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EBM COMMENTARY

IS THE COMBINATION OF ASPIRIN AND CLOPIDOGREL ALWAYS BETTER THAN ASPIRIN ALONE?
Or will it be too much of a good thing?

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Confucious was probably the person who once said, "All things good not cheap, all things cheap not good."

Aspirin is one medicine that tests this aphorism because it is both cheap and good. Enough evidence exists to show that low dose aspirin helps to reduce cardiovascular risk in those with coronary heart disease, ischaemic strokes and others with established atherosclerotic vascular disease.

In 1998 the results of the Second International Study of Infarct Survival (ISIS-2)[1] were reported. Here aspirin was shown to be beneficial in the management of patients after an acute myocardial infarction. This benefit was in addition to the benefit of thrombolysis.

Aspirin is also useful for primary prevention in selected patients through its ability to reduce the risk of heart attacks and strokes in people without any overt cardiovascular disease. The Physicians Health Study[2] showed that healthy males, particularly those fifty years of age and older, taking 325mg of aspirin every other day could reduce their risk of myocardial infarctions significantly. However there is a tendency for increased gastrointestinal bleeding and haemorrhagic strokes because of aspirin and hence such prescriptions need to be individualised. The Women's Health Study[3] showed that healthy women who were forty-five years of age and older and who took 100mg of aspirin every other day had a significantly lower risk of strokes.

The Clopidogrel versus Aspirin in Patients at Rrisk of Ischaemic Events (CAPRIE) study[4] in 1996 compared clopidogrel, a drug different from aspirin in its mechanism of inhibiting platelets, with aspirin in patients at increased risk for ischaemic events. The study showed that clopidogrel was marginally better than aspirin in reducing cardiovascular risk in patients who already had established atherosclerotic vascular disease.

After CAPRIE, a number of studies were published on the clinical benefits of combined platelet inhibition with aspirin and clopidogrel. The Clopidogrel in Unstable Angina to Prevent. Recurrent Events (CURE) trial[5], the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY –TIMI 28) trial[6] and the COMMIT / 2nd Chinese Cardiac Study[7], all studied patients with different types of acute coronary syndromes and found that the combination of clopidogrel and aspirin was indeed better than aspirin alone in reducing the rates of cardiovascular death, recurrent myocardial infarctions and strokes. The CLARITY trial also demonstrated, with angiograms, the improved patency rate of coronary arteries following thrombolysis when clopidogrel and aspirin were used together.

Clopidogrel with aspirin has also been shown to be superior to aspirin alone for reducing the rates of re-occlusion after percutaneous coronary interventions. The PCI-CURE study[8] and the CREDO study[9] both demonstrated this benefit.

With so much benefit reported for the combined therapy with clopidogrel and aspirin, the results of a trial called CHARISMA[10] came as a complete surprise. CHARISMA explored the role of this combination in patients with stable cardiovascular disease and in those who had only cardiovascular risk factors. The results of this trial showed that the combination of aspirin and clopidogrel was not beneficial in patients who had stable cardiovascular disease. In fact this combination was likely to be more dangerous than aspirin alone in such patients. *In other words, the combination of aspirin and clopidogrel should not be used for primary prevention.* This was also the message from a cochrane review[11] on aspirin versus dual platelet therapy for preventing cardiovascular disease.

Analysis of the data from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, published in the European Heart Journal[12], showed that when those not suffering from acute coronary syndromes took the combination of aspirin and clopidogrel, they had a significant increase in cardiovascular deaths. There was also an increase in moderate and severe bleeding with dual antiplatelet therapy but this increase was not significant and could not be the explanation for the increase in cardiovascular mortality.

We know that platelets are responsible for the thrombi that develop on fissured or ruptured atherosclerotic plaques. Preventing platelets from aggregating and forming thrombi help prevent cardiac and other vascular problems in those with atherosclerosis.

The results of the CHARISMA trial tell us that the degree of platelet inhibition should depend on the clinical situation. Strong platelet inhibition with aspirin and clopidogrel is not beneficial in all clinical situations. It is not a case of one size fits all.

The authors of the CHARISMA trial suggest that in acute coronary syndromes, the platelets are likely to be in a hyperactive state because of the cytokines produced from eroded atherosclerotic vascular plaques. In asymptomatic individuals with stable atherosclerosis, the platelets are not likely to be in that kind of activated state. The ratio of benefit versus risk when inhibiting platelets at any time probably depends on the tendency of the platelets to aggregate and clump together at that point in time. When the likelihood of platelet aggregation is high, as in acute coronary syndromes, a stronger inhibition of platelets is beneficial. Such strong inhibition is bad when the clinical condition is different.

Homeostasis within the body is a delicate balance between too much and too little. Platelets stand on the line between bleeding and clotting. Inhibiting platelet function is good in a wide variety of clinical situations. What we must know however, are those boundaries which, when crossed, make good interventions dangerous.

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