Intervention & Prevention: Keeping Current with
ACUTE CORONARY SYNDROME
A Journal Club for Primary Care
A supplement to *Monthly Prescribing Reference* December 2010 • Issue # 10

Dose comparisons of clopidogrel and aspirin in acute coronary syndromes.

The CURRENT-OASIS 7 Investigators. *N Engl J Med*. 2010;363:930-942.

ABSTRACT

Background Clopidogrel and aspirin are widely used for patients with acute coronary syndromes and those undergoing percutaneous coronary intervention (PCI). However, evidence-based guidelines for dosing have not been established for either agent. **Methods** We randomly assigned, in a 2-by-2 factorial design, 25,086 patients with an acute coronary syndrome who were referred for an invasive strategy to either double-dose clopidogrel (a 600-mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter) and either higher-dose aspirin (300 to 325 mg daily) or lower-dose aspirin (75 to 100 mg daily). The primary outcome was cardiovascular death, myocardial infarction, or stroke at 30 days. **Results** The primary outcome occurred in 4.2% of patients assigned to double-dose clopidogrel as compared with 4.4% assigned to standard-dose clopidogrel (hazard ratio, 0.94; 95% confidence interval [CI], 0.83 to 1.06; P=0.30). Major bleeding occurred in 2.5% of patients in the double-dose group and in 2.0% in the standard-dose group (hazard ratio, 1.24; 95% CI, 1.05 to 1.46; P=0.01). Double-dose clopidogrel was associated with a significant reduction in the secondary outcome of stent thrombosis among the 17,263 patients who underwent PCI (1.6% vs. 2.3%; hazard ratio, 0.68; 95% CI, 0.55 to 0.85; P=0.001). There was no significant difference between higher-dose and lower-dose aspirin with respect to the primary outcome (4.2% vs. 4.4%; hazard ratio, 0.97; 95% CI, 0.86 to 1.09; P=0.61) or major bleeding (2.3% vs. 2.3%; hazard ratio, 0.99; 95% CI, 0.84 to 1.17; P=0.90). **Conclusions** In patients with an acute coronary syndrome who were referred for an invasive strategy, there was no significant difference between a 7-day, double-dose clopidogrel regimen and the standard-dose regimen, or between higher-dose aspirin and lower-dose aspirin, with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke.

SYNOPSIS

Further Evaluation of Clopidogrel and Aspirin Dosing Needed to Determine Impact on Cardiovascular Morbidity and Mortality

Although clopidogrel and aspirin are commonly used for the treatment of cardiovascular disease (CVD), including in patients undergoing percutaneous coronary intervention (PCI), the optimal doses of either agent have not been established. The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial was designed to determine whether a doubling of the loading and initial maintenance doses of clopidogrel (300 mg and 75 mg daily, respectively) was more effective than the standard doses, and whether higher-dose aspirin (300 to 325 mg daily) was superior to a lower dose regimen (75 to 100 mg daily). Using a 2x2 factorial design, the patients were randomized to treatment with higher-dose clopidogrel with higher- or lower-dose aspirin, or to standard-dose clopidogrel with higher- or lower-dose aspirin over a 7-day treatment period.

The trial enrolled 25,086 patients with ACS, of whom 17,263 underwent PCI. The study population was composed primarily of white males, and the mean

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This CME activity was supported by an educational grant from Daiichi Sankyo, Inc. and Lilly USA, LLC

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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:

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 Biosite and Roche; and reseach grants from Biosite.

Jarett D. Berry, MD, MS, has received speakers' honoraria from Merck/Schering.

Benjamin Scirica, MD, MPH, has received grants/research support from CV Therapeutics, Inc.; Novartis; AstraZeneca; and Daiichi Sankyo, Inc.; and consulting fees from CV Therapeutics, Inc.; AstraZeneca; and Merck & Co., Inc.

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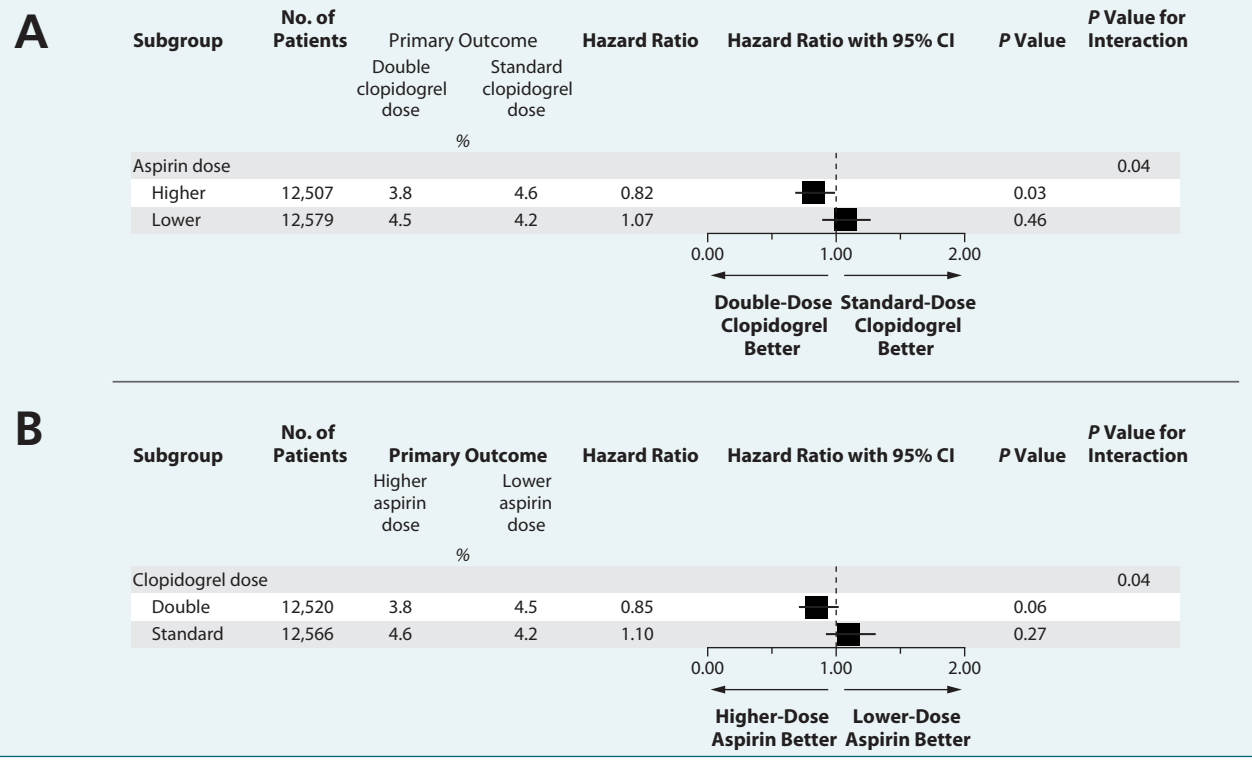
Figure. Hazard Ratios for the Primary Outcome in the Clopidogrel and Aspirin Dose Groups According to the Factorial Design



Panel A shows the comparison of double-dose clopidogrel with standard-dose clopidogrel, according to aspirin dose, and **Panel B** shows the comparison higher-dose aspirin with lower-dose aspirin, according to clopidogrel dose. P values were calculated with the use of the log-rank test. Hazard ratios were calculated with the use of a Cox proportional-hazards model. The size of the squares is proportional to the number of patients and represents the point estimate of the treatment effect. The horizontal line through each square spans the 95% confidence interval.

age was 61 years; about 13% were over age 75. At presentation, 71% of patients had non-ST-segment derived myocardial infarction (NSTEMI) or unstable angina; the remainder presented with STEMI.

There was no significant difference in the occurrence of the primary outcome—CV death, myocardial infarction (MI), or stroke at 30 days—between the higher-dose and standard-dose clopidogrel groups (4.2% vs. 4.4%, *P*=0.30). Similar results were observed for the individual components of the primary outcome, including a significant reduction in the incidence of stent thrombosis (ST) in patients undergoing PCI treated with higher-dose clopidogrel (1.6% vs. 2.3%, *P*=0.001). Mortality rates in the higher-dose and standard-dose groups were comparable (2.3% and 2.4%, respectively; *P*=0.61). There was a significant increase in major bleeding episodes in the higher-dose clopidogrel group (2.5% vs. 2.0%, *P*=0.01). The incidence of severe bleeding also was higher in the higher-dose clopidogrel group; however, treatment with the higher dose of clopidogrel did not increase the risk for fatal or intracranial bleeding.

As with the clopidogrel arm of the study, the higher-dose and standard-dose aspirin groups had comparable occurrences of the primary outcome as those treated with the lower-dose regimen (4.2% vs. 4.4%, *P*=0.61) and results for each component of the primary outcome. In addition, treatment with higher-dose aspirin reduced the occurrence of recurrent ischemia compared with the lower-dose regimen (0.3% vs. 0.5%, *P*=0.02). There was no significant difference between the higher- and lower-dose aspirin groups with respect to mortality (2.2% vs. 2.5%, *P*=0.10), major bleeding (*P*=0.90), or severe bleeding (*P*=0.93). Minor bleeding was reported for 5.0% of patients in the higher-dose aspirin group and 4.4% in the lower-dose group (*P*=0.04), and six patients in each aspirin group experienced intracranial bleeding.

Analysis for interaction between the clopidogrel and aspirin dose found that the primary outcome occurred in 3.8% of patients treated with higher-dose clopidogrel and higher-dose aspirin, compared with 4.6% of patients assigned to standard-dose clopidogrel with higher-dose aspirin (*P*=0.03) (**Figure**). Among patients randomized to lower-dose aspirin, the incidence of the primary outcome was not significantly different between the high- and standard-dose clopidogrel groups (4.5% and 4.2%, *P*=0.46).

In most prespecified subgroups, including age, sex, weight, race, presence of diabetes or coronary artery disease (CAD), and prior medications for CVD, there was a consistent treatment effect for the primary outcome in favor of the higher-dose clopidogrel regimen compared with the standard dose and of the higher-dose versus lower-dose aspirin regimen. The effect of higher-dose clopidogrel on the primary outcome was significant effect among patients who underwent PCI after randomization (*P*=0.03).

A number of factors may have contributed to the lack of a significant difference between a higher-dose versus standard-dose regimen of clopidogrel in combination with a higher-dose versus lower-dose

regimen of aspirin on the occurrence of CV death, MI, or stroke in patient with ACS, including the relatively short duration of the trial (7 days) and the early discontinuation of treatment in patients found to have no clinically significant CAD.

COMMENTARY

Oasis in the Antiplatelet Field or Only a Mirage?

Although clopidogrel has become an integral component of the treatment of patients with acute coronary syndromes (ACS), a number of limitations of this agent have been identified, including a slow onset of action and high variability in drug response, which may contribute to suboptimal outcomes in some patients. Strategies proposed to overcome these limitations include the use of newer medications, such as prasugrel and ticagrelor, that have more rapid onset and less response variability, and the use of higher dose regimens of clopidogrel, that have been shown in vitro to reduce response variability and improve platelet inhibition.

The CURRENT/OASIS-7 study, which involved more than 25,000 patients with ACS referred for invasive therapy, was intended to test whether higher dosages of clopidogrel improved clinical outcomes. In a 2x2 factorial design, the authors compared clopidogrel at high dose (600 mg load, 150 mg for one week, then 75 mg/day) versus low dose (300 mg load, 75 mg/day), as well as high- (300-325 mg/day) versus low-dose aspirin (75-100 mg/day). The authors reported no overall difference between high-dose and standard-dose clopidogrel, but did report an interaction based on whether patients received a percutaneous coronary intervention (PCI): in those undergoing PCI, high-dose clopidogrel reduced the rate of cardiovascular death, MI and stroke (HR 0.86; 95% CI 0.74-0.99) and the rate of stent thrombosis (HR 0.68; 95% CI 0.55-0.85), but no benefit was seen in those who did not receive PCI. Major bleeding was increased in the high-dose clopidogrel arm (2.5 vs. 2.0%, P=0.01). No difference in efficacy or safety was seen between the high- and low-dose aspirin arms.[1]

This trial does have potentially important implications both for clinical practice as well as our interpretation of newer therapies, but several flaws in the design, conduct, and reporting of the trial challenge our interpretation. The 2x2 factorial design of the study requires that there be no expected interaction between the two therapies undergoing evaluation. However, the authors report a statistically significant interaction between aspirin dose and clopidogrel dose, which technically requires that each of the four potential randomization groups be analyzed separately, which was not done.

> "It is concerning that almost a full year elapsed between when the trial was presented with great fanfare and finally published, and that the data in the final paper differ from the data originally presented."

It is concerning that almost a full year elapsed between when the trial was presented publically (with great fanfare) and finally published—and that the data in the final paper differ from the data originally presented. In this intervening year, some clinicians may have used the high-dose clopidogrel strategy in situations in which newer agents such as prasugrel may, in retrospect, have been more suitable alternatives. Finally, the same authors simultaneously reported results from the PCI subgroup in the *Lancet*; whereas the *New England Journal of Medicine* paper concluded that there was no significant advantage of the high-dose clopidogrel strategy, the *Lancet* paper reached an opposite conclusion, stating the high-dose clopidogrel strategy "can be considered for all patients with acute coronary syndromes treated with an early invasive strategy and intended early PCI."[2]

The fundamental issue to interpretation of this trial is whether, despite the controversial issues raised above, one "believes" the interaction based on whether PCI was performed to be plausible and valid. If so, then the high-dose clopidogrel strategy is a reasonable option for early treatment of patients with ACS managed with planned PCI and, as such, may offer an alternative strategy to prasugrel and ticagrelor. In the landmark trials demonstrating efficacy of these newer agents, lower dose clopidogrel was used, so it is plausible that the higher dose clopidogrel strategy may mitigate to some extent the advantages of prasugrel and ticagrelor over clopidogrel. However, if one discounts the PCI interaction, then the newer agents look to be more attractive alternatives to clopidogrel.

Several other implications are less confounded by the trial limitations. First, in patients with ACS *not undergoing PCI*, the higher-dose clopidogrel strategy does not improve outcomes and increases bleeding, and thus should not be used. Second, the similar results seen with low- and high-dose aspirin, even among a population with high rates of intracoronary stenting, suggests that in patients receiving concomitant clopidogrel, the preferred aspirin dose after discharge is probably 81 mg.

—James A. de Lemos, MD

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Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis.

Bhatt DJ, Eagle KA, Ohman EM, et al. *JAMA*. 2010;304:1350-1357.

ABSTRACT

Context Clinicians and trialists have difficulty with identifying which patients are highest risk for cardiovascular events. Prior ischemic events, polyvascular disease, and diabetes mellitus have all been identified as predictors of ischemic events, but their comparative contributions to future risk remain unclear. **Objective** To categorize the risk of cardiovascular events in stable outpatients with various initial manifestations of atherothrombosis using simple clinical descriptors. **Design, Setting, and Patients** Outpatients with coronary artery disease, cerebrovascular disease, or peripheral arterial disease or with multiple risk factors for atherothrombosis were enrolled in the global Reduction of Atherothrombosis for Continued Health (REACH) Registry and were followed up for as long as 4 years. Patients from 3647 centers in 29 countries were enrolled between 2003 and 2004 and followed up until 2008. Final database lock was in April 2009. **Main Outcome Measures** Rates of cardiovascular death, myocardial infarction, and stroke. **Results** A total of 45 227 patients with baseline data were included in this 4-year analysis. During the follow-up period, a total of 5481 patients experienced at least 1 event, including 2315 with cardiovascular death, 1228 with myocardial infarction, 1898 with stroke, and 40 with both a myocardial infarction and stroke on the same day. Among patients with atherothrombosis, those with a prior history of ischemic events at baseline (n=21 890) had the highest rate of subsequent ischemic events (18.3%; 95% confidence interval [CI], 17.4%-19.1%); patients with stable coronary, cerebrovascular, or peripheral artery disease (n=15 264) had a lower risk (12.2%; 95%CI, 11.4%-12.9%); and patients without established atherothrombosis but with risk factors only (n=8073) had the lowest risk (9.1%; 95%CI, 8.3%-9.9%) (P<.001 for all comparisons). In addition, in multivariable modeling, the presence of diabetes (hazard ratio [HR], 1.44; 95%CI, 1.36-1.53; P<.001), an ischemic event in the previous year (HR, 1.71; 95%CI, 1.57-1.85; P<.001), and polyvascular disease (HR, 1.99; 95%CI, 1.78-2.24; P<.001) each were associated with a significantly higher risk of the primary end point. **Conclusion** Clinical descriptors can assist clinicians in identifying high-risk patients within the broad range of risk for outpatients with atherothrombosis.

SYNOPSIS

Easily Identifiable Clinical Characteristics Predict Risk for Future Ischemic Events

Until recently, the ability to identify factors that predisposed patients to the greatest risk for cardiovascular (CV) events was unclear. Bhatt et al. analyzed 4-year data from the international Reduction of Atherothrombosis for Continued Health (REACH) registry to categorize the risk for CV events in a population of 45,227 outpatients that included asymptomatic adults with risk factors for atherosclerosis (18%); patients with stable atherosclerosis without a prior ischemic event (34%); and patients with a history of ischemic events (48%), of which 28% had experienced an event in year prior to study enrollment.

A total of 5481 patients experienced CV death, myocardial infarction (MI), or stroke. Using multivariate analysis, Bhatt et al. determined the following, in rank order, were significant predictors of these adverse outcomes at 4 years (P<0.001 for all): polyvascular disease, congestive heart failure, ischemic event <1 year of study enrollment, history of diabetes, ischemic event >1 year of study enrollment, single vascular disease, body mass index <20 kg/m^2, current smoking, atrial fibrillation or flutter, male sex, and age (per 1 year increase).

Among patients with atherosclerosis, the highest rate of ischemic events occurred in those with prior ischemic events (18.3%), compared with patients with stable atherosclerosis (12.2%). Patients with only risk factors for atherosclerosis had an ischemic event rate of 9.1%. The presence of diabetes or polyvascular disease at baseline conferred an additional and significant risk (P<0.001 for both) in all three groups. Over 4 years, the cumulative rate of CV death, MI, stroke, or CV-related hospitalization was 16.6% for patients with risk factors only and increased to 31.1% and 29.9% in those with stable atherosclerosis and those with a prior ischemic event who had singular vascular disease. The presence of polyvascular disease increased the event rate further, to 45.0% and 47.1% in patients with stable atherosclerosis and those with a prior ischemic event, respectively. Furthermore, experiencing a prior ischemic event within 1 year of study enrollment increased the risk for CV death, MI, or stroke by 29% (P<0.001) compared with no ischemic event.

These findings should alert clinicians to the wide spectrum of risk for future ischemic events and the clinical characteristics associated with high risk. This may allow clinicians to identify high-risk populations that may benefit from intensive preventive measures.

COMMENTARY

New Risk Scoring System Identifies Stable Patients at Highest Risk for Future Ischemic Events

Many risk scores have been developed for the primary prevention setting and in acute coronary syndrome. However, there are few, if any, validated tools for risk stratifying patients with established, though stable, cardiovascular disease. This is important for several reasons. First, it is always important for clinicians to systematically risk stratify patients they are evaluating. Secondly, a more quantifiable risk stratification technique should improve research and optimize clinical trial design by appropriately

enrolling those patients at greatest risk with the goal of improving their cardiovascular outcomes.

The large Reduction of Atherothrombosis for Continued Health (REACH) Registry examined the risk of cardiovascular death, MI, or stroke in more than 45,000 patients in 29 countries. Patients were separated into three broad cohorts based on whether they had 1) a prior ischemic episode (MI or stroke), 2) documented but stable atherosclerosis without any prior MI or stroke, or 3) risk factors only.

Over a four-year follow-up, patients with a documented prior ischemic event experienced the highest incidence of CV death, MI, or stroke, followed by those with stable established disease and then patients with risk factors alone. This is an important observation as we consider the optimal long-term medical treatment regarding antiplatelet choices or lipid goals.

Patients who have had a symptomatic thrombotic event are at higher risk of subsequent events, even when compared with those patients with documented but stable disease. Moreover, the risk was greatest within the first year of the ischemic episode. Whether these patients should receive different or more intense therapy based on their baseline risk will require us waiting on the results of several ongoing clinical trials.

Consistent with other studies, diabetes was associated with more than a 40% increased risk of CV death, MI or stroke, regardless of the baseline vascular status. Among patients with established CV disease, polyvascular disease—atherosclerosis in more than one vascular bed—was the most striking risk factor and almost doubled the risk of a subsequent cardiovascular event.

—Benjamin Scirica, MD, MPH

New P2Y12 inhibitors versus clopidogrel in percutaneous coronary intervention. A meta-analysis.

Bellemain-Appaix A, Brieger D, Beygui F, et al. *J Am Coll Cardiol*. 2010;56:1542-1551.

ABSTRACT

Objectives The purpose of this study was to perform a meta-analysis of randomized trials that compare new P2Y12 inhibitors with clopidogrel to determine whether they improve clinical outcomes after percutaneous intervention (PCI). **Background** Ticlopidine/clopidogrel prevents major adverse cardiac events after PCI, but no trials have shown an effect on mortality. New P2Y12 inhibitors are more potent and evaluated in PCI. Whether they decrease mortality after PCI compared with clopidogrel is unknown. **Methods** MEDLINE and Cochrane Controlled Trials Register databases were searched from January 1980 through January 2010. Randomized, placebo-controlled trials that compared new P2Y12 antagonists with clopidogrel in PCI were selected. Data from 8 studies were evaluated and analyses performed for all randomized patients, PCI patients (any PCI), and PCI for ST-segment elevation myocardial infarction (STEMI) patients. All-cause mortality was the primary efficacy end point. Thrombolysis In Myocardial Infarction major bleeding was the primary safety end point. **Results** A total of 48,599 patients were included with 94% of patients with acute coronary syndrome and 84% of patients undergoing PCI. New P2Y12 inhibitors significantly decreased death (odds ratio [OR]: 0.83, 95% confidence interval [CI]: 0.75 to 0.92, $p < 0.001$ for the whole cohort; OR: 0.85, 95% CI: 0.75 to 0.96, $p = 0.008$ for any PCI; and OR: 0.78, 95% CI: 0.66 to 0.92, $p = 0.003$ for PCI for STEMI). In PCI patients, new P2Y12 inhibitors also significantly decreased major adverse cardiac events by 18% ($p < 0.001$) and stent thrombosis by 40% ($p < 0.001$). Although there was an increase in Thrombolysis In Myocardial Infarction major bleeding for any PCI (OR: 1.23, 95% CI: 1.04 to 1.46, $p = 0.01$), no difference was observed in PCI for STEMI (OR: 0.98, 95% CI: 0.85 to 1.13, $p = 0.76$), with similar outcomes in primary PCI for STEMI. Results were confirmed in sensitivity analyses that removed the largest study. **Conclusions** New P2Y12 inhibitors decrease mortality after PCI compared with clopidogrel. The risk/benefit ratio is particularly favorable in PCI for STEMI patients.

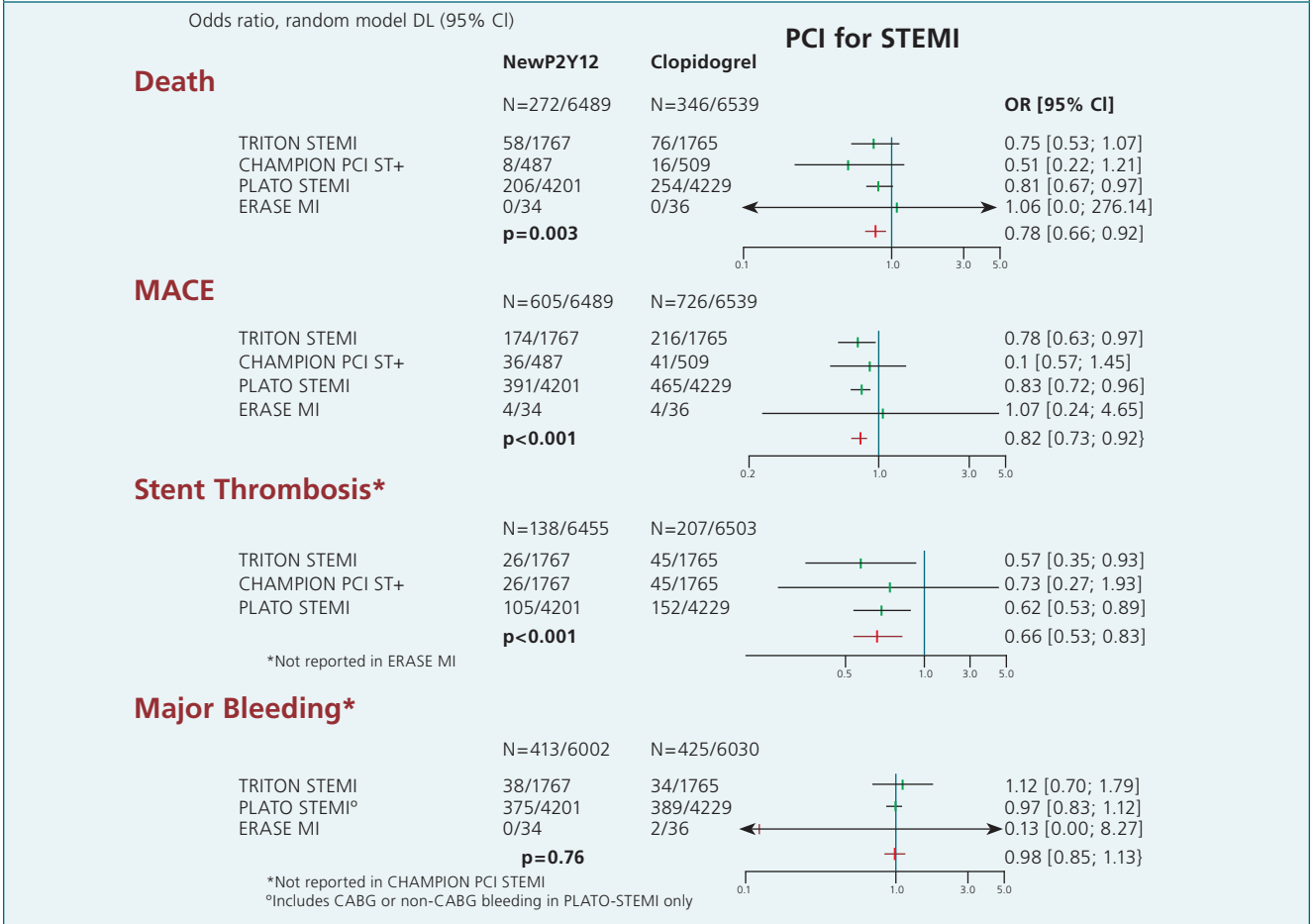
SYNOPSIS

New P2Y12 Receptor Inhibitors Show Favorable Risk/Benefit Ratio After PCI for STEMI

Treatment with clopidogrel and other thienopyridines—inhibitors of the P2Y12 receptor—is a standard of care to reduce 30-day mortality rates following percutaneous coronary intervention (PCI). Four new P2Y12 inhibitors—prasugrel, ticagrelor, cangrelor, and elinogrel—are more potent and have a more rapid onset of action than clopidogrel; however, clinical trials have not been sufficiently powered to detect a difference in mortality compared with clopidogrel. Bellemain-Appaix and colleagues recently reported the results of a meta-analysis of eight randomized, double-blind trials to determine whether treatment with these new agents improve clinical outcomes relative to clopidogrel.

The trials comprised 48,599 patients, of which 94% had acute coronary syndrome (ACS) and 84% had undergone PCI; about half the patients received a new P2Y12 inhibitor. Overall, the new agents reduced mortality by 17%, cardiovascular (CV) mortality by 18%, and major adverse cardiac events (MACEs) by 14% compared with clopidogrel ($P<0.001$ for all). The rates of myocardial infarction (MI), stent thrombosis (ST), and target vessel revascularization also decreased significantly with the new P2Y12 inhibitors, but there was no difference between the groups in the rate of stroke. Treatment with the new P2Y12 agents was associated with a significant increase in Thrombolysis in Myocardial

Figure. Effect of New P2Y12 in PCI for STEMI



There was a stronger anti-ischemic effect of new P2Y12 antagonists in PCI for STEMI than in the any PCI analysis, with a significant decrease in death by 22% (from 2.56% to 2.09%), in MACE by 16% (from 5.29% to 4.19%), and in stent thrombosis by 33% (from 3.18% to 2.14%). Thrombolysis In Myocardial Infarction major bleeding was not different between the 2 groups. Abbreviations as in Figures 2 and 3.

Infarction (TIMI)-defined major bleeding (P=0.009) and a slight increase in TIMI major or minor bleeding (P=0.04).

Subset analyses found similar positive clinical outcomes. In addition to significant decreases in mortality and CV death, patients treated by any PCI in the new P2Y12 group had 18% fewer MACEs (P<0.001) and a 40% decrease in ST (P<0.001). An even stronger anti-ischemic effect of the new P2Y12 inhibitors was seen in the analysis of PCI treatment after ST-segment deviation MI (STEMI), with highly significant decreases in mortality (22%, P=0.003), MACEs (16%, P<0.001), and ST (33%, P<0.001), and a significant decrease in CV death (P=0.02) (**Figure**). A significant increase in TIMI major bleeding was associated with the new P2Y12 agents after any PCI (P<0.001) but not after PCI for STEMI (P=0.76). These findings persisted even after removal of the largest dataset (n=18,624) from the analysis.

In patients undergoing PCI, the new P2Y12 inhibitors decrease mortality and major ischemic events compared with clopidogrel, and provide a particular benefit for STEMI patients with no increase in TIMI major bleeding.

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COMMENTARY

The P2Y12 Inhibitors Have a Role in Select Populations

Dual antiplatelet therapy with both aspirin and P2Y12 inhibitors represent the standard of care for patients undergoing PCI. Until recently, clopidogrel was the most commonly used P2Y12 inhibitor available for clinical use. However, the broad variability in platelet inhibition with clopidogrel has led to the search for and development of novel P2Y12 inhibitors such as ticagrelor and prasugrel.

Although beneficial in reducing stent thrombosis and recurrent myocardial infarction among patients treated with PCI, these novel agents have not been consistently associated with a reduction in mortality when compared with clopidogrel treatment. However, a large study (PLATO) recently demonstrated a reduction in mortality among patients treated with ticagrelor compared to clopidogrel.[1] Because other prior studies were not adequately powered to detect an association with mortality, the authors pooled the results of these studies to determine if newer P2Y12 inhibitors were associated with a reduction in mortality in comparison to clopidogrel among patients treated with PCI.

The authors noted several important observations. First, compared to clopidogrel, novel P2Y12 inhibitors were associated with a reduction in mortality among patients treated with PCI. Second, as expected, these agents were also associated with an increased risk of bleeding. However, among patients at the highest risk for stent thrombosis and recurrent MI, i.e., CI for ST elevation MI, the authors observed a reduction in mortality without an increase in risk for bleeding.

Several limitations of this study should be noted. In particular, the study represents a pooled analysis of a heterogeneous group of studies with varying clinical populations and different follow-up periods. In addition, some of these studies compared novel P2Y12 inhibitors with smaller loading doses of clopidogrel that may have biased the treatment effect in favor of the newer agent.

Nevertheless, the study's findings highlight the importance of matching the antiplatelet treatment strategy with the clinical circumstances. For patients at the highest risk for bleeding who are treated medically for a low-risk ACS, clopidogrel likely remains the most reasonable choice. In contrast, among patients treated invasively with PCI for ST elevation MI, physicians should consider the use of novel P2Y12 inhibitors with more effective platelet inhibition. Although these agents may increase the risk for bleeding, there appears to be a population of patients at the highest risk for thrombosis in which these agents provide a consistent, net clinical benefit.

—Jarett D. Berry, MD, MS

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A risk score to predict bleeding in patients with acute coronary syndromes.

Mehran R, Pocock SJ, Nikolsky E, et al. *J Am Coll Cardiol*. 2010;58:2556-2566.

ABSTRACT

Objectives The aim of this study was to develop a practical risk score to predict the risk and implications of major bleeding in acute coronary syndromes (ACS).

Background Hemorrhagic complications have been strongly linked with subsequent mortality in patients with ACS.

Methods A total of 17,421 patients with ACS (including non–ST-segment elevation myocardial infarction [MI], ST-segment elevation MI, and biomarker negative ACS) were studied in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) and the HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) trials. An integer risk score for major bleeding within 30 days was developed from a multivariable logistic regression model. **Results** Non-coronary artery bypass graft surgery (CABG)-related major bleeding within 30 days occurred in 744 patients (7.3%) and had 6 independent baseline predictors (female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, non–ST-segment elevation MI, or ST-segment elevation MI) and 1 treatment-related variable (use of heparin + a glycoprotein IIb/IIIa inhibitor rather than bivalirudin alone) (model *c*-statistic = 0.74). The integer risk score differentiated patients with a 30-day rate of non–CABG-related major bleeding ranging from 1% to over 40%. In a time-updated covariate-adjusted Cox proportional hazards regression model, major bleeding was an independent predictor of a 3.2-fold increase in mortality. The link to mortality risk was strongest for non–CABG-related Thrombolysis In Myocardial Infarction (TIMI)-defined major bleeding followed by non-TIMI major bleeding with or without blood transfusions, whereas isolated large hematomas and CABG-related bleeding were not significantly associated with subsequent mortality. **Conclusions** Patients with ACS have marked variation in their risk of major bleeding. A simple risk score based on 6 baseline measures plus anticoagulation regimen identifies patients at increased risk for non–CABG-related bleeding and subsequent 1-year mortality, for whom appropriate treatment strategies can be implemented.

SYNOPSIS

Using a Risk Score to Identify ACS Patients at Risk for Major Bleeding May Facilitate Clinical Decision Making

Among patients presenting with acute coronary syndromes (ACS) and undergoing percutaneous coronary intervention (PCI), hemorrhagic complications are an independent risk factor for mortality. Given the improved potency of antithrombotic medications used in the management of ACS, a method for identifying patients at risk may reduce the potential for hemorrhagic complications and improve outcomes.

To develop an integer risk score to predict the risk for major bleeding in ACS, Mehran et al. applied a multivariable logistic regression model to the pooled data from two randomized, double-blind trials in a total of 17,421 patients undergoing PCI, coronary artery bypass grafting (CABG), or medical management for non-ST-segment deviation myocardial infarction (NSTEMI), STEMI, or biomarker-negative ACS.

A total of 744 patients experienced non-CABG-related major bleeding within 30 days. Six baseline demographic and laboratory variables and one treatment-related variable emerged as independent predictors of non-CABG-related major bleeding: female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, STEMI and NSTEMI elevated biomarkers, and heparin plus a glycoprotein IIb/IIIa inhibitor (rather than bivalirudin monotherapy).

Based on these six variables, the integer risk score, shown in the **Table**, identified a wide variation in the likelihood for an individual patient to develop non-CABG-related major bleeding, ranging from 1% to 40%. Non-CABG-related major bleeding within 30 days was an independent

Table. Integer-based Risk Score for Non-CABG-related Major Bleeding Within 30 Days of Patient Presentation With Acute Coronary Syndrome

								Add to score
Gender	Male 0					Female +8		
Age (years)	<50 0	50-59 +3		60-69 +6		70-79 +9	>80 +12	
Serum creatinine (mg/dL)	<1.0 0	1.0- +2	1.2- +3	1.4- +5	1.6- +6	1.8- +8	≥2.0 +10	
White blood cell count (giga/L)	<10 0	10- +2	12- +3	14- +5	16- +6	18- +8	≥20 +10	
Anemia	No 0					Yes +6		
Presentation	STEMI +6		NSTEMI - Raised biomarkers +2			NSTEMI- Normal biomarkers 0		
Antithrombotic medications	Heparin plus a GPI 0				Bivalirudin monotherapy -5			
	Total Score*							

Example: For a patient who is female, 72 years of age, creatinine 1.3 mg/dL, white cell count 11 giga/L, not anemic, and non–ST-segment elevation myocardial infarction (NSTEMI) without raised biomarkers, her risk score is: 8 + 9 + 3 + 2 + 0 + 0 = 22 total score, signifying a 9.6% chance of a non–coronary artery bypass graft (CABG)-related major bleed within 30 days.

*If patient is on bivalirudin alone rather than heparin plus glycoprotein IIb/IIIa inhibitor (GPI), the total score should be reduced by 5.
STEMI = ST-segment elevation myocardial infarction.

predictor of mortality at 1 year, increasing the risk by a factor of 3.2 (P<0.001) and similar to the 3-fold increase in mortality risk associated with MI within 30 days (P<0.001). Non-CABG-related bleeding meeting the Thrombolysis in Myocardial Infarction (TIMI) major criteria independently conferred a 4.45-fold increased risk for mortality. If a non-CAGB-related major bleed required a blood transfusion, the risk for mortality increased by 3-fold, and a non-TIMI major bleed that did not require transfusion doubled the risk of 1-year mortality. In contrast, development of a large hematoma (>5 cm) independent of other bleeding criteria was not a significant predictor of mortality.

The integer risk score for non-CABG-related major bleeding is a rapid and reliable tool to identify those patients with ACS at higher risk and the impact of bleeding on subsequent mortality.

COMMENTARY

A Step Closer to Assessing Bleeding Risk, But Still No Closer to Determining Cause of Fatal Events

In general, reducing ischemia with more potent anticoagulant regimens comes at the cost of an increased risk of bleeding. Not surprisingly, the overall incidence and risk of bleeding in patients with acute coronary syndromes has increased with more intense anticoagulation. No clinician likes bleeding, however it was felt to be a necessary evil to reduce ischemic events. But accepting this slightly higher risk of bleeding with more potent anticoagulation agents has been called into question and some have suggested that any bleeding may actually worsen overall outcomes even if it also reduces ischemic risk.

The first step is to prospectively identify patients at highest risk of bleeding by developing a "bleeding risk score." Investigators from several large databases, including the CRUSADE Registry, have developed and validated bleeding risks scores in patients with non-ST-segment elevation acute coronary syndrome. In the article by Mehran et al, the investigators from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY)[1] and the HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction)[2] studies pooled their databases to develop a bleeding risk score in a well characterized clinical-trial population undergoing PCI who were randomized to heparin + glycoprotein IIb/IIIa inhibitor or bivalirudin across the ACS spectrum.

The investigators found that six patient characteristics—gender, age by decade, serum creatinine, white blood cell count, anemia, and index diagnosis—together with treatment with heparin plus glycoprotein IIb/IIIa inhibitor were independently associated with the risk of a non-CABG related TIMI major bleed. There was a wide spectrum of 30-day risk of bleeding ranging from 1% in the lowest risk groups to more than 30% in the highest risk groups.

Moreover, the 1-year risk of death was significantly higher in patients who had a TIMI major or a non-TIMI major bleed, regardless of transfusions. Isolated large groin hematomas that did not meet TIMI major criteria were not associated with poor outcomes.

This report is consistent with other reports that identify a similar list of baseline characteristics that increases a patient's risk of bleeding, and poor outcomes in general. The finding that the use of heparin plus a glycoprotein IIb/IIIa inhibitor is associated with increased risk of bleeding is consistent with the primary results of the two trials, though based on the trial designs, the risk of bleeding most likely due to the glycoprotein IIb/IIIa inhibitor rather than the anticoagulant itself.

The observation that a major bleed carries a similar 1-year risk as a subsequent MI is sobering and motivation for adopting strategies to minimize bleeding. A lower utilization of the glycoprotein IIb/IIIa inhibitors based on the negative results of

the EARLY ACS trial[3] and the greater utilization of radial artery access in ACS will hopefully minimize the risk of bleeding. However, whether there is a true *causal* relationship between bleeding and death, i.e., bleeding led to death, rather than *associative*, i.e., sick patients both bleed and die, has yet to be convincingly demonstrated and will require further investigation.

—Benjamin Scirica, MD, MPH

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Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease.

Cooper-DeHoff RM, Gong Y, Handberg EM, et al. *JAMA*. 2010;304:61-68.

ABSTRACT

Context Hypertension guidelines advocate treating systolic blood pressure (BP) to less than 130 mm Hg for patients with diabetes mellitus; however, data are lacking for the growing population who also have coronary artery disease (CAD). **Objective** To determine the association of systolic BP control achieved and adverse cardiovascular outcomes in a cohort of patients with diabetes and CAD. **Design, Setting, and Patients** Observational subgroup analysis of 6400 of the 22 576 participants in the International Verapamil SR-Trandolapril Study (INVEST). For this analysis, participants were at least 50 years old and had diabetes and CAD. Participants were recruited between September 1997 and December 2000 from 862 sites in 14 countries and were followed up through March 2003 with an extended follow-up through August 2008 through the National Death Index for US participants. Intervention Patients received first-line treatment of either a calcium antagonist or β-blocker followed by angiotensin-converting enzyme inhibitor, a diuretic, or both to achieve systolic BP of less than 130 and diastolic BP of less than 85 mm Hg. Patients were categorized as having tight control if they could maintain their systolic BP at less than 130 mm Hg; usual control if it ranged from 130 mm Hg to less than 140 mm Hg; and uncontrolled if it was 140 mm Hg or higher. **Main Outcome Measures** Adverse cardiovascular outcomes, including the primary outcomes which was the first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke. **Results** During 16 893 patient-years of follow-up, 286 patients (12.7%) who maintained tight control, 249 (12.6%) who had usual control, and 431 (19.8%) who had uncontrolled systolic BP experienced a primary outcome event. Patients in the usual control group had a cardiovascular event rate of 12.6% vs a 19.8% event rate for those in the uncontrolled group (adjusted hazard ratio [HR], 1.46; 95% confidence interval [CI], 1.25-1.71; *P*<.001). However, little difference existed between those with usual control and those with tight control. Their respective event rates were 12.6% vs 12.7% (adjusted HR, 1.11; 95%CI, 0.93-1.32; *P*=.24). The all-cause mortality rate was 11.0% in the tight-control group vs 10.2% in the usual-control group (adjusted HR, 1.20; 95% CI, 0.99-1.45; *P*=.06); however, when extended follow-up was included, risk of all-cause mortality was 22.8% in the tight control vs 21.8% in the usual control group (adjusted HR, 1.15; 95% CI, 1.01-1.32; *P*=.04). **Conclusion** Tight control of systolic BP among patients with diabetes and CAD was not associated with improved cardiovascular outcomes compared with usual control.

SYNOPSIS

Tight Systolic Blood Pressure Control Is Not Associated With Reduced Mortality in Patients With Diabetes and CAD

Evidence-based guidelines have recommended a blood pressure (BP) goal of <130/80 mm Hg for patients with diabetes for more than 20 years to prevent hypertension-related macrovascular and microvascular complications. However, data to support tight BP control in patients with diabetes to reduce adverse cardiovascular (CV) outcomes is limited, particularly for lower systolic BP goals. To provide further insight, Cooper-DeHoff and colleagues analyzed data from a cohort of 6400 patients with diabetes and coronary artery disease (CAD) in the International Verapamil SR-Trandolapril Study (INVEST).

The patients were randomized to tight (<130 mm Hg), usual (130 to <140 mm Hg), or uncontrolled (>140 mm Hg) systolic BP during treatment with a calcium antagonist- or β-blocker-based antihypertensive treatment regimen. The primary outcome measure was the first occurrence of all-cause mortality, nonfatal myocardial infarction (MI), or nonfatal stroke.

After 24 months, the reduction in mean systolic BP did not differ among the groups, despite the fact that a higher proportion of patients in the tight control group (~50%) than in the usual and uncontrolled groups (>66%) were taking three or more antihypertensive agents. The occurrence of the primary outcome increased with less systolic BP control, from 12.7% in the tight control group and 12.6% in the usual control group to 19.8% in the uncontrolled group (*P*<0.001). However, there was no significant difference between the tight control and usual control groups for the primary outcome (*P*=0.24). Similarly, the risks for nonfatal MI and stroke did not differ between the tight and usual control groups (*P*=0.49 and *P*=0.38, respectively) (**Figure**). All-cause mortality rates did not differ significantly between the tight and usual control groups (11.0% vs. 10.2%, *P*=0.06); however, inclusion of 5-year follow-up data for the US cohort indicated tight control was associated a significantly greater risk for all-cause mortality (22.8% vs. 21.8%, *P*=0.04).

This post-hoc subset analysis of INVEST trial data was the first to demonstrate not only that systolic BP control to <130 mm Hg does not reduce mortality among patients with diabetes and CAD but also that tighter systolic BP control may increase all-cause mortality.

Therefore, the investigators suggest that clinicians emphasize maintaining systolic BP between 130 and 139 mm Hg, as well as positive lifestyle habits and other strategies to reduce long-term CV risk.

COMMENTARY

Diabetic Patients at Risk of Stroke May Benefit from the "Lower Is Better" Blood Pressure Strategy

Over the past 40 years, we have observed a 50% decline in cardiovascular disease (CVD) event rates resulting in part from more effective treatment of hypertension and hypercholesterolemia among high-risk subgroups such as patients with diabetes. Throughout this time period, we have observed a consistent story with lipid lowering therapy: namely, that lower cholesterol is better across most patient populations, including patients with diabetes.

The story with hypertension treatment is somewhat different. Treatment of diabetic patients with high blood pressure, i.e., systolic blood pressures >160 mm Hg, translates into a clinical benefit observed consistently across multiple clinical trials. Based on these and other data, guidelines adopted the "lower is better" hypothesis for hypertension treatment in patients with diabetes. Until recently, however, there was relatively little data to support this strategy.

In early 2010, the ACCORD study compared two different systolic blood pressure treatment strategies (goal <120 mm Hg vs. goal <140 mm Hg) among patients with diabetes.[1] This trial observed that a more aggressive blood pressure treatment strategy was not associated with a reduction in overall cardiovascular events. However, this study did observe a 40% reduction in stroke rates in the more aggressive treatment arm.

In the present study by Cooper-DeHoff et al, the authors conducted a secondary analysis of the INVEST trial,[2] comparing cardiovascular event rates among patients with diabetes and coronary artery disease across three levels of blood pressure control: tight control (<130 mm Hg), usual control (130-139 mm Hg), and uncontrolled (≥140 mm Hg). Similar to ACCORD, the authors observed that tight blood pressure control was not associated with improved cardiovascular outcomes compared to usual control.

In addition, the authors also observed that patients treated to systolic blood pressure levels <110 mm Hg actually had an increase in all cause mortality. Because these are secondary, post-hoc analyses, patients were not randomized to these different blood pressure lowering strategies. Rather, their blood pressure was low because of any number of potential reasons unrelated to treatment.

Taken together, the findings from both INVEST and ACCORD suggest several important implications. First, secondary analyses from clinical trials should be interpreted with caution. In contrast to INVEST, there was no increased risk among patients randomized to an aggressive blood pressure lowering strategy in ACCORD. Therefore, this is likely not a harmful clinical strategy. Second, aggressive blood pressure lowering may not have a consistent effect across all outcomes, with greater potential benefit in stroke risk reduction compared with other CVD events. In spite of these overall negative findings, it would still be reasonable to consider an aggressive blood pressure lowering strategy in a diabetic patient with a prior stroke history.

—Jarett D. Berry, MD, MS

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Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts. The MONICA, Risk, Genetics, Archiving, and Monogram (MORGAM) Biomarker Project.

Blankenberg S, Zeller T, Saarela O, et al. *Circulation*. 2010;121:2388-2397.

ABSTRACT

Background Cardiovascular risk estimation by novel biomarkers needs assessment in disease-free population cohorts, followed up for incident cardiovascular events, assaying the serum and plasma archived at baseline. We report results from 2 cohorts in such a continuing study. **Methods and Results** Thirty novel biomarkers from different pathophysiological pathways were evaluated in 7915 men and women of the FINRISK97 population cohort with 538 incident cardiovascular events at 10 years (fatal or nonfatal coronary or stroke events), from which a biomarker score was developed and then validated in the 2551 men of the Belfast Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohort (260 events). No single biomarker consistently improved risk estimation in FINRISK97 men and FINRISK97 women and the Belfast PRIME Men cohort after allowing for confounding factors; however, the strongest associations (with hazard ratio per SD in FINRISK97 men) were found for N-terminal pro-brain natriuretic peptide (1.23), C-reactive protein (1.23), B-type natriuretic peptide (1.19), and sensitive troponin I (1.18). A biomarker score was developed from the FINRISK97 cohort with the use of regression coefficients and lasso methods, with selection of troponin I, C-reactive protein, and N-terminal pro-brain natriuretic peptide. Adding this score to a conventional risk factor model in the Belfast PRIME Men cohort validated it by improved c-statistics (P=0.004) and integrated discrimination (P<0.0001) and led to significant reclassification of individuals into risk categories (P=0.0008). **Conclusions** The addition of a biomarker score including N-terminal pro-brain natriuretic peptide, C-reactive protein, and sensitive troponin I to a conventional risk model improved 10-year risk estimation for cardiovascular events in 2 middle-aged European populations. Further validation is needed in other populations and age groups.

Table. HRs of Future Cardiovascular Events According to Optimal Cut Points

	FINRISK 97 Men		Belfast PRIME Men		
Biomarker	**Data-Derived Optimal Cut Point***	**Percentile**	**Percentile**	**HR (95% CI)**	***P***
C-reactive protein	6.81 mg/L	93.1	91.0	1.948 (1.392-2.726)	0.0004
NT-proBNP	187 pg/mL	94.5	97.2	2.289 (1.393-3.759)	0.0011
Troponin I	0.008 ng/mL	91.9	97.6	1.870 (1.017-3.438)	0.0440
Score: 0.38468 x C-reactive protein$^{1/3}$+0.11005 x NT-proBNP$^{1/3}$+ 1.27006 x troponin I$^{1/3}$	1.35686	92.5	95.7	2.346 (1.564-3.520)	<0.0001

CI indicates confidence interval.
*Cut point giving the best discrimination by the IDI criterion when added into fully adjusted baseline model.

SYNOPSIS

A New Scoring System Using Novel Biomarkers Improves Cardiovascular Risk Assessment in a Middle-aged Population

A number of novel biomarkers have been identified with increased cardiovascular (CV) risk in the community. Among them, C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have most consistently improved CV risk assessment over traditional risk models. Blankenberg and colleagues sought to derive a score based on multiple biomarkers that could be used to refine CV risk estimates. They evaluated retrospectively the incremental value of 30 biomarkers for cardiovascular disease (CVD), including markers of renal function, oxidative stress, necrosis, angiogenesis, and coagulation, in 10,466 middle-aged European individuals with 798 incident CVD events. The investigators then compared the value of these biomarkers with readily available simple risk factors for CVD and assessed their incremental value to improve CV risk assessment.

Blankenberg et al. found that only NT-proBNP, CRP, and troponin I were consistently associated with CV events in both men and women. The addition of any single biomarker to a standard risk assessment model did not improve risk estimates; however, incorporating a composite biomarker score for these three variables significantly improved 10-year risk assessment (P=0.004) and resulted in significant reclassification of individuals into risk categories (P=0.008).

The investigators also determined optimal cut points for the three novel biomarkers comprising the composite biomarker score. The cut points for NT-proBNP, CRP, and troponin I were 187 pg/mL, 6.81 mg/L, and 0.008 ng/mL, respectively, and each was associated with an increased risk for future CV events (P=0.0440) (**Table**). The three-biomarker score—the sum of one third of each value for NT-proBNP, CRP, and troponin I multiplied by a factor of 0.38468—also significantly predicted future CV risk (P<0.0001). Each of the biomarkers included in the score can be measured easily in the community using standardized and reproducible assays that are available at reasonable cost. Furthermore, each biomarker represents a different pathophysiological pathway in CVD, thereby providing an independent and incremental contribution to risk assessment.

This study did not address whether reduction of any or all three biomarkers may reduce future CV risk, nor did it determine if the new score will drive treatment decisions that may improve outcomes. Nonetheless, the improved 10-year risk assessment by the addition of these biomarkers to a traditional risk model in this population warrants further prospective evaluation in other patient cohorts.

COMMENTARY

Many Biomarkers Studied, But Only Handful Demonstrate Utility in Predicting CV Events

What is the best method to determine the risk of future cardiovascular events in primary prevention? The gold standard is the Framingham Risk Score, which calculates a person's 10-year risk based on age, gender, cholesterol levels, blood pressure, diabetes, and smoking history (http://www.framinghamheartstudy.org/risk/coronary.html). Determining whether a patient's risk is low (<5%) or high (>10%) can help guide lipid therapy and motivate high-risk patients to modify any risk factors. The clinical risk scores, though, are far definitive in terms of risk stratification.

Several studies have now tested whether incorporating cardiac biomarkers can improve the ability to identify those patients at highest risk. The results have been far from uniform not only in terms of whether the biomarker improves risk stratification but also regarding the magnitude of improvement. C-reactive protein, in particular, has been the subject of much debate, in particular whether it should be tested more widely in patients without established vascular disease.

In this report, Blankenberg and colleagues evaluated 30 new biomarkers in two cohorts that included more than 10,000 men and women without any vascular disease. A great strength of this paper is the simultaneous assessment of multiple biomarkers that were chosen to represent various pathologic processes such as inflammation (C-reactive protein, IL-18), vascular or hemodynamic stress (NT-proBNP, C-terminal provasopressin, or copeptin), lipid metabolism (APO A1 and B100), metabolism (leptin and adiponectin), renal function (cystatin-C), necrosis (troponin I), coagulation (D-dimer), and oxidative stress (myeloperoxidase).

In the end, only C-reactive protein, NT-proBNP, and troponin I, when combined together, were the only biomarkers found to significantly improve the dis-

crimination (the ability to correctly identify patients who will have an event) or correctly reclassify patients into the correct risk category. As seen in other studies, the greatest value of adding biomarkers to the risk score was through improving risk stratification among patients who are at intermediate risk (10-year risk of 5-10%) as determined by the clinical score alone. The addition of biomarkers did not significantly alter the risk of either the low (10-year risk <5%) or high groups (10-year risk >10%) in which the clinical score performed quite well. These data are consistent with several other studies that have shown that natriuretic peptides and the more sensitive troponin assays improve risk stratification.

Data that improve risk stratification are always important and welcome; however, we sorely lack evidence regarding the therapeutic implications of identifying a patient at high risk. In other words, what should a clinician do if they measure any of these new markers and find that a patient is at greater risk than previously expected? There are no data to answer these questions. The JUPITER trial, which demonstrated that intense statin therapy was beneficial compared to placebo in patients with normal cholesterol but with elevated levels of C-reactive protein, was a first step in the evaluation of whether one therapy is better than another in high-risk patients.[1] However, few other studies have been designed similarly. Without a clear therapeutic implication associated with an elevated biomarker, it is unlikely that it will be widely incorporated into clinical care.

—Benjamin Scirica, MD, MPH

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Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis.

Mega JL, Close SI, Wiviott SD, et al. *Lancet*. 2010;376:1312-1319.

ABSTRACT

Background Clopidogrel and prasugrel are subject to efflux via P-glycoprotein (encoded by ABCB1, also known as MDR1). ABCB1 polymorphisms, particularly 3435C→T, may affect drug transport and efficacy. We aimed to assess the effect of this polymorphism by itself and alongside variants in CYP2C19 on cardiovascular outcomes in patients treated with clopidogrel or prasugrel in TRITON–TIMI 38. We also assessed the effect of genotype on the pharmacodynamic and pharmacokinetic properties of these drugs in healthy individuals. **Methods** We genotyped ABCB1 in 2932 patients with acute coronary syndromes undergoing percutaneous intervention who were treated with clopidogrel (n=1471) or prasugrel (n=1461) in the TRITON–TIMI 38 trial. We evaluated the association between ABCB1 3435C→T and rates of the primary efficacy endpoint (cardiovascular death, myocardial infarction, or stroke) until 15 months. We then assessed the combined effect of ABCB1 3435C→T genotype and reduced-function alleles of CYP2C19. 321 healthy individuals were also genotyped, and we tested the association of genetic variants with reduction in maximum platelet aggregation and plasma concentrations of active drug metabolites. **Findings** In patients treated with clopidogrel, ABCB1 3435C→T genotype was significantly associated with the risk of cardiovascular death, myocardial infarction, or stroke (p=0·0064). TT homozygotes had a 72% increased risk of the primary endpoint compared with CT/CC individuals (Kaplan-Meier event rates 12·9% [52 of 414] vs 7·8% [80 of 1057 participants]; HR 1·72, 95% CI 1·22–2·44, p=0·002). ABCB1 3435C→T and CYP2C19 genotypes were significant, independent predictors of the primary endpoint, and 681 (47%) of the 1454 genotyped patients taking clopidogrel who were either CYP2C19 reduced-function allele carriers, ABCB1 3435 TT homozygotes, or both were at increased risk of the primary endpoint (HR 1·97, 95% CI 1·38–2·82, p=0·0002). In healthy participants, 3435 TT homozygotes had an absolute reduction in maximum platelet aggregation with clopidogrel that was 7·3 percentage points less than for CT/CC individuals (p=0·0127). ABCB1 genotypes were not significantly associated with clinical or pharmacological outcomes in patients with an acute coronary syndrome or healthy individuals treated with prasugrel, respectively. **Interpretation** Individuals with the ABCB1 3435 TT genotype have reduced platelet inhibition and are at increased risk of recurrent ischaemic events during clopidogrel treatment. In patients with acute coronary syndromes who have undergone percutaneous intervention, when both ABCB1 and CYP2C19 are taken into account, nearly half of the population carries a genotype associated with increased risk of major adverse cardiovascular events while on standard doses of clopidogrel.

SYNOPSIS

ABCB1 Polymorphisms and CYP2C19 Variants May Explain Some Variability of Response to Clopidogrel Following PCI

Treatment with the thienopyridine in clopidogrel patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) has been associated with variability of platelet-inhibiting response and an increased risk for adverse cardiovascular (CV) events. In contrast, greater platelet inhibition and less variability in response have been reported with prasugrel. The diminished response to clopidogrel may

be explained, at least in part, to reduced-function genetic variants in the cytochrome P450 enzyme CYP2C19 and/or alterations in thienopyridine absorption due to genetic variants in ABCB1, which encodes the efflux pump P-glycoprotein.

Mega and colleagues genotyped a subset of 2932 patients with ACS undergoing PCI in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 for *ABCB1* and *CYP2C19* to assess the association between polymorphisms and adverse CV outcomes during treatment with clopidogrel or prasugrel. They also evaluated the pharmacogenetic effects in 321 healthy volunteers.

Within the study population, 27% were homozygotes for the *ABCB1* 3435→T variant (TT), 23% were homozygotes for the C-allele (CC), and 50% were heterozygotes (CT). Compared with CT/CC individuals treated with clopidogrel, TT homozygotes had an increased risk for the primary end point—CV death, myocardial infarction (MI), or stroke—over 15 months. With rates of 12.9%, 8.2%, and 7.7% for the TT, CC, and CT genotypes, respectively (P=0.0064 across genotypes), TT homozygotes had a 72% increased risk for the primary end point compared with CT/CC individuals (P=0.02). *CYPC19* genotype also was an independent predictor of the primary end point, with reduced-function allele carriers at significant risk compared with non-carriers (P=0.0155).

In healthy individuals with the *ABCB1* 3435→T variant, platelet aggregation was significantly diminished in TT homozygotes compared with CT/CC individuals (P=0.0127) in response to a clopidogrel loading dose but not during maintenance dosing. In contrast, there were no significant associations between the *ABCB1* variants and clinical or pharmacodynamic outcomes in patients or healthy participants treated with prasugrel.

These results suggest that the pharmacogenetic effects of *ABCB1* 3435→T are independent of those of *CYPC19*, and the roles of both genotypes should be taken into account when the role of genetic factors on thienopyridine response.

COMMENTARY

Match the Right Patient With the Right Thienopyridine

Dual antiplatelet therapy with both aspirin and thienopyridines has become the standard of care for patients with acute coronary syndromes and in patients undergoing percutaneous coronary intervention (PCI). Thienopyridines block the P2Y12 receptor on circulating platelets leading to the inhibition of platelet activation, thereby reducing thrombotic complications such as recurrent myocardial infarction and stent thrombosis.

The most commonly prescribed thienopyridine, clopidogrel, must be metabolized from an inactive prodrug to the active metabolite through multiple cytochrome P450-dependent steps. Multiple prior studies have identified an important isoform of one of these enzymes, *CYP2C19*, which is associated with a decrease in the active metabolite and diminished platelet inhibition. More importantly, the observation that this particular enzyme was associated with higher rates of cardiovascular events among individuals randomized to clopidogrel led to the recent decision by the FDA to place a boxed warning on clopidogrel, warning that individuals with two copies of this particular isoform are at increased risk for recurrent cardiovascular events.

These findings have led to ongoing investigations into additional genetic variation in the metabolism of theinopyridines. In this study, the authors assess the association between genetic variants of *ABCB1* and recurrent cardiovascular events using data from TRITON-TIMI 38. *ABCB1* is an efflux pump involved in the absorption of thienopyridines, and therefore represents a potential additional source of genetic variation in the metabolism of these drugs.

The authors observed three important findings. First, individuals randomized to clopidogrel and possessing a particular genetic variant of *ABCB1* (TT genotype) had reduced platelet inhibition and increased risk of recurrent cardiovascular events compared with patients with other genotypes. Of note, this finding appeared to be additive to the *CYP2C19* genotype. Second, these associations were not observed among participants randomized to prasugrel. And third, the prevalence of *CYP2C19* and the TT variant of *ABCB1* are common, with nearly 50% of the population possessing one of these genetic variants.

Although these findings are of significant interest, they should be interpreted with caution. Findings from a similar study published from the PLATO study observed discordant findings: namely, that the TT genetic variant of *ABCB1* was associated with a lower rate of recurrent cardiovascular events.[1] These contrasting findings suggest that for the present time, the role of *ABCB1* variants in influencing clopidogrel metabolism remains unclear.

In spite of these discordant results, several things remain clear. First, effective, dual anti-platelet therapy with both aspirin and a thienopyridine is critically important for patients with ACS with or without PCI. Second, there is considerable variability in the metabolism of clopidogrel leading to clinically relevant differences in platelet inhibition. Thus, for patients at the highest risk for recurrent events, physicians may consider confirmatory tests to ensure adequate platelet inhibition. Alternatively, in the highest-risk patients, physicians should consider treatment with prasugrel, as this thienopyridine possesses more robust platelet inhibition properties and does not appear to be as susceptible to genetic variants influencing their metabolism.

—Jarett D. Berry, MD, MS

REFERENCE

1. Wallentin L, et al. *Lancet*. 2010;376:1320-1328.

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. **In a meta-analysis by Bellemain-Appaix et al, treatment with newer thienopyridines following percutaneous intervention (PCI) showed a significant difference from treatment with clopidogrel for:**
   A. Cardiovascular (CV)-related mortality and stroke
   B. Thrombolysis in Myocardial Infarction (TIMI)-defined major and minor bleeding
   C. CV-related mortality and major adverse cardiac events (MACE)
   D. Mortality and stroke

2. **A subset analysis in the Bellemain-Appaix et al meta-analysis found that the newer thienopyridines were particularly beneficial for patients with PCI for ST-segment elevation myocardial infarction (STEMI) because:**
   A. There were significant reductions in adverse outcomes with no increased risk for TIMI major bleeding
   B. Treatment reduced the risk for stroke as well as mortality and CV-related outcomes
   C. There was a greater reduction in stent thrombosis compared with patients receiving any PCI
   D. Treatment reduced the risk for both TIMI major and minor bleeding

3. **According to registry data analyzed by Bhatt and colleagues, which of the following are the most significant predictors of CV death, MI, or stroke?**
   A. A recent ischemic event and a history of diabetes
   B. Polyvascular disease and congestive heart failure
   C. Congestive heart failure and low body mass index
   D. Polyvascular disease and current smoking

4. **Data from the MORGAM Biomarker Project analyzed by Blankenberg et al indicated that when added to a traditional CV risk assessment model, values for N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP), and troponin I:**
   A. Individually improve 10-year CV risk estimates
   B. Predict 10-year CV risk only in men
   C. Improve estimates for individuals with a history of MACE
   D. Can significantly predict future CV risk when used in a composite score

5. **In a post-hoc analysis of data from the INVEST trial in patients with diabetes and coronary artery disease, Cooper-DeHoff and colleagues found that:**
   A. Tight blood pressure (BP) control was associated with an increase in all-cause mortality at 5 years
   B. Tight BP control significantly reduced BP compared with usual BP control after 2 years
   C. Tight BP control did not significantly reduce the incidence of all-cause mortality, nonfatal MI, or nonfatal stroke
   D. Tight BP control significantly reduced the risk for nonfatal MI or stroke compared with usual BP control

6. **According to the results of the CURRENT-OASIS trial in patients with acute coronary syndrome, the occurrence of CV death, MI, or stroke at 30 days:**
   A. Was significantly lower among patients treated with a higher-dose aspirin regimen than those treated with a lower-dose aspirin regimen
   B. Was significantly higher among patients treated with standard-dose clopidogrel than those treated with a higher-dose aspirin regimen
   C. Was not significantly reduced with the use of a double-dose clopidogrel or a higher-dose aspirin regimen
   D. Was significantly higher among patients treated with double-dose clopidogrel than those treated with standard-dose clopidogrel

7. **Another important finding of the CURRENT-OASIS trial was that the risk for major bleeding was:**
   A. Higher in patients treated with a higher-dose aspirin regimen than those treated with a lower-dose aspirin regimen
   B. Higher in patients treated with double-dose clopidogrel than those treated with standard-dose clopidogrel
   C. Higher in patients treated with double-dose clopidogrel than those treated with a higher-dose aspirin regimen
   D. Higher in patients treated with double-dose clopidogrel combined with a higher-dose aspirin regimen than in those treated with standard-dose clopidogrel combined with a lower-dose aspirin regimen

8. **According to a genotyping study by Mega et al, with genetic variants of the *ABCB1* increased the risk for ischemic events:**
   A. In patients with ACS during treatment with clopidogrel over 15 months
   B. In healthy individuals during treatment with prasugrel at 30 days
   C. In patients with ACS during treatment with prasugrel over 15 months
   D. In healthy individuals during treatment with clopidogrel at 30 days

9. **Mega and colleagues also found that carriers of the reduced-function allele in the *CYPC19* gene treated with clopidogrel had an increased risk for CV death, nonfatal MI, or stroke:**
   A. Compared with carriers of *ABCB1* genetic variants taking clopidogrel
   B. Compared with non-carriers of the *CYPC19* reduced-function allele taking prasugrel
   C. Compared with carriers of *ABCB1* genetic variants taking prasugrel
   D. Compared with non-carriers of the *CYPC19* reduced-function allele taking clopidogrel

10. **Based on their risk scoring system, Mehran et al found that non-coronary artery bypass graft (CABG)-related major bleeding within 30 days of treatment for ACS:**
    A. Independently predicted MI within 30 days
    B. Occurred at a similar incidence in men and women
    C. Independently predicted mortality at 1 year
    D. Occurred at a similar rate across the patient population

Evaluation and Answer Sheet

December 2010

INTERVENTION & PREVENTION: KEEPING CURRENT WITH ACUTE CORONARY SYNDROME. A JOURNAL CLUB FOR PRIMARY CARE

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The amount of time I spent on this activity was _____ (max 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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