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Scientific Update™

The Role of Antiplatelet Agents in the Prevention of Atherothrombosis

A Discussion and Analysis of presentations from the Late-Breaking Clinical Trials session at the 55th Annual Scientific Session of the American College of Cardiology

Originally presented by: Gabriel Steg, MD, and Deepak L Bhatt, MD

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Atherothrombosis, or the link between the development of thrombotic arterial occlusion and atherosclerosis, is an important cause of myocardial infarction (MI) and stroke. Major advances in the prevention of acute vascular events with statins, angiotensin-converting enzyme inhibitors (ACEIs), and blood pressure control, have resulted in a significant reduction in the incidence of heart attack and stroke. The role of antiplatelet drugs in the prevention of atherothrombosis in patients with stable chronic atherosclerosis has largely been extrapolated from the clear benefit seen in those with recent acute vascular events. The recently reported Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial has now challenged this concept. This issue of *Cardiology Scientific Update* reviews new information about patients with, or at risk for, atherothrombosis, and the evidence for using antiplatelet therapy in the prevention of atherothrombotic events in those with chronic atherosclerotic disease and in primary prevention in those at high risk.

Risk for vascular events in patients with atherothrombosis: insights from the REACH Registry

REduction of Atherothrombosis for Continued Health (REACH) is an industry-sponsored registry that has thus far recruited >67,000 contemporary stable patients from 44 countries who have had, or are at high risk of having symptoms of atherothrombosis. Patients were followed for up to 2 years and the 1-year follow-up data were presented at the recent American College of Cardiology (ACC) Scientific Sessions. Atherosclerotic disease was documented in 1 vascular territory (coronary, cerebrovascular, or peripheral vascular) in 65% of subjects, multiple vascular territories were documented in 15.8%, and multiple risk factors for atherothrombosis were documented in 18.3%. Patients with multiple risk factors had to have at least 3 of the following:

- older age (male ≥65, female ≥70 yrs)
- current smoking (≥15 cigarettes /day)
- diabetes (type 1 or 2)
- hypercholesterolemia
- diabetic nephropathy
- hypertension
- ankle brachial index (ABI) <0.9
- asymptomatic carotid artery stenosis or the presence of ≥1 carotid arterial plaques.

The demographics of the population are typical of a group at high risk for atherothrombosis (mean age 69 years, male 64%, diabetes 44%, hypertension 82%, hypercholesterolemia 72%, obese or overweight 61%, previous/past smoker 57%). Patients received contemporary vascular protective treatment (on-entry medications consisted of beta-blockers 48.6%, ACEIs 48.2%, angiotensin-receptor blockers [ARBs] 25.4%, antiplatelet medications 78.6%, and lipid-lowering therapy 75.2%).

The event rates at 1 year in this population are shown in Table 1. The annual event rates were substantial in this high-risk population, with 14.5% of the patients with known atherosclerotic disease suffering cardiovascular death (CVD), non-fatal MI, stroke, or hospitalization for an atherothrombotic event. When vascular disease is present in multiple territories (coronary artery, cerebrovascular, or peripheral vascular disease), the risk of an atherothrombotic event increases substantially (Figure 1).

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Table 1: Major adverse CV events at 1 year for patients in the REACH Registry

	Total group N = 63,129	"Symptomatic" N = 51,685	Risk factors only N = 11,444
CV death	1.5%	1.7%	0.6%
Nonfatal MI	1.2%	1.2%	0.8%
Nonfatal stroke	1.6%	1.8%	0.8%
CVD + MI + stroke	3.5%	3.9%	1.7%
CVD + MI + stroke + hospitalization for atherothrombotic event	12.9%	14.5%	5.4%

CV = cardiovascular, CVD = cardiovascular death, MI = myocardial infarction

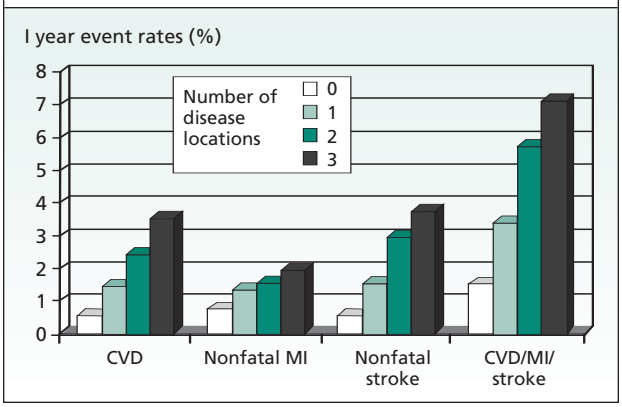
For patients with coronary artery disease (CAD), the presence of atherosclerotic disease in other areas has a particularly large impact. In the patients with CAD and no evidence of disease in another territory, the annual event rates were CVD 1.5%, CVD + MI + stroke 3.1%, CVD + MI + stroke + need for hospitalization 13.3%. When patients had CAD, cerebrovascular disease, and peripheral vascular disease, the event rates doubled (CVD 3.6%, CVD + MI + stroke 7.4%, CVD + MI + stroke + need for hospitalization 26.9%). In the group managed with contemporary therapy, bleeding that resulted in hospitalization and transfusion was more common in patients with known atherosclerotic disease (0.8%) than in those with only risk factors (0.5%). However, the atherothrombotic event rates, as shown in Table 1, were several-fold greater than the bleeding rates (the rate of CVD + MI + stroke in patients with known atherosclerosis was 3.9%; whereas, in those with risk factors only, the rate was 1.7%).

The REACH Registry demonstrates that, despite aggressive treatment with medications to prevent adverse outcomes, atherothrombotic events remain common and greatly outweigh the incidence of important bleeding events (some of which were the result of treatment). The patients at the highest risk for events have evidence for symptomatic atherosclerotic disease in ≥1 vascular territory. Data from the REACH Registry, therefore, highlight the characteristics of the high-risk population studied in the CHARISMA study. The remainder of this *Cardiology Scientific Update* discusses the role of enhanced antiplatelet therapy in this high-risk population in the CHARISMA study.

Antiplatelet therapy in the prevention of atherothrombotic events

Platelets play a pivotal role in the pathogenesis of atherothrombosis. Inhibition of platelet function with long-term aspirin treatment has been shown to prevent recurrent atherothrombotic events in patients with a history of MI and stroke by 25% and 22%, respectively. The Clopidogrel and Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial revealed that the ADP PY_{12} receptor blocker, clopidogrel, further reduced atherothrombotic events by 8% compared to that achieved by aspirin alone.[1] An enhanced benefit from clopidogrel

Figure 1: One-year event rates for patients in the REACH Registry according to the number of vascular sites with symptomatic disease



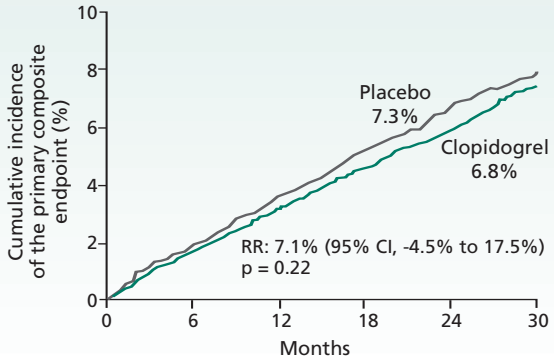
was observed in higher risk patients with diabetes[2] and in those with a history of coronary bypass surgery.[3] Combined treatment with aspirin and clopidogrel might be expected to have added benefit since inhibition of the cycloxygenase pathway with aspirin leaves platelet activation by ADP PY_{12} receptor stimulation unaffected.

In patients with acute coronary syndromes, dual antiplatelet treatment with clopidogrel and aspirin employed in the Clopidogrel in Unstable Angina to Prevent Recurrent Event (CURE) trial[4,5] reduced CV death/MI and stroke by 20% over a 1-year treatment period. Similar benefits with dual antiplatelet therapy were observed in patients following ST segment elevation myocardial infarction (STEMI)[6] and in those undergoing angioplasty and stenting.[7] However, in the MATCH trial,[8] the combination of clopidogrel and aspirin in patients with recent ischemic stroke or transient ischemic attack (TIA) was associated with a nonsignificant reduction in major vascular events and a 30% increase in life-threatening or major bleeding compared to patients receiving clopidogrel alone. No trial had, until recently, addressed the hypothesis that long-term dual antiplatelet treatment with aspirin and clopidogrel would reduce atherothrombotic outcomes in patients at high risk of, but who had not as yet experienced, a recent CV event.

The CHARISMA Trial[9]

The CHARISMA trial evaluated the efficacy and safety of the combination of clopidogrel + aspirin compared to placebo + aspirin in patients aged >45 years who were at high risk of atherothrombotic events. Patients included in the trial had either a history of CAD (ie, stable angina with documented multivessel CAD, prior multi-vessel coronary angioplasty or bypass surgery, or prior MI), cerebrovascular disease (documented TIA or stroke), peripheral arterial disease (intermittent claudication with either an ABI <0.85 or a history of vascular surgery or peripheral vessel angioplasty) or no symptoms, but at high risk in the presence of multiple risk factors for atherothrombosis.

Figure 2: The cumulative incidence of the primary endpoint (first occurrence of cardiovascular death, MI, or stroke) in CHARISMA



The high-risk entry criteria were 2 major, or 3 minor, or 1 major and 2 minor risk factors. The major risk factors included:

- diabetes (types 1 and 2)
- diabetic nephropathy
- ABI <0.9
- asymptomatic carotid stenosis, at least 1 carotid artery plaque

The minor risk factors were:

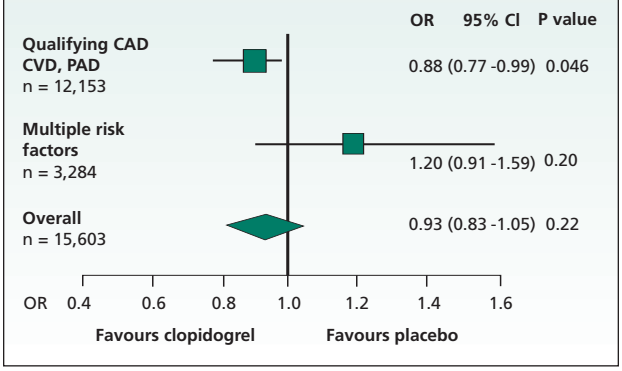
- systolic blood pressure >150 mm Hg
- primary hypercholesterolemia
- current smoking >15 cigarettes /day
- age ≥65 years for men, ≥70 years for women.

The CHARISMA trial randomized 15,603 patients from 32 countries to receive either clopidogrel 75 mg daily or placebo, in addition to aspirin 75-162 mg daily. Documented vascular disease was the enrollment criteria in 78% and multiple risk factors in 21%. Patient demographics were relatively similar to those observed in the REACH Registry discussed earlier. The patients were slightly younger (64.9 years), 70% were male, 76% were either obese or overweight, 35% had a history of prior MI, 25% prior stroke, and 23% peripheral arterial disease (PAD). A history of revascularization was common: 23% had percutaneous coronary intervention (PCI); 20% had coronary artery bypass graft (CABG) surgery; 5.3% carotid endartectomy; and 11.1% peripheral vascular surgery or angioplasty. There was high compliance with the use of vascular protective medications by high-risk patients during the trial (aspirin was used in 99%, beta-blockers 56%, ACEIs 61%, ARBs 26%, statins 77%, and anti-diabetic medications 42%).

Results of CHARISMA

The primary results of CHARISMA have recently been reported and published.[9] Following a median follow-up period of 28 months, the primary endpoint of CV death, nonfatal or fatal MI, or stroke, was reached in a similar proportion of the active- and placebo-treated patients (Figure 2). The principal

Figure 3: Primary efficacy results by pre-specified entry categories in CHARISMA



secondary endpoint of CV death, nonfatal or fatal MI or stroke, or hospitalization for TIA or unstable angina or revascularization was reduced in patients receiving clopidogrel [clopidogrel 16.7%, placebo 17.8%, risk reduction (RR) 7.7%, 95% confidence interval (CI), 0.5 to 14.4, p = 0.04]. Of the individual components of the primary and principal secondary endpoints, only stroke [odds ratio (OR) 0.8; 95% CI, 0.65-0.997, p = 0.05] and hospitalization (OR 0.90; 95% CI, 0.82-0.98, p = 0.02) were significantly reduced. There was a trend towards more major or severe hemorrhage according to the GUSTO criteria (clopidogrel 1.7%, placebo 1.3%, OR 1.25; 95% CI, 0.97-1.61, p = 0.09); and moderate bleeding was significantly increased by clopidogrel (clopidogrel 2.1%, placebo 1.3%, OR 1.62; 95% CI, 1.27-2.10).

When the prespecified entry subgroups were examined individually, different efficacy outcomes were observed in the patients with documented vascular disease as compared to those enrolled with only multiple risk factors (Figure 3). The patients with documented vascular disease and treated with clopidogrel, had a modest, but statistically significant, reduction in primary combined endpoint. Similar benefits (albeit not statistically significant) were observed in patients included with documented CAD, cerebrovascular disease, and peripheral vascular disease. In contrast, patients enrolled with only multiple risk factor criteria had no significant benefit from clopidogrel treatment. A trend towards increased bleeding in clopidogrel-treated patients was observed in both subgroups. In the patient group with multiple risk factors, there was an increased rate of CV death in clopidogrel-treated patients (clopidogrel 3.9%, placebo 2.2% p = 0.01).

Discussion

The analysis of these entry subgroups has to be interpreted with extreme caution, especially when the primary endpoint was not positive and the interaction between enrollment status and therapy was only marginally significant. Furthermore, some of the patients in the multiple risk factor group likely had established vascular disease, but did not meet entry criteria for inclusion in

the high-risk group with established disease (ie, MI >5 years ago or no multi-vessel CAD). Still, these data support the hypothesis that patients with established CVD could accrue benefits from long-term treatment with dual antiplatelet therapy comprising aspirin + clopidogrel. This observation will hopefully provide the stimulus for a further trial to determine whether secondary prevention with dual antiplatelet therapy is beneficial in high-risk patients with established CVD.

Why did dual antiplatelet therapy with clopidogrel + aspirin fail to show benefit beyond the use of aspirin alone in this trial? It is possible that the beneficial effect of dual antiplatelet therapy is maximal only in patients with recent acute vascular events. In the CHARISMA trial, the average time from qualifying MI to randomization was 23.3 months, whereas the average time to randomization from qualifying stroke and TIA was only 3.5 and 2.7 months, respectively. This might explain, in part, why only stroke was reduced with dual antiplatelet therapy. Furthermore, a similar explanation may be relevant for patients in the group with multiple risk factors who either had no history of vascular events or had vascular events that occurred many years previously.

The data supporting the use of antiplatelet therapy for the primary prevention of cardiovascular events is less robust than for patients with established disease. The recently reported Women's Health Study[10] failed to show an overall benefit from aspirin in a large cohort of women with no history of CVD. A recent study[11] suggests that there is a reduced benefit from aspirin for the primary prevention of CVD in diabetic patients, as compared to subjects with other risk factors. It is possible that the antiplatelet effects of aspirin in diabetic patients are overwhelmed by aspirin-insensitive mechanisms of platelet activation and thrombus formation, thus making the balance between the benefit and harm of aspirin treatment unfavourable. Similar arguments can be applied to the antiplatelet effects of clopidogrel for primary prevention in the patient with diabetes.

It would appear that there is a gradient of benefit from dual antiplatelet therapy with aspirin + clopidogrel along the CV disease continuum. The benefit ranges from maximal benefit in acute vascular disease, to lesser benefit in sub-acute and chronic disease, and minimal benefit – if any – for primary prevention.

What is the impact of CHARISMA on clinical practice?

The CURE trial in patients with acute coronary syndromes showed that dual antiplatelet therapy with aspirin + clopidogrel resulted in a highly significant absolute 2% reduction in death, MI, and stroke. In contrast, the CHARISMA trial in patients with chronic stable vascular disease revealed that clopidogrel + aspirin results in a more modest 1% and nonsignificant reduction in the same primary endpoint. Results of the CHARISMA trial should not cause any changes to the current use of dual antiplatelet therapy with clopidogrel + aspirin in the management of patients with acute coronary syndromes or following coronary angioplasty and stent insertion. It is important that the negative media coverage on the use on clopidogrel since the release of the CHARISMA trial results be balanced with a public and professional educational campaign such as the statements issued by the American Heart Association, the ACC, and the European Society of Cardiology urging physicians to ensure that appropriate patients, who are known to benefit from clopidogrel, are not deprived of this life-saving treatment.

Dr. Fitchett discloses that he has served on the Plavix Advisory Board for sanofi-aventis and provided CME for Bristol-Myers Squibb.

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