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Stabilization, Management, and Avoidance (CHARISMA) study

## INTERPRETING THE CHARISMA STUDY

# What is the role of dual antiplatelet therapy with clopidogrel and aspirin?

## ■ ABSTRACT

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study (N Engl J Med 2006; 354:1706–1717, J Am Coll Cardiol 2007; 49:1982–1988) assessed the effect of dual antiplatelet therapy with clopidogrel (Plavix) and aspirin in patients at risk of atherothrombotic events. At a median of 28 months, the rate of the primary efficacy end point (a composite of myocardial infarction, stroke, and death from cardiovascular causes) was not significantly lower in the group receiving clopidogrel plus aspirin than in the group receiving placebo plus aspirin. However, one subgroup may have derived some benefit from the combination: those at higher risk owing to a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease.

## ■ KEY POINTS

Platelets are key players in atherothrombosis, and antiplatelet drugs such as aspirin and clopidogrel prevent events in patients at risk.

In studies leading up to CHARISMA, the combination of clopidogrel and aspirin was found to be beneficial in patients with acute coronary syndromes and in those undergoing percutaneous coronary interventions.

Clopidogrel should not be combined with aspirin as a primary preventive therapy (ie, for people without established vascular disease). How dual antiplatelet therapy should be used as secondary prevention in stable patients needs further study.

**I**N PATIENTS AT RISK of myocardial infarction or stroke, two antiplatelet drugs are not always better than one. In a large recent trial,<sup>1,2</sup> adding clopidogrel (Plavix) to aspirin therapy did not offer much benefit to a cohort of patients at risk of cardiovascular events, although a subgroup did appear to benefit: those at even higher risk because they already had a history of myocardial infarction, ischemic stroke, or peripheral arterial disease.

These were the principal findings in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study,<sup>1,2</sup> in which one of us (D.L.B.) was principal investigator.

These findings further our understanding of who should receive dual antiplatelet therapy, and who would be better served with aspirin therapy alone. In this article, we discuss important studies that led up to the CHARISMA trial, review CHARISMA's purpose and study design, and interpret its results.

## ■ PREVENTING ATHEROTHROMBOSIS BY BLOCKING PLATELETS

Platelets are key players in the atherothrombotic process.<sup>3–5</sup> The Antiplatelet Trialists'

\*Dr. Bhatt has disclosed that he or his department has received research support (which was conveyed directly to the institution), honoraria, or consulting fees (which were donated to nonprofit organizations) from Abraxis, Alexion Pharma, Astellas, AstraZeneca, Atherogenics, Aventis, Biosense Webster, Biosite, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, Cardionet, Centocor, Cogentus, Converge Medical Inc., Cordis, Daiichi-Sankyo, Dr. Reddy's, Edwards Lifesciences, Eisai, Eli Lilly, Esperion, Ethicon, GE Medical Genentech, Gilford, Glaxo SmithKline, Guidant, HeartScape, Johnson & Johnson, Kensey-Nash, McNeil, MedTronic, Merck, Millennium, Mytogen, Novartis, Novo Nordisk, Orphan Therapeutics, Otsuka, Paringenex, PDL, Portola, Procter and Gamble Pharma, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, Scios, St. Jude Medical, Takeda, The Medicines Company, tns Healthcare, VasoGenix, Vertex, and Viacor.

TABLE 1

## Key trials of clopidogrel therapy

| TRIAL*                                            | FINDINGS                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CAPRIE</b> <sup>16–21</sup>                    | Lower risk of myocardial infarction (MI), stroke, or vascular death with clopidogrel than with aspirin in 19,185 patients with recent MI, ischemic stroke, or symptomatic peripheral arterial disease; absolute risk reduction (ARR) 0.5%, relative risk reduction (RRR) 8.7%, $P = .043$ ; followed 1–3 years                                                                                                                                                            |
| <b>CURE</b> <sup>22–24</sup>                      | Lower risk of MI, stroke, or cardiovascular death with clopidogrel plus aspirin than with placebo plus aspirin in 12,562 patients with acute non–ST-segment elevation MI; ARR at 12 months 2.1%, RRR 20%, $P = .001$                                                                                                                                                                                                                                                      |
| <b>CLARITY-TIMI 28</b> <sup>25</sup>              | Lower risk of recurrent MI, recurrent ischemia requiring urgent revascularization, or cardiovascular death with clopidogrel plus aspirin than with placebo plus aspirin in 3,491 patients with acute ST-segment elevation MI treated with fibrinolytics; ARR at 30 days 2.5%, odds reduction 20%, $P = .03$                                                                                                                                                               |
| <b>COMMIT</b> <sup>26</sup>                       | Lower risk of death, reinfarction, or stroke with clopidogrel plus aspirin than with placebo plus aspirin in 45,852 patients with acute MI; ARR 0.9%, RRR 9%, $P = .002$ , followed up to 4 weeks                                                                                                                                                                                                                                                                         |
| <b>CREDO</b> <sup>28</sup>                        | Lower risk of death, MI, or stroke with clopidogrel in 2,116 patients undergoing elective percutaneous coronary intervention (PCI); ARR 3%, RRR 27%, $P = .02$ , followed 1 year                                                                                                                                                                                                                                                                                          |
| <b>PCI-CLARITY</b> <sup>29</sup>                  | Lower risk of cardiovascular death, MI, or stroke with clopidogrel than with placebo in 1,863 patients with ST-elevation MI treated with fibrinolytics undergoing PCI; ARR at 30 days 2.6%, adjusted odds reduction 46%, $P = .008$                                                                                                                                                                                                                                       |
| <b>PCI-CURE</b> <sup>30</sup>                     | Lower risk of cardiovascular death, MI, or urgent revascularization at 30 days with clopidogrel plus aspirin than with placebo plus aspirin in 2,658 patients with non–ST-segment elevation acute coronary syndrome undergoing PCI; ARR 1.9%, RRR 30%, $P = .03$                                                                                                                                                                                                          |
| <b>CHARISMA</b> <sup>1</sup>                      | Overall, no significant risk of MI, stroke, or cardiovascular death with clopidogrel plus aspirin than with placebo plus aspirin in 15,603 patients with clinically evident cardiovascular disease or multiple risk factors; ARR at 28 months 0.5%, RRR 7%, $P = .22$<br>Lower rate of hospitalization for unstable angina, transient ischemic attack, or revascularization<br>Suggestion of benefit with clopidogrel in patients with symptomatic cardiovascular disease |
| <b>“CAPRIE-like” CHARISMA cohort</b> <sup>2</sup> | Lower rate of cardiovascular death, MI, or stroke with clopidogrel plus aspirin than with placebo plus aspirin in a subgroup of 9,478 CHARISMA patients with prior MI, prior ischemic stroke, or symptomatic peripheral arterial disease; ARR at 28 months 1.5%, RRR 17%, $P = .01$                                                                                                                                                                                       |

\*See text for full names of trials

Collaboration,<sup>6</sup> in a meta-analysis of trials performed up to 1997, calculated that antiplatelet therapy (mostly with aspirin) reduced the vascular mortality rate by 15% in patients with acute or previous vascular disease or some other predisposing condition. Thus, aspirin has already been shown to be effective as primary prevention (ie, in patients at risk but without established vascular disease) and as secondary prevention (ie, in those with established disease).<sup>7,8</sup>

Yet many patients have significant vascular events in spite of taking aspirin.<sup>6</sup> Aspirin

failure is thought to be multifactorial, with causes that include weak platelet inhibition, noncompliance, discontinuation due to adverse effects (including severe bleeding), and drug interactions. In addition, aspirin resistance has been linked to worse prognosis and may prove to be another cause of aspirin failure.<sup>9–11</sup>

Clopidogrel, an adenosine diphosphate (ADP) receptor antagonist, has also been studied extensively as an antiplatelet agent.<sup>5,12</sup> Several studies have indicated that clopidogrel and ticlopidine (Ticlid, a

related drug) may be more potent than aspirin, both in the test tube and in real patients.<sup>13–15</sup>

## ■ KEY TRIALS LEADING TO CHARISMA

Before the CHARISMA trial, clopidogrel had been tested in a number of large clinical trials in various types of patients (TABLE 1).<sup>16–26</sup> Findings:

- Clopidogrel is more effective and slightly safer than aspirin as secondary prevention, as shown in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.<sup>16–21</sup>
- The combination of clopidogrel plus aspirin is more beneficial than placebo plus aspirin in patients with acute coronary syndromes, as shown in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial,<sup>22–24</sup> the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI 28) trial,<sup>25</sup> and the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT).<sup>26</sup>
- The combination of clopidogrel plus aspirin is beneficial in patients undergoing percutaneous coronary interventions, with or without drug-eluting stent placement,<sup>27–30</sup> as shown in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial,<sup>28</sup> the Effect of Clopidogrel Pretreatment Before Percutaneous Coronary Intervention in Patients With ST-Elevation Myocardial Infarction With Fibrinolytics (PCI-CLARITY) study,<sup>29</sup> and the Effects of Pre-treatment With Clopidogrel and Aspirin Followed by Long-term Therapy in Patients Undergoing Percutaneous Coronary Intervention (PCI-CURE) study.<sup>30</sup> In fact, most patients undergoing percutaneous interventions now receive a loading dose of clopidogrel before the procedure and continue to take it for up to 1 year afterward. However, the ideal long-term duration of clopidogrel treatment is still under debate.

In view of these previous studies, we wanted to test dual antiplatelet therapy in a broader population at high risk of atherothrombosis, ie, in patients with either established vascular disease or with multiple risk factors for it.

**TABLE 2**

## Inclusion criteria in the CHARISMA study

### MULTIPLE RISK FACTORS\*

#### Major risk factors

- Type 1 or 2 diabetes
- Diabetic nephropathy
- Ankle-brachial index < 0.9
- Asymptomatic carotid stenosis (≥ 70% of luminal diameter)
- More than one carotid plaque (evidenced by intima-media thickness)

#### Minor risk factors

- Systolic blood pressure ≥ 150 mm Hg (despite 3 months of therapy)
- Primary hypercholesterolemia
- Current smoking (> 15 cigarettes/day)
- Male sex and age ≥ 65 years, or female sex and age ≥ 70 years

### ESTABLISHED CARDIOVASCULAR DISEASE

#### Documented coronary disease

- Angina with documented multivessel coronary disease
- History of multivessel percutaneous coronary intervention
- History of multivessel coronary artery bypass grafting
- Myocardial infarction

#### Documented cerebrovascular disease

- Transient ischemic attack during prior 5 years
- Ischemic stroke during prior 5 years

#### Documented symptomatic peripheral arterial disease

- Current intermittent claudication and ankle-brachial index ≤ 0.85
- History of intermittent claudication and previous intervention (ie, amputation, peripheral bypass, or angioplasty)

\*To be included on the basis of having multiple atherothrombotic risk factors, patients had to have two major risk factors or three minor risk factors or one major plus two minor risk factors.

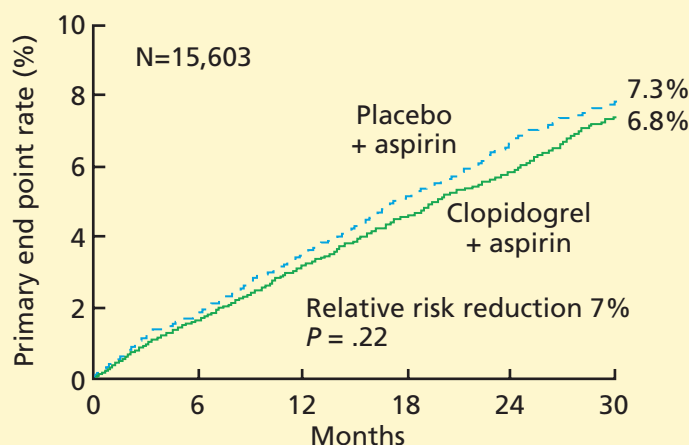
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## ■ CHARISMA STUDY DESIGN

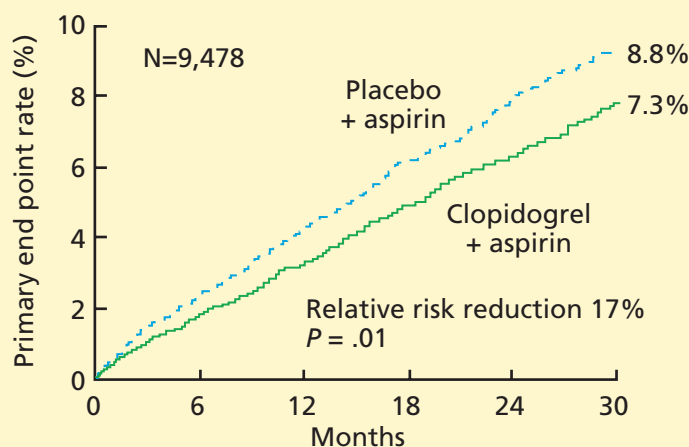
CHARISMA was a prospective, randomized, double-blind, placebo-controlled study of the efficacy and safety of clopidogrel plus aspirin vs placebo plus aspirin in patients at high risk of cardiovascular events.

A total of 15,603 patients, all older than 45 years, were randomly assigned to receive clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day or placebo plus aspirin, in addition to standard therapy as directed by individual clinicians (eg, statins, beta-blockers). Patients were followed up at 1, 3, and 6 months and

### CHARISMA: No benefit from dual antiplatelet therapy in the overall cohort of stable patients studied...



### ...but possible benefit in subgroup with prior MI, stroke, or symptomatic PAD



**FIGURE 1.** Incidence of the primary end point (myocardial infarction, stroke, or cardiovascular death) in the entire cohort (top panel) and in a high-risk ("CAPRIE-like") subgroup with prior myocardial infarction (MI), stroke or symptomatic peripheral arterial disease (PAD) (bottom panel).

FROM BHATT DL, FOX KA, HACKE W, ET AL. CLOPIDOGREL AND ASPIRIN VERSUS ASPIRIN ALONE FOR THE PREVENTION OF ATHEROTHROMBOTIC EVENTS. *N ENGL J MED* 2006; 354:1706-1717 (TOP PANEL) AND BHATT DL, FLATHER MD, HACKE W, ET AL. PATIENTS WITH PRIOR MYOCARDIAL INFARCTION, STROKE, OR SYMPTOMATIC PERIPHERAL ARTERIAL DISEASE IN THE CHARISMA TRIAL. *J AM COLL CARDIOL* 2007; 49:1982-1988. COPYRIGHT 2006 MASSACHUSETTS MEDICAL SOCIETY AND 2007 ELSEVIER. ALL RIGHTS RESERVED.

every 6 months thereafter until study completion, which occurred after 1,040 primary efficacy end points. The median duration of follow-up was 28 months.<sup>1</sup>

Patients had to have one of the following to be included: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented peripheral arterial disease (TABLE 2). Specific exclusion criteria included the use of oral antithrombotic or chronic nonsteroidal anti-inflammatory medications.<sup>1</sup>

#### End points

The **primary end point** was the combined incidence of the first episode of myocardial infarction or stroke, or death from cardiovascular causes.

The **secondary end point** was the combined incidence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or revascularization procedure.

The **primary safety end point** was severe bleeding, as defined in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study<sup>31</sup> as intracranial hemorrhage, fatal bleeding, or bleeding leading to hemodynamic compromise. Moderate bleeding was defined as bleeding that required transfusion but did not meet the GUSTO definition of severe bleeding.

#### ■ OVERALL, NO BENEFIT

At 28 months, the incidence of the primary end point (see above) was 6.8% in the clopidogrel group and 7.3% in the placebo group (absolute risk reduction 0.5%; relative risk reduction 7%;  $P = .22$ , FIGURE 1).<sup>1</sup>

The rates of the secondary end point were 16.7% vs 17.9% (absolute risk reduction 1.2%; relative risk reduction 8%;  $P = .04$ ).

The primary safety end point (severe bleeding as defined in GUSTO) occurred in 1.7% of the patients in the clopidogrel group and 1.3% in the placebo group (relative risk 1.25;  $P = .09$ ). Moderate bleeding occurred in 2.1% in the clopidogrel group and 1.3% in the placebo group (relative risk 1.62;  $P < .001$ ; TABLE 3).<sup>1</sup>

#### Possible benefit in symptomatic patients

In a prespecified analysis, patients were classified as being "symptomatic" (having documented cardiovascular disease, ie, coronary,

cerebrovascular, or symptomatic peripheral arterial disease) or “asymptomatic” (having multiple risk factors without established cardiovascular disease).<sup>1</sup>

In the symptomatic group (n = 12,153), the primary end point was reached in 6.9% of patients treated with clopidogrel vs 7.9% with placebo (absolute risk reduction 1.0%; relative risk reduction 13%;  $P = .046$ ). The 3,284 asymptomatic patients showed no benefit; the rate of the primary end point for the clopidogrel group was 6.6% vs 5.5% in the placebo group ( $P = .20$ ).

In a post hoc analysis, we examined the data from 9,478 patients who were similar to those in the CAPRIE study (ie, with documented prior myocardial infarction, prior ischemic stroke, or symptomatic peripheral arterial disease). The rate of cardiovascular death, myocardial infarction, or stroke was 8.8% in the placebo-plus-aspirin group and 7.3% in the clopidogrel-plus-aspirin group (absolute risk reduction 1.5%; relative risk reduction 17%;  $P = .01$ ; **FIGURE 1**).<sup>2</sup>

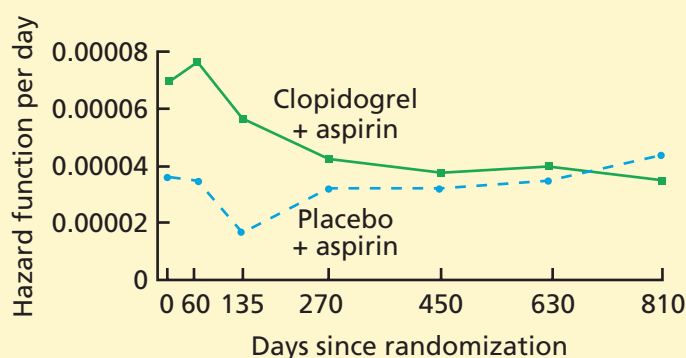
Thus, it appears that stable patients with a history of plaque rupture and thrombosis are most likely to benefit from protracted dual antiplatelet therapy. Interestingly, in this subgroup, there was no incremental risk of even moderate bleeding after a year of dual antiplatelet therapy in patients who tolerated it for a year without a bleeding episode (**FIGURE 2**).<sup>2</sup>

## ■ HOW SHOULD WE INTERPRET THESE FINDINGS?

CHARISMA was the first trial to evaluate whether adding clopidogrel to aspirin therapy would reduce the rates of vascular events and death from cardiovascular causes in stable patients at risk of ischemic events. As in other trials, the benefit of clopidogrel-plus-aspirin therapy was weighed against the risk of bleeding with this regimen. How are we to interpret the findings?

- In the group with multiple risk factors but without clearly documented cardiovascular disease, there was no benefit—and there was an increase in moderate bleeding. Given these findings, physicians should not prescribe dual antiplatelet therapy for primary prevention in patients without known vascular disease.

## The risk of bleeding with clopidogrel is highest in the first few months



**FIGURE 2.** Instantaneous hazard for severe or moderate bleeding in a subset of 9,478 CHARISMA patients with prior myocardial infarction, stroke, or peripheral arterial disease receiving clopidogrel plus aspirin or placebo plus aspirin

BHATT DL, FLATHER MD, HACKE W, ET AL. PATIENTS WITH PRIOR MYOCARDIAL INFARCTION, STROKE, OR SYMPTOMATIC PERIPHERAL ARTERIAL DISEASE IN THE CHARISMA TRIAL. J AM COLL CARDIOL 2007; 49:1982-1988. COPYRIGHT 2007 ELSEVIER. ALL RIGHTS RESERVED.

- A potential benefit was seen in a prespecified subgroup who had documented cardiovascular disease. Given the limitations of subgroup analysis, however, and given the increased risk of moderate bleeding, this positive result should be interpreted with some degree of caution.
- CHARISMA suggests that there may be benefit of protracted dual antiplatelet therapy in stable patients with documented prior ischemic events.

A possible reason for the observed lack of benefit in the overall cohort but the positive results in the subgroups with established vascular disease is that plaque rupture and thrombosis may be a precondition for dual antiplatelet therapy to work.

Another possibility is that, although we have been saying that diabetes mellitus (one of the possible entry criteria in CHARISMA) is a “coronary risk equivalent,” this may not be absolutely true. Although it had been demonstrated that patients with certain risk factors, such as diabetes, have an incidence of ischemic events similar to that in patients with prior MI and should be considered for antiplatelet therapy to prevent vascular events,<sup>32</sup> more recent

**Do not prescribe dual antiplatelet therapy in patients without known vascular disease**

TABLE 3

## Outcomes in CHARISMA

| END POINT                                                                               | CLOPIDOGREL<br>AND ASPIRIN<br>(N = 7,802) | PLACEBO<br>AND ASPIRIN<br>(N = 7,801) | RELATIVE<br>RISK WITH<br>CLOPIDOGREL | P<br>VALUE |
|-----------------------------------------------------------------------------------------|-------------------------------------------|---------------------------------------|--------------------------------------|------------|
| <b>Efficacy end points</b>                                                              |                                           |                                       |                                      |            |
| Primary efficacy end point <sup>a</sup>                                                 | 6.8%                                      | 7.3%                                  | 0.93                                 | .22        |
| Death from any cause                                                                    | 4.8%                                      | 4.8%                                  | 0.99                                 | .90        |
| Death from cardiovascular causes                                                        | 3.1%                                      | 2.9%                                  | 1.04                                 | .68        |
| Myocardial infarction (nonfatal)                                                        | 1.9%                                      | 2.0%                                  | 0.94                                 | .59        |
| Ischemic stroke (nonfatal)                                                              | 1.7%                                      | 2.1%                                  | 0.81                                 | .07        |
| Stroke (nonfatal)                                                                       | 1.9%                                      | 2.4%                                  | 0.79                                 | .03        |
| Secondary efficacy end point <sup>b</sup>                                               | 16.7%                                     | 17.9%                                 | 0.92                                 | .04        |
| Hospitalization for unstable angina,<br>transient ischemic attack, or revascularization | 11.1%                                     | 12.3%                                 | 0.90                                 | .02        |
| <b>Safety end points</b>                                                                |                                           |                                       |                                      |            |
| Severe bleeding                                                                         | 1.7%                                      | 1.3%                                  | 1.25                                 | .09        |
| Fatal bleeding                                                                          | 0.3%                                      | 0.2%                                  | 1.53                                 | .17        |
| Primary intracranial hemorrhage                                                         | 0.3%                                      | 0.3%                                  | 0.96                                 | .89        |
| Moderate bleeding                                                                       | 12.1%                                     | 1.3%                                  | 1.62                                 | < .001     |

<sup>a</sup> Myocardial infarction, stroke, or death from cardiovascular causes

<sup>b</sup> Myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or revascularization procedure

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### Clopidogrel plus aspirin is beneficial in acute coronary syndromes or percutaneous coronary interventions

data have shown that patients with prior ischemic events are at much higher risk than patients without ischemic events, even if the latter have diabetes.<sup>33,34</sup>

- The observation in CHARISMA that the incremental bleeding risk of dual antiplatelet therapy vs aspirin does not persist beyond a year in patients who have tolerated therapy for a year without a bleeding event may affect the decision to continue clopidogrel beyond 1 year, such as in patients with acute coronary syndromes or patients who have received drug-eluting stents.<sup>35,36</sup>

- Another important consideration is cost-effectiveness. Several studies have analyzed the impact of cost and found clopidogrel to be cost-effective by preventing ischemic events and adding years of life.<sup>37,38</sup> A recent analysis from CHARISMA also shows cost-effectiveness in the subgroup of patients enrolled with established cardiovascular disease.<sup>39</sup> Once clopidogrel becomes generic, the cost-effectiveness will become even better.

Further studies should better define which stable patients with cardiovascular disease should be on more than aspirin alone. ■

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