Dual antiplatelet therapy in cardiovascular disease: does aspirin increase clinical risk in the presence of potent $P2Y_{12}$ receptor antagonists?

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ABSTRACT

Aspirin is now widely accepted as the first-line antithrombotic platelet therapy for at-risk individuals. During the last decade or so it has also become established that co-administering antagonists of the ADP receptor $P2Y_{12}$ with aspirin further reduces the risk of acute thrombotic events. By the nature of its evolution, this therapeutic approach assumes that $P2Y_{12}$ receptor antagonists will be added to aspirin, and this therefore dominates the design of clinical trials. This strategy has resulted in the generation of a large body of clinical evidence showing the benefit of aspirin plus $P2Y_{12}$ receptor antagonists, largely from studies with clopidogrel and more recently from those with prasugrel and ticagrelor, but with obvious limitations in terms of residual ischaemic event rates and bleeding complications. It is our hypothesis, however, that when administered in the presence of potent $P2Y_{12}$ receptor antagonists, aspirin could actually increase total cardiovascular risk, although this has never been tested in large outcome studies. Clearly, this potentially negative interaction could be of relevance to millions of patients.

Aspirin is established in clinical practice as the default antiplatelet therapy in cardiovascular disease. This is based on robust widely-accepted data that, for at-risk patients, low-dose aspirin reduces thrombotic events by around 30%.[1] Aspirin acts by irreversibly blocking the cyclo-oxygenase enzyme within platelets, inhibiting the production of thromboxane A_2 (TXA_2).[1] TXA_2, when unchecked, drives further aggregation through stimulation of receptors for TXA_2 (TP receptors) on neighbouring platelets. However, aspirin alone has not been found sufficient to reduce ischaemic events in several clinical settings such as acute coronary syndromes and in patients receiving coronary stents. As a result, the concept of dual antiplatelet therapy has become established. In particular, the administration of clopidogrel, an antagonist of the ADP receptor $P2Y_{12}$, together with aspirin has been shown to further reduce the risk of acute thrombotic events (figure 1A),[2] even though in the landmark CURE study there was no reduction in deaths from cardiovascular causes despite a reduction of non-fatal myocardial infarctions.[3] Because of the manner in which this therapeutic approach has evolved (ie, initial treatment with aspirin alone followed by dual antiplatelet therapy), outcome studies of newer and stronger $P2Y_{12}$ receptor antagonists—notably prasugrel and ticagrelor—have all been conducted in the presence of aspirin.[4 5] The reasons behind this are at least twofold. First, aspirin is seen as a default therapy[1] so it appears unethical for aspirin not to be included. Second, in some clinical settings such as in patients receiving coronary stents, data from studies comparing clopidogrel alone with clopidogrel plus aspirin suggest that it would be less beneficial for a patient to be on antiplatelet monotherapy without aspirin.[6] However, conducting studies into the newer and stronger $P2Y_{12}$ receptor antagonists only in the presence of aspirin means that we have no answer to the very important question: 'What is the net clinical effect of aspirin in patients receiving newer and more potent $P2Y_{12}$ receptor antagonists?' We hypothesise that, when administered with potent $P2Y_{12}$ receptor antagonists, aspirin could actually increase clinical risk (figure 1B).

At first sight this hypothesis is undoubtedly challenging and perhaps even counterintuitive, but it is based upon clear, albeit indirect, evidence that forms a logical argument. This argument begins with the clear demonstration by a number of groups that blockade of $P2Y_{12}$ receptors on platelets strongly reduces their ability to produce TXA_2 and their ability to aggregate following stimulation of their TP receptors[7–10]; in other words, blockade of platelet $P2Y_{12}$ receptors mimics much of the antiplatelet effects of aspirin. From these findings we can conclude that, in an individual receiving a potent $P2Y_{12}$ receptor antagonist, TXA_2-dependent pathways of platelet activation are markedly blunted, leading us to the question of what would be the net effect of additional dosing with aspirin? Clearly it is logical to suggest that aspirin will provide only little further antithrombotic benefit (as the TXA_2 pathway is already functionally blunted). However, aspirin has many effects in the body in addition to those on the platelet, and we need now to consider these. As has been well characterised in many studies, aspirin will increase the risk of bleeding, particularly gastrointestinal bleeds.[11] Such bleeds are not only immediately dangerous in their own right but are also strongly associated with a reduction in patient compliance as well as increased medium-term mortality.[12 13] Aspirin will also inhibit cyclo-oxygenase in the vascular endothelium, which will reduce the release of the antithrombotic and therefore beneficial prostanoid, prostaglandin I_2.[14] Finally, aspirin will inhibit cyclo-oxygenase within the kidney, leading in susceptible individuals to an increase in blood pressure.[14]

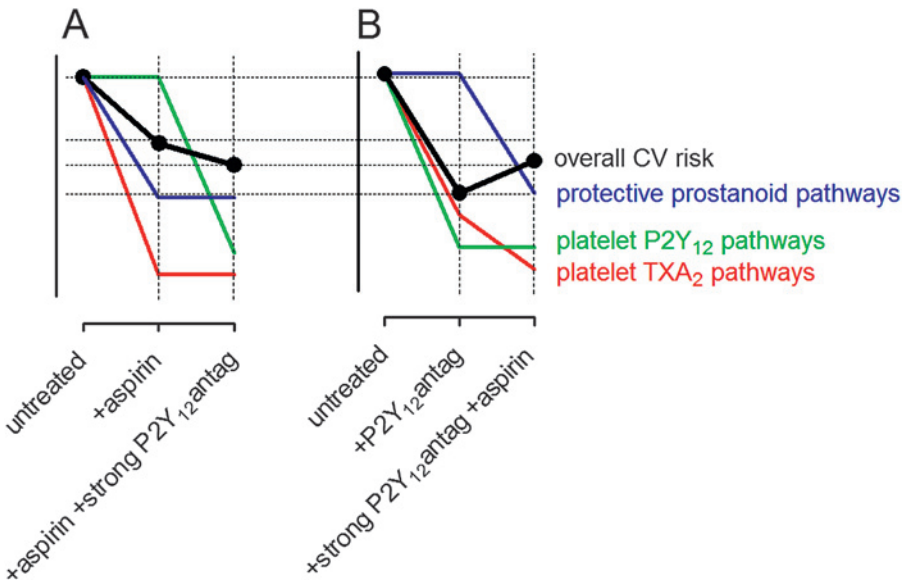

Figure 1 (A)Clinical trials have proved the idea that treatment with aspirin is beneficial in individuals at cardiovascular (CV) risk and that addition of $P2Y_{12}$ antagonists provide a further benefit. (B) Clinical trials have not tested what effects aspirin has in the presence of potent $P2Y_{12}$ antagonists. As potent $P2Y_{12}$ antagonists blunt aspirin therapeutic targets on the platelet, the net effect of adding aspirin could be an increase in total CV risk as a result of aspirin inhibiting protective prostanoid pathways at other sites, notably the stomach, vascular endothelium and kidney. TXA_2, thromboxane A_2.

To summarise our hypothesis, when aspirin is used alone as an antithrombotic agent in high-risk patients, its potentially deleterious cardiovascular effects are more than balanced by its inhibitory effects on the platelet providing a net beneficial effect (figure 1A). By contrast, if the antiplatelet effects of aspirin are negated by virtue of strong $P2Y_{12}$ receptor blockade, the potentially deleterious effects could be proportionately greater (figure 1B).

The proof of this hypothesis will require further data. Unfortunately, data from studies employing clopidogrel plus different doses of aspirin or placebo—such as MATCH[15] which showed no benefit of adding aspirin to clopidogrel in high-risk patients with recent ischaemic stroke or transient ischaemic attack and OASIS-7[16]—do not help us to explore this question because the response to clopidogrel is variable, unlike that to the newer more potent $P2Y_{12}$ receptor antagonists. So, in these trials the substantial minority of patients receiving clopidogrel who have only incomplete $P2Y_{12}$ receptor may experience a net beneficial effect of aspirin, masking a net harmful effect of aspirin in those patients responsive to clopidogrel. Overall, therefore, the variability in response to clopidogrel clouds assessment of any potential interaction with aspirin. For this reason, evaluation of the clinical relevance and value of the hypothesis presented here will demand data regarding the additional effects of aspirin in individuals receiving potent $P2Y_{12}$ receptor antagonists such as prasugrel and ticagrelor. Tantalisingly, results from the PLATO study suggest that there are more thrombotic effects when ticagrelor is administered in conjunction with aspirin in the dose range 300–325 mg than in the range 75–125 mg.[17]

In conclusion, while millions of patients will be prescribed dual antiplatelet therapy consisting of potent $P2Y_{12}$ receptor antagonists plus aspirin for the foreseeable future, this will be done with an important lack of evidence regarding the clinical benefit of aspirin in this partnership. Just as we have recently understood that aspirin may not provide therapeutic benefit in primary prevention,[18] so we should consider the notion that we can achieve potent control of more than one pro-aggregatory pathway in platelets with a single agent and reconsider both the status of aspirin as a gold standard antiplatelet agent and the necessity for dual antiplatelet therapy in important patient subgroups.

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Heart

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Notes