels ($P=0.002$ for each). In a logistic-regression analysis that included known risk factors for CAD (diabetes, hypertension, smoking, and low-density lipoprotein cholesterol), both HDL-C level and cholesterol efflux capacity were inversely associated with CAD risk; however, only efflux capacity was a significant predictor of CAD status ($P=0.002$) (***Figure***).

Cholesterol efflux capacity was also found to increase after 12 weeks of treatment with pioglitazone but not after 16 weeks of treatment with a statin, a difference that may have reflected an effect of pioglitazone to enhance transcription of apo A-I and the inability of statins to promote cholesterol efflux.

Further study of cholesterol efflux capacity may increase our understanding of the role of HDL in atheroprotection and provide valuable information for the development of therapies targeting HDL metabolism and reverse cholesterol transport.

COMMENTARY

Is HDL, the Good Cholesterol, Also a Good CHD Risk Predictor?

Low high-density lipoprotein cholesterol (HDL-C) is associated with increased risk for coronary heart disease (CHD) and levels <40 mg/dL in men and <50 mg/dL in women are considered major risk factors for CHD. However, therapies that raise HDL-C such as fibrates and estro-

gen-based hormone replacement therapy have yielded inconsistent results in CHD protection.

These inconsistencies may, in part, be due to the remarkable heterogeneity in the composition and biological function of HDL particles. Many experts in the field believe that static measurements of HDL-C do not fully capture the dynamic properties of HDL and its effects on atherosclerosis in the arterial wall.

This study by Khera et al. is the first comprehensive evaluation of the relation of HDL function to atherosclerosis in humans. They measured a key property of HDL by isolating patients' HDL and testing its ability to remove cholesterol from macrophages. This property, termed cholesterol efflux, is considered to be the central mechanism by which HDL confers atheroprotection.

The investigators tested the cholesterol efflux capacity of HDL in patients undergoing coronary angiography and also correlated cholesterol efflux capacity with carotid intima-media thickness, a surrogate measure of peripheral atherosclerosis associated with increased risk for CHD. They found that though cholesterol efflux capacity increases with increasing HDL-C, there is marked variation in the ability to promote cholesterol efflux within the normal range of HDL-C levels (40-60 mg/dL). Khera et al. also demonstrated for the first time that the ability of HDL to promote cholesterol efflux was inversely associated with prevalent coronary and carotid atherosclerosis, independent of HDL-C levels and other major risk factors.

This study is the largest one of HDL function in humans reported to date. Other major strengths include measurement in two independent groups of patients and confirmation of significant associations with atherosclerosis in two distinct vascular beds, the coronary and carotid arteries.

> "These findings called into question the ability of HDL-C levels to predict response to lipid-modifying therapies."

Weaknesses include study design allowing for only cross-sectional associations with prevalent atherosclerosis and lack of hard end points such as myocardial infarction, stroke, and cardiovascular death.

Recently, a phase III trial of a cholesteryl ester transport protein (CETP) inhibitor, torcetrapib, was reported to increase HDL-C levels by more than 60%, the largest pharmacologic increase in HDL-C ever reported (niacin increases HDL-C by 20-25%).[1] Unfortunately, the trial was halted due to an increased risk for death and cardiovascular events in patients receiving torcetrapib compared to placebo.

Furthermore, there was no improvement in coronary or carotid atherosclerosis in those receiving the CETP-inhibitor.[2,3] These findings called into question the ability of HDL-C levels alone to predict response to lipid-modifying therapies. The study by Khera et al. has firmly established the first observations that measuring functional properties of HDL such as cholesterol efflux may provide more accurate metrics of the ability of HDL to confer atheroprotection. Further studies are needed to validate these findings. Whether clinical testing of cholesterol efflux or any other HDL function will improve CHD risk prediction—or predict response to therapy—remains to be seen. Whether therapies that modify cholesterol efflux can reduce the risk for CV events is now a tantalizing question.

– Anand Rohatgi, MD

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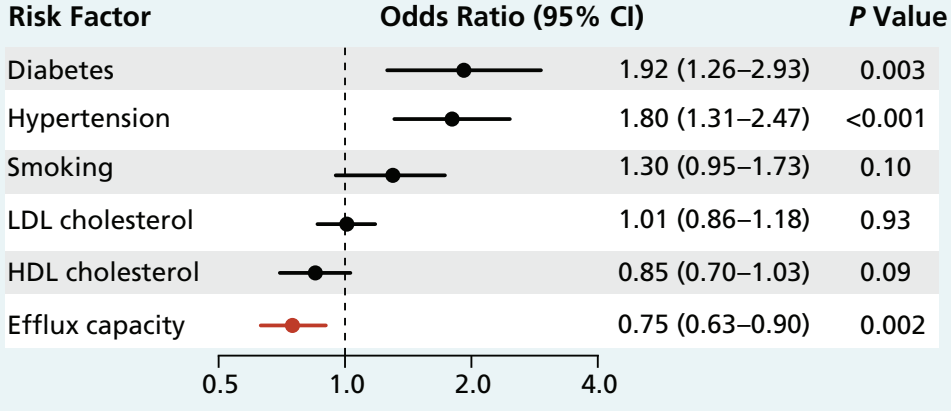
1. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109-2122.
2. Nissen SE, Tardif JC, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007;356:1304-1316.
3. Kastelein JJ, van Leuven SI, Burgess L, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med*. 2007;356:1620-1630.

Figure. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors



The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

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ACS JOURNAL CLUB CME POST-TEST

To obtain credit, you must have 70 percent or more of the answers correct. This CME is offered at no cost to participants. Please darken the circle with the correct answer for each question on the answer sheet (page 16) and send the completed answer sheet and evaluation to: Albert Einstein College of Medicine • Center for Continuing Medical Education • 3301 Bainbridge Avenue • Bronx, NY 10467, or fax to 718-798-2336.

1. **The prospective Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial by Bhatt et al. was designed to:**
   a. Evaluate any potential interaction between clopidogrel and omeprazole that may blunt the response to clopidogrel
   b. Evaluate the risk for gastrointestinal (GI) bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria
   c. Evaluate the effect of treatment with clopidogrel and omeprazole on GI complications
   d. Evaluate the efficacy of clopidogrel and omeprazole in patients undergoing percutaneous coronary intervention (PCI)

2. **The addition of omeprazole to dual antiplatelet therapy with clopidogrel and aspirin in the COGENT study significantly reduced the rate of:**
   a. GI obstruction
   b. Overt gastroduodenal bleeding
   c. GI perforation
   d. Overt lower gastrointestinal bleeding

3. **Compared with patients in the COGENT study who received clopidogrel and placebo, those who were treated with clopidogrel and omeprazole:**
   a. Had a higher rate of adverse cardiovascular (CV) events
   b. Had a higher rate of diarrhea caused by *Clostridium difficile*
   c. Had a lower rate of serious adverse events
   d. Had a comparable rate of adverse CV events

4. **In the 14-day SWitching Anti Platelet (SWAP) study by Angiolillo et al., switching patients with acute coronary syndrome (ACS) from a standard maintenance dose of clopidogrel to loading and maintenance doses of prasugrel:**
   a. Significantly reduced platelet aggregation at all time points in the study
   b. Had a similar effect on platelet aggregation as a placebo loading dose and a maintenance dose of prasugrel throughout the study
   c. Significantly reduced platelet aggregation beginning 7 days after administration
   d. Had a similar effect on platelet aggregation as loading and maintenance doses of clopidogrel

5. **Multimodality imaging of lesions causing recurrent events in patients with ACS previously treated with PCI by Stone et al. indicated that:**
   a. Nonculprit lesions caused a comparable proportion of recurrent events as originally treated culprit lesions
   b. Most nonculprit lesions for the index event that caused recurrent events showed ≥50% stenosis on angiography
   c. Nonculprit lesions caused more recurrent CV events than culprit lesions
   d. About one in three patients in the study experienced a recurrent event

6. **Nonculprit lesions causing recurrent events were indepen–dently associated with which of the following:**
   a. Plaque burden ≥40%, degree of stenosis, thin-cap fibroatheromas
   b. Degree of stenosis, minimal lumen area ≤4.0 mm^2, plaque burden ≥70%
   c. Thin-cap fibroatheroma, minimal lumen area ≤4.0 mm^2, plaque burden ≥70%
   d. Minimal lumen area ≤2.0 mm^2, plaque burden ≥70%, thin-cap fibroatheromas

7. **The single-center study of radiation exposure in patients undergoing myocardial perfusion imaging (MPI) conducted by Einstein et al. indicated that:**
   a. Fewer than 10% of patients received repeat MPIs
   b. The cumulative effective doses of radiation in these patients far exceeded the exposure to natural background radiation in 1 year
   c. Radiation exposure for all imaging procedures was higher in women than in men
   d. The incidence of cancer in these patients correlated with the number of procedures involving radiation exposure

8. **Patients with high on-treatment reactivity (OTR) to adenosine phosphate in the study by Barker et al.:**
   a. Had no change in OTR on standard clopidogrel maintenance therapy
   b. Were homozygous for the *CYP2C19* loss-of-function allele
   c. Were less tolerant of high-dose clopidogrel maintenance therapy
   d. Had a significant reduction in OTR on high-dose clopidogrel maintenance therapy

9. **In the study that evaluated the cardiac troponin T (cTnT) assay in participants in the Cardiovascular Health Study, deFilippi et al. found that:**
   a. Most elderly individuals in the community had undetectable cTnT levels at baseline
   b. Higher baseline cTnT levels did not correlate with CV morbidity
   c. There was a linear relationship between cTnT level and the incidence rates of new-onset heart failure (HF) and CV mortality
   d. Lower baseline cTnT levels correlated with traditional CV risk factors

10. **When Khera et al. measured cholesterol efflux capacity in healthy volunteers and patients with angiographically confirmed coronary artery disease (CAD), they found that:**
    a. Increased carotid artery intima-medial thickness did not correlate with cholesterol efflux capacity levels in healthy volunteers
    b. Patients with CAD had higher levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apo A-I) and increased cholesterol efflux capacity compared with case controls
    c. There was a linear correlation between cholesterol efflux capacity and CAD risk in healthy volunteers
    d. Cholesterol efflux capacity was a more significant predictor of CAD status than other known risk factors for CAD

EVALUATION AND ANSWER SHEET

May 2011

INTERVENTION & PREVENTION: KEEPING CURRENT WITH ACUTE CORONARY SYNDROME

Please darken the circle with the correct answer for each question and return a copy of this page to: Albert Einstein College of Medicine • Center for Continuing Medical Education • 3301 Bainbridge Avenue • Bronx, NY 10467, or fax to 718-798-2336. For questions about CME, please call Einstein CME at 718-920-6674. CME credit will be awarded if a score of 70% or better is achieved. A certificate of credit will be sent within 6 weeks of receipt of the test answers to those who successfully complete the examination.

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The amount of time I spent on this activity was _____ (maximum of 2.0 hours).

EXAMINATION ANSWER FORM

Darken the circle with the correct answer to each question in the CME activity.

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ					
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ					

PROGRAM EVALUATION

1. How would you rate this activity overall?

5=excellent, 1=poor; please circle one. 5 4 3 2 1

2. Do you feel each of the learning objectives (see page 2) was met?

Objective 1	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 2	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 3	❑ Yes	❑ Partially	❑ No	❑ N/A
Objective 4	❑ Yes	❑ Partially	❑ No	❑ N/A

3. In your opinion, did you perceive any commercial bias?

❑ Yes ❑ No

If yes, please specify: _____

4. Please rate the content of this activity. *5=excellent, 1=poor; please circle one.*

a. Timely, up to date?	5	4	3	2	1
b. Relevant to your practice?	5	4	3	2	1

5. Do you feel that the information in this activity was based on the best evidence available? ❑ Yes ❑ No

If no, please explain: _____

6. Do you intend to make changes in your practice as a result of this activity? ❑ Yes ❑ No

If yes, please explain: _____

7. Please make suggestions for future programs.

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