Editorial

Oral Anti-Platelet Therapy: The Good and the Bad

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In 1998, 16.6 and 10.1% of patients died of heart and cerebrovascular diseases respectively. The main disease process is underlying atherosclerosis. In the coronary arteries, rupture or fissure of a vulnerable plaque is followed by thrombosis, with acute narrowing of the coronary artery that results in acute coronary syndrome (ACS).[1] The key to thrombotic occlusion is the platelets, which can be activated by multiple mechanisms including thromboxane A_2, ADP, thrombin, collagen, and others. Once activated, platelet thrombus will be formed by fibrinogen binding to IIb/IIIa receptors.

If platelet activation is the critical step from atherosclerosis to thrombosis, then anti-platelet agents will have beneficial effects in patients with established atherosclerosis. The evidence is compelling and extends to patients with high risk of atherosclerosis such as those with diabetes or on haemodialysis. On the other hand, evidence for primary prevention remains more controversial, and has to be balanced against the "bad" side effects of treatment. This editorial addresses the controversy in the use of oral anti-platelet therapy. The role of IIb IIIa inhibitors which are only effective with intravenous administration in ACS has been reviewed.[2]

The Antithrombotic Trialists' Collaboration recently published a meta-analysis of randomized trials of anti-platelet therapy in patients with high risk of occlusive vascular disease.[3] They reviewed 287 trials before September 1997, involving a total of 212,000 patients. With the endpoints of "serious vascular events" that include non-fatal myocardial infarction, non-fatal stroke and vascular death, this meta-analysis shows that anti-platelet therapy reduces a serious vascular event in 3.6 patients per 1000 treated for 2 years. This risk reduction is about 1/3 for non-fatal myocardial infarction, 1/4 for non-fatal stroke and 1/6 for vascular death (Table). The benefits exceed the bleeding risks in all categories of high risk patients.

This analysis also sheds light on the following practical aspects of anti-platelet prescriptions. Aspirin is most widely used, and a dose of 75-325 mg is at least as effective as higher daily doses. Indeed, a recent study on the use of high (700 mg/day) versus low dose (≤325 mg/day) of aspirin in patients undergoing carotid endartherectomy suggested that the higher dose was associated with more vascular events than the lower dose.[4] While doses <75 mg/day may be less ulcerogenic by preserving endothelial prostacycline, this low dose has only been examined in a few studies.

Are newer thienopyridines better than aspirin? In patients who presented with ACS treated with aspirin alone, recurrent myocardial infaction or death still occurred in about 10% at 1 year.[5] Thus the use of thienopyridines either alone or in combination with aspirin for maximum anti platelet effects is attractive. In the randomized trial of clopidogrel versus aspirin in patients with ACS (CAPRIE trial)[6], clopidogrel reduced major vascular events by 8.7% [95% CI 0.3-16.5%] over aspirin. The benefit was marginal and occurred mainly in patients with an initial diagnosis of peripheral vascular disease. However, the combined treatment of aspirin and

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Table. Summary of major vascular risk reduction with anti-platelet therapy in various high risk vascular diseases from the Antithrombotic Trialists' Collaboration study[3]

Disease status	Trials (n)	Patients / controls	Risk reduction
Old Myocardial Infarction	12	9984 / 10022	- 25%
Acute Myocardial Infarction	15	9658 / 9644	- 30%
Unstable Angina	12	2497 / 2534	- 46%
Coronary Artery Bypass Grafting	25	3105 / 3126	- 4%
Percutaneous Coronary Intervention	9	1592 / 1620	- 53%
Heart Failure	2	66 / 68	- 41%
Old Stroke / Transient Ischaemic Attack	21	11493 / 11527	- 22%
Acute Stroke	7	20418 / 20403	- 11%
Carotid Disease	6	339 / 337	- 19%
Grafting for Peripheral Vascular Disease	12	1249 / 1248	- 22%
Peripheral Angioplasty	4	472 / 474	- 29%
Haemodialysis	14	1333 / 1371	- 41%
Diabetes	9	2568 / 2558	- 7%
Atrial Fibrillation	4	1390 /1380	- 34%

clopidogrel is now standard for patients undergoing coronary stenting. In patients with ACS, the combination is shown to be superior to aspirin alone in reducing major vascular events by about 20%.[7] Interestingly, the benefits occurred early within hours of initiating treatment, were maintained for up to 12 months, and were present for patients who subsequently underwent coronary angioplasty.[8] There was a small risk of extracranial bleeding, most related to vascular access site for angioplasty. An excellent cost-benefit analysis of clopidogrel versus aspirin use has recently been published in the Journal.[9]

An important complication of aspirin is gastrointestinal bleeding (GIB). While aspirin may cause three times lower bleeding complications than other non-steroidal anti-inflammatory agents,[10] acute endoscopic study suggested that >60% of patients had gastric abnormalities.[11] Chronic long term bleeding is less common, and clinically evident GI bleeding occurred in 3% of elderly patients receiving 100 mg/day of aspirin for 12 months.[12] High risk factors for aspirin related bleeding include advanced age, previous ulcer, concomitant use of non-steroidal anti-inflammatory drugs or wafarin. Infection with Helicobacter pylori may increase the risk for GIB.[13] Several pieces of information become available to guide our management and prevention of aspirin related GIB (Figure). Obviously, modifiable factors should be corrected or avoided. Proton pump inhibitor in addition to aspirin is effective to prevent a re-bleed.[14] Another option is to eradicate H. pylori, and to continue aspirin afterwards.[15] This is as effective as proton pump inhibitor to prevent re-bleeding over a 6-month period. Theoretically, clopidogrel may be used as it is unlikely to be ulcerogenic, but as yet there is no trial in this setting.

Do we prescribe ulcer prophylactic treatment or screen all cases for H. pylori (with a view to eradication) before we initiate aspirin treatment? Due to the general safety of aspirin and low incidence of GIB, the latter option is probably not a cost effective measure. While enteric coated aspirin may reduce dyspepsia, it does not prevent GIB. For low-risk subjects, low dose aspirin can be started without prophylaxis. In high risk subjects, co-therapy with a proton pump inhibitor may be a useful strategy. Clopidogrel is associated with a lower incidence of primary GIB than aspirin in this setting [0.71 vs 0.49%].[6]

Finally, do we prescribe aspirin for primary prevention? There are only 4 clinical trials on selected patients: The US Physician Study, UK Doctors Study and Thrombosis Prevention Trial all concerned male subjects, and the Hypertensive Optimal Treatment trial

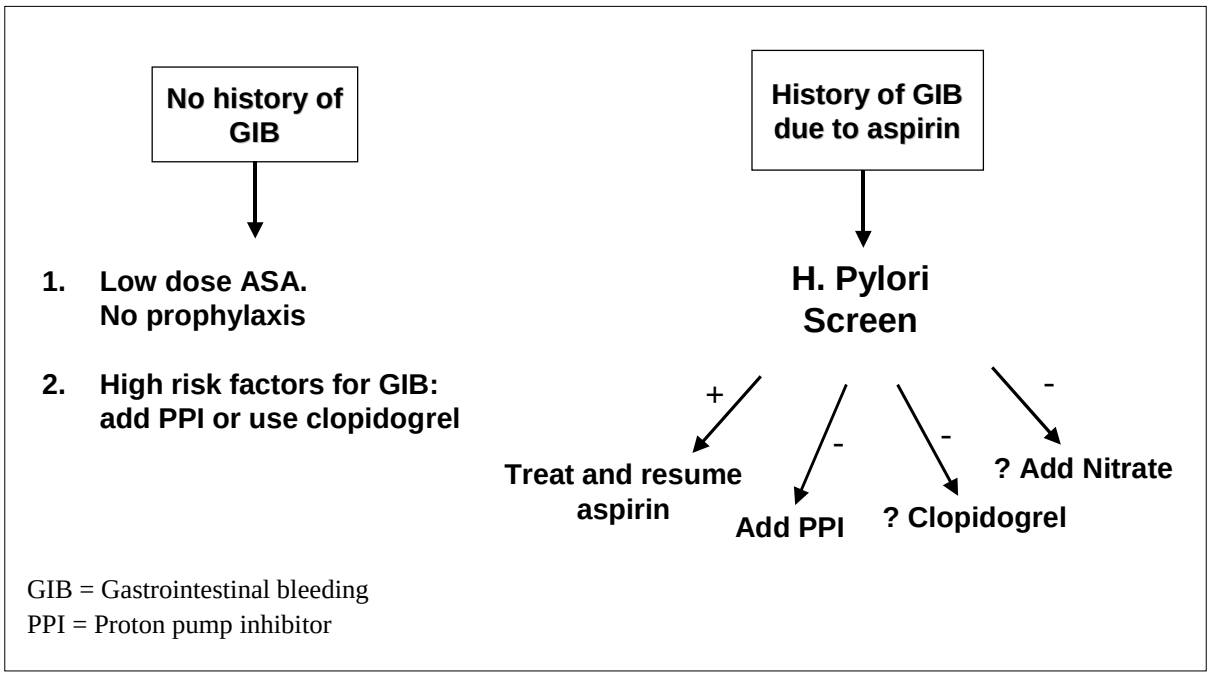

Figure. *Prevention of aspirin related gastrointestinal bleeding.*

only concerned hypertensive subjects.[16] A recent benefit: risk ratio analysis[16] suggests that because of the risk of cerebral and extracerebral bleeding, aspirin prophylaxis is only justified when the coronary risk exceeds 0.8%/year. At a risk of 1%/year, it would be necessary to treat 67 patients over 5 years to prevent a myocardial infarction, and 182 to prevent a myocardial infarction without important bleeding. It is here where the "good" has to be carefully balanced against the "bad" before a physician should recommend primary aspirin prophylaxis.

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