

## ANTIPLATELET THERAPY IN THE MANAGEMENT OF CARDIOVASCULAR DISEASE

Cardiovascular disease is the leading cause of death in developed countries. Every year over one million people in the United States and greater than 19 million people world-wide experience either an acute coronary artery syndrome or sudden cardiac death. Plaque rupture accounts for the etiology of most acute myocardial infarctions or sudden coronary deaths. Preventing the development of a “vulnerable plaque” has been the source of intense research in recent years. While modifying traditional risk factors has been the cornerstone in the approach to vascular disease, antiplatelet therapy has played a pivotal role in the therapy of these clinical disorders. Risk factors for plaque rupture include local factors intrinsic to the plaque itself, i.e., the thickness and inflammation of the fibrous cap of the plaque; systemic factors such as smoking, dyslipidemia, diabetes mellitus, and fibrinogen levels are important as well. The sequence of events, therefore, in acute coronary syndromes include plaque rupture followed by thrombosis and microembolization which may further cause inflammation, spasm, and endothelial dysfunction and microvascular obstruction distal to the unstable plaque area. Platelet activation followed by adhesion and aggregation are the common inciting events leading to thrombus formation that is responsible for the clinical events of myocardial infarction, stroke (non-embolic), and peripheral arterial disease events. Therefore, while focal intervention of a vulnerable plaque such as intracoronary stent implantation, is used to treat the culprit unstable plaque, systemic intervention such as platelet inhibitor therapy (aspirin and thienopyridine therapy, statins, ACE inhibitors, and beta blockers) are also needed in the chronic treatment of vascular disease. With the growing use of stent technology in the coronary circulation – particularly with the advent of drug eluting stents (DES) - platelet inhibitor therapy has become increasingly important in clinical medicine and will be the focus of this discussion.

The use of aspirin has long been used as therapy in vascular disease. The Physician’s Health Study<sup>1</sup> studied over 22,000 healthy middle-aged physicians (no history of vascular disease) and aspirin led to a 44% reduction in the risk of a first myocardial infarction. This risk reduction, however, was only apparent in those over 50 years of age. The dose of aspirin was 325 mg every other day. The Women’s Health Study<sup>2</sup> showed a reduction in the incidence of stroke in women on aspirin therapy, but not of myocardial infarction, though elderly women seemed to have a favorable benefit in myocardial infarction, death, and cerebral vascular events. Although the trend in neurology has been to treat patients with cerebrovascular events with higher doses of aspirin (325 mg bid), recent evidence from these and other studies<sup>3</sup> suggests there is no benefit to aspirin prophylaxis beyond 81 to 162 mg daily. In addition, although inconclusively studied, neurovascular disease may be best treated with Aggrenox (sustained release dipyridamole and immediate release aspirin) as “dual platelet therapy” as opposed to aspirin and thienopyridine therapy (clopidogrel, Ticlopidine). That aspirin probably would benefit higher risk patients (men over the age of 50 and more elderly women) was also underscored by the CHARISMA study<sup>4</sup> that compared the addition of Clopidogrel to aspirin (75 to 162 mg qd) in patients with established vascular disease (secondary prevention), to those who simply are at higher risk such as individuals with established risk factors (primary prevention).

This study showed no benefit with combined clopidogrel and aspirin in those who only have risk factors for vascular disease. Although there was a somewhat higher risk of bleeding in both groups, this risk is outweighed by the clinical benefit in individuals with established vascular disease. This study has sometimes been interpreted as suggesting that patients should not be on long-term dual platelet therapy, but there was a benefit of dual aspirin/clopidogrel therapy in those with established vascular disease.

From the standpoint of patients who undergo stent implantation, the CREDO study<sup>5</sup> also showed that patients who have a percutaneous coronary intervention (and in this study patients received bare metal stents), there was a 27% reduction in myocardial infarction, stroke, and death at one year in the cohort that continued both clopidogrel and aspirin over 12 months. As is well known, the risk of stent thrombosis with bare metal stents (BMS) may extend to 3 to 4 months after implantation, but has been reported at up to 18 months with drug eluting stents (DES) because of delayed endothelialization of the DES struts. Thus, although dual platelet therapy is currently recommended for one month with a BMS, three months for Cypher stents and six months for Taxus stents, late stent thrombosis with drug eluting stents is a concern that suggests continuing dual antiplatelet therapy for at least one year may be most prudent. This important point has been underscored by at least two recent publications. Iakovou, et al<sup>6</sup>, published a perspective observational study conducted in one academic hospital and two community hospitals in Germany and Italy. 2,229 consecutive patients who underwent successful implantation of either a sirolimus-eluting stent or a paclitaxel-eluting stent were followed for up to nine months following stent implantation. Twenty nine patients (1.3%) had stent thrombosis; 14 of these patients had subacute thrombosis (from implantation through 30 days), and 15 patients had late thrombosis. Premature discontinuation of antiplatelet therapy was the most important predictor of stent thrombosis after implantation. The PREMIER registry<sup>7</sup>, a study of myocardial infarction (MI) patients in 19 United States centers, examined the prevalence and predictors of thienopyridine discontinuation 30 days after drug eluting stent implantation. Almost 1 in 7 myocardial infarction patients who received a drug eluting stent were no longer taking thienopyridines by 30 days. Those who prematurely stopped this medication within 30 days of their myocardial infarction had a significantly higher likelihood of dying within 12 months post MI. All-cause mortality was 7.5% for patients who discontinued thienopyridine therapy within 30 days compared with 0.7% for those who continued taking this medication. Finally, the BASKET-LATE study<sup>8</sup> was a single center study from Basel, Switzerland that looked at the rates of 18 month cardiac death or myocardial infarction between patients who received drug eluting stents and bare metal stents. In this study, patients who had not had any adverse cardiac event six months following stent implantation were advised to stop the clopidogrel, but to continue with 100 mg of aspirin daily long-term. Although not statistically significant in the sample size of the study, documented late stent thrombosis and related death or target vessel myocardial infarction were twice as frequent after drug eluting stent versus bare metal stent implantation (2.6% versus 1.3%). This growing database certainly suggests that great care must be given before stopping dual platelet therapy in patients who receive drug eluting stents.

What conclusions can be drawn from this information at this time?

1. Aspirin monotherapy for primary (preventative) therapy of ischemic events is reasonable in older or higher risk patients, both men and woman, and at a dose of 81 to 162 mg qd.
2. Individuals with established cardiovascular disease, and perhaps more advanced vascular disease (peripheral arterial disease, cerebrovascular disease, longstanding coronary artery disease), seem to have a statistically significant advantage with clopidogrel monotherapy versus aspirin monotherapy as noted in the CAPRI study, though this modest advantage comes at a higher financial cost.
3. High risk individuals may also benefit from dual antiplatelet therapy (aspirin and clopidogrel).
4. Patients who only have risk factors – but not established vascular disease - do not appear to benefit from dual antiplatelet therapy, and such therapy is given at the risk of higher bleeding complications.
5. Although data is conflicting, treatment with aspirin and sustained-release dipyridamole (Aggrenox) may be the drug of choice for secondary prophylaxis in patients with cerebrovascular disease.
6. There is significant benefit from the uninterrupted continuation of dual antiplatelet therapy for one year (as opposed to one month) in patients with bare metal stents, and this recommendation should likely be extended for both types of drug eluting stents as well (sirolimus and paclitaxel) because of the possibility of very late stent thrombosis. Consideration, in fact, for continuing dual anti-platelet therapy for 18 to 24 months with DES perhaps should be given to higher risk patients such as individuals with bifurcation lesions, long stent lengths or stents in small vessels, or reduced ejection fractions, though further information is needed.

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