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Gathering intelligence on antiplatelet drugs: the view from 30 000 feet

When combined with other information overviews lead to conviction

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The efficacy of aspirin in the secondary prevention of myocardial infarction and stroke is widely accepted. The evidence which supports this perception includes its identification as an inhibitor of cyclo-oxygenase and platelet aggregation; identification of the major product of platelet cyclo-oxygenase as thromboxane A_2, a vasoconstrictor and platelet agonist; the discovery that aspirin irreversibly acetylates cyclo-oxygenase, permitting cumulative inhibition by low doses of thromboxane A_2 formation in the presystemic circulation; the discovery that thromboxane A_2 biosynthesis is increased during ischaemic episodes of unstable angina; and the demonstration in individual, controlled, prospective double blind trials that aspirin reduces both myocardial infarction and death in unstable angina by 50%, whether given at 75 mg, 324 mg, or 1300 mg/day.[1 2]

Following these discoveries Collins, Peto, Baigent, and their colleagues in Oxford organised the Antithrombotic Trialists' Collaboration to share data and permit overview analyses of controlled trials of antiplatelet drugs. At the time of the initial reports, these trials mainly involved aspirin and confirmed its efficacy in syndromes of acute vascular occlusion such as unstable angina, while suggesting a net benefit in the secondary prevention of stroke.[3–5] Today, Baigent and colleagues report further analyses (p 71),[6] though a critic of the approach questions whether it has all been worthwhile (p 103).[7]

What is the value of overview analyses? Firstly, they serve to summarise the field for the busy practitioner, who has not read in detail the individual trials. A complementary effort is the annual weighting of clinical trials performed by the American College of Chest Physicians.[8] The development of a combined Antithrombotic Trialists' Collaboration endpoint—non-fatal myocardial infarction, non-fatal stroke, and vascular death—and the visual display of data in a manner that reflects the size of drug effect and the size of the dataset helps spread the word.

Remarkably, aspirin continues to be underused in conditions where its efficacy has been well established. A message from the present review is that patients with peripheral vascular disease and those at risk of embolic events may also benefit from aspirin. However, whether such data alone preclude placebo controlled evaluation of antiplatelet drugs in such populations is arguable. Secondly, overviews may be helpful when the balance of drug efficacy and risk is critical and the datasets in individual trials are too small to address the issue definitively. For example, while antiplatelet drugs prevent thrombotic strokes, they exacerbate cerebral bleeds. However, as thrombotic strokes are the more common events, this translates into a net benefit. As might be expected, the absolute reduction in serious vascular events, while significant, is smaller in patients with acute stroke than in other high risk categories. Thirdly, overviews may address hypotheses raised elsewhere. A good example is the similar efficacy for doses of aspirin above and below 325 mg/day in the current report.

Despite the outcome of trials in unstable angina and the mechanistic support for the use of low doses of aspirin, a cultural lag which favoured the use of high doses in preventing stroke persists in some quarters. Perhaps the overview will lay that issue to rest. Furthermore, the literature is replete with effects of aspirin at concentrations that, if ever attained in vivo, would require industrial dosing. Again, the overview affords strong support for using lower doses of aspirin for cardioprotection. Finally, the existence of an academic group such as the Antithrombotic Trialists' Collaboration offers the potential for drug companies to use an honest broker to seek heterogeneity of drug effects within a given class or to address thorny, but expensive issues, such as the perceived cardiovascular hazard of cyclooxygenase-2 inhibitors.[9] The interests of regulatory bodies, healthcare providers, and consumers would seem to be served by such an exercise.

And yet, might this intelligence be misleading? Firstly, the manner of data selection for inclusion, revision, and exclusion is retrospective and unblinded. These analyses cannot substitute fully for the critical review of individual trials. This is exemplified by the studies of the aspirin and dipyridamole combination in the current report. The authors caution that the added benefit from the combination is heavily influenced by a single study, ESPS-2. However, this is precisely what one would expect: dipyridamole, as originally formulated, had limited bioavailability and failed to inhibit platelet function. It was, unsurprisingly, ineffective in clinical trials.[10] The reformulated compound used at higher doses in ESPS-2 is predictably bioavailable and inhibits platelet function ex vivo.[10] One might question the decision to combine trials of the two preparations. A second limitation is their relevance to current clinical challenges. Perhaps overviews were more useful when the individual clinical trials were smaller than is the case today. It is easy to forget that a decade of

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confusion, based on inadequately sized clinical trials, preceded demonstration of the cardioprotective effects of aspirin. However, today, a choice of antiplatelet drug combinations confronts the practitioner. Individual trials suggest similar effectiveness of aspirin, clopidogrel, and dipyridamole.[10]

Indirect comparisons from the overview may be helpful in choosing aspirin first. But selection between potential combinations and their interactions with other drug classes, such as statins, will be driven by the outcome of rapidly performed specific prospective trials, not overviews. Similarly, the present overview confirms the benefit of adding parenteral glycoprotein IIb/IIIa inhibitors to aspirin. However, this is old news. It has been superseded by the predictable demise of the oral inhibitors. Overviews are also reductionist, blunt instruments. They are unlikely to elucidate "aspirin resistance," a phenomenon that may embrace non-compliance, drug interactions, and genetic variations in the cyclooxygenase protein among its causes. Finally, neither overview analyses nor the original clinical trials can substitute for informed advice tendered to individual patients by their own practitioners. The decision to use aspirin in a patient with a recent history of ulcer and congestive heart failure after his or her myocardial infarction is more complex than was the case in patients admitted to clinical trials of cardioprotection.

In summary, the antiplatelet trialists' exercise has well served the public health in drawing attention to the utility of long term therapy with antiplatelet drugs, especially aspirin. It has distilled often copious, complex, and apparently conflicting data for the end user, the medical practitioner. The exercise, like all approaches to intelligence gathering, is imprecise and potentially misleading. However, when combined with information from other sources, it is likely to lead to conviction.

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Treating extremely low birthweight infants with prophylactic indomethacin

Evidence for short term benefits only

A primary aim of perinatal and neonatal interventions for extremely low birthweight infants (birth weight less than 1000 g) is to increase the likelihood of survival without neurological disability.[1] Although interventions, such as prophylactic antenatal steroids[2] or exogenous surfactants,[3] have improved certain outcomes, the overall prognosis for extremely low birthweight infants remains poor. In North America a multicentre cohort study of extremely low birthweight infants found that less than two thirds of those admitted to intensive care survived to hospital discharge. A quarter of surviving children, assessed at 18-22 months post term, had an abnormal neurological examination, and about a third had evidence of significant neurological developmental delay.[4] In the United Kingdom and Eire, the EPICure Study Group evaluated the outcome for infants born before 26 weeks' gestation. The overall survival of infants admitted for intensive care was 39%.[5] When assessed at a mean age of 30 months post term, about half the children had disability, and about half of these met the predefined criteria for severe disability.[6]

A significant predictor of neurodevelopmental morbidity in extremely low birthweight infants is severe intraventricular haemorrhage or periventricular leucomalacia.[4] Since interventions that reduce the occurrence of these conditions might improve longer term neurological outcomes these conditions have been used as a short term outcome measure in perinatal and neonatal intervention studies. One such intervention is prophylactic indomethacin. In addition to closing the patent ductus arteriosus and improving cardiovascular stability, indomethacin may have a more direct neuroprotective effect.[7] A Cochrane review of the use of prophylactic indomethacin in very low birthweight babies (birth weight less than 1500 g) found evidence that indomethacin reduced the incidence of symptomatic patent ductus arteriosus and of severe intraventricular haemorrhage.[8] Indomethacin, however, has potential side effects, including an increased risk of cerebral hypoxia[9] that may oppose any putative neurological benefit. Therefore, the Cochrane review concluded that more data on longer term neurological outcomes were needed to clarify whether the use of prophylactic administration of indomethacin for very low birthweight babies or extremely low birthweight babies should be adopted.[8]

Such data are now available. A large multicentre randomised trial of indomethacin prophylaxis

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