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"CHARISMA" Sparks Risk & Debate

PUBLIC HEALTH WARNING FROM American College of Cardiology (ACC)

Risk of stopping Clopidigrel (Plavix): On March 16th. The American College of Cardiology (ACC) sent out a public health alert. Recent reports regarding the results of the *CHARISMA* Trial may be misinterpreted by patients with coronary stents and other conditions, causing these patients to inappropriately stop taking the anti-clotting drug clopidogrel. **According to the 2006 ACC/AHA/SCAI Guideline Update for Percutaneous Coronary Intervention (PCI), Class I recommendations indicate the use of aspirin (81mg) and clopidigrel (75mg) in patients undergoing angioplasty with stent implantation (contraindications include aspirin resistance, allergy or risk of bleeding).**[1] Patients taking Plavix for any reason should consult with their cardiologist or other health care provider before stopping this medication.

Presentation of the results of the **C**lopidogrel for **H**igh **A**therothrombotic **R**isk and **I**schemic **S**tabilization **M**anagement and **A**voidance (**CHARISMA**) trial was presented at the Annual Scientific Sessions of the American College of Cardiology on Sunday, March 12 in Atlanta and simultaneously published in the New England Journal of Medicine.[2] Although the *CHARISMA* trial showed no benefit to combining Plavix® and aspirin and for certain patients, this study does not invalidate use of the drug for approved indications, such as stenting. Certain other patients are given Plavix after hospitalization for heart attack or stroke. Patients with these conditions must discuss the benefits and risks of anti-clotting medication with their health care provider and should not stop Plavix on their own. Discontinuation of Plavix in patients with recently-placed stents can cause clot formation within the stent, resulting in serious harm or death.

CHARISMA

This *Heartbeat* will discuss the future usage of clopidigrel based on the results of the exciting and controversial *CHARISMA* trial. The goal of this trial was to evaluate antiplatelet therapy with aspirin (ASA) alone (75 to 162 mg/ day) vs ASA plus clopidigrel (75 mg/ day) among high-risk patients with stable cardiovascular disease (CVD). Based on previous trials and Guidelines, combination antiplatelet therapy is indicated in patients with acute coronary syndrome (ACS) and patients pre- and post- PCI out to 9 months, resulting in improved outcomes[3] [4] [5] [6] [7] (POEM—Patient Oriented Evidence that Matters). For the past few years, the Sanofi-Aventis and Bristol-Myers Squibb pharmaceutical companies have been pushing physicians to use this combination over just ASA alone *making the assumption* that dual antiplatelet therapy with ASA plus clopidigrel will be superior to ASA monotherapy for high-risk primary prevention and secondary prevention among patients with stable CVD—

mostly based on the acute CVD data and some *soft* CAPRIE[8] data. As stated in our last *Heartbeat*, assumptions can easily be wrong and dangerous.[9] *CHARISMA* represented the next logical step of evaluation of the potential role of this approach in a broad population of patients with established CVD or multiple risk factors to verify this hypothesis.

Principal Findings

Patients in the trial were high-risk, with 78% symptomatic, including 37.4 % with coronary artery disease (CAD), 27.7% with cerebral vascular disease, and 18.2% with peripheral arterial disease (PAD). Diabetes was present in 42% of patients and 33.4% were obese. For the purposes of the trial, those described as symptomatic were enrolled because of a history of documented vascular disease. Patients were excluded from the study if they had an established indication for clopidigrel such as recent ACS or recent PCI. A total of 15,603 patients were randomly assigned equally to the two treatment groups with adequate background therapy (e.g. beta blockers, ACE inhibitors, statins etc.) and followed for 28 months.

Efficacy Endpoints: There was no difference in rates of the primary endpoint of CV death, myocardial infarction (MI), or stroke between the clopidigrel + ASA group (6.8%) and the placebo + ASA group (7.3% relative risk)—P = 0.22. The rate of the secondary endpoint of first occurrence of MI, stroke, death from CV or hospital admission for unstable angina, transient ischemic attack or a revascularization procedure was 16.7% in the clopidigrel group vs 17.9% in the placebo group—P = 0.04. There was no difference in the individual endpoints of CV death (3.1% for clopidogrel vs 2.9% for placebo, p = 0.68) or non-fatal MI (1.9% vs 2.0%, p = 0.48), but stroke was lower in the clopidogrel group (1.9% vs 2.4%, p = 0.05). Among the pre-specified subgroups, some benefit of clopidogrel was evident in the symptomatic cohort (documented CVD at enrollment) for the primary endpoint (6.9% for clopidogrel vs 7.9% for placebo, p = 0.046), but not in the asymptomatic cohort (6.6% for clopidogrel vs 5.5% for placebo—p = 0.20; interaction p=0.045). In the asymptomatic cohort (those high-risk patients without documented CVD), both all-cause mortality (5.4% vs 3.8%, p = 0.04) and CV mortality (3.9% vs 2.2%, p = 0.01) was significantly higher in the clopidogrel group.

Safety Endpoints: Severe bleeding trended higher in the clopidogrel group (1.7% vs 1.3%, p = 0.09), while moderate bleeding was significantly higher in the clopidogrel group (2.1% vs 1.3%, p = < 0.001). There was no difference in intracranial hemorrhage (0.3% each).

Conclusions/Clinical Implications

- The combination of clopidigrel plus ASA was not significantly more beneficial than ASA alone in reducing MI, stroke or death from CV causes among patients with stable CVD.
- The risk of moderate to severe bleeding was increased.
- The findings in this study do not support addition of clopidigrel to low dose ASA (81mg to 162mg) in patients with chronic stable CVD (CAD, PAD and carotid or cerebral vascular disease) for secondary prevention. Although there was a modest benefit (1% absolute risk reduction compared to 2% in CURE) in this subgroup, moderate bleeding was also increased (requiring transfusion). Further study is needed.
- In patients without documented CVD, but who are at high-risk for CVD, the increased risk (excess bleeding and increased mortality, etiology not known) with the addition of clopidigrel to ASA for primary prevention exceeded the benefit (none), so therefore it is contra-indicated. "The bottom line, in primary prevention, is that there is no reason to use clopidigrel based on lack of efficacy

and excessive bleeding seen", stated Dr Deepak Bhatt (Cleveland Clinic, OH), lead author of the study.

- Basically, our usage and indications for clopidigrel shouldn't change, based on this study. This study reaffirms the favorable benefit-to-risk and benefit-to-cost ratio of ASA for the primary and secondary prevention of MI and stroke. Dr Paul Armstrong, another moderator at the convention, said he believed the *CHARISMA* results were "charismatic, because I don't have to use clopidigrel now, and that's cheaper."
- Most importantly, it must be remembered that these statements and data are applicable to the type of patients studied. Clopidigrel added to ASA is beneficial in the acute settings of ACS, acute MI and before and after PCI. This treatment should extend out to a minimum of 6 months and probably out to one year. After a year these patients would fall into the "symptomatic" type of patients as characterized in *CHARISMA* and the continuation of clopidigrel should be individualized based on their ischemic risk, their bleeding risk and affordability—again really no different then before the study.
- In summary, dual antiplatelet studies and *CHARISMA* show us that as we shift from the higher risk ACS patients to more stable secondary prevention, benefit is attenuated. Risk (bleeding) and cost no longer seem to justify the minimal—if any benefits, of dual antiplatelet treatment in most stable patients. Cheaper ASA may be enough.

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