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Aspirin Should Be First-Line Antiplatelet Therapy in the Secondary Prevention of Stroke

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Long-term management after an ischemic stroke (or transient ischemic attack [TIA]) boils down to reducing not just the high risk of a stroke but also the risk of other serious events due to similar underlying vascular pathology, such as myocardial infarction (MI) and sudden cardiac death.[1] Therefore, minimizing causal vascular risk factors (blood pressure, cholesterol, smoking, and diabetes) and lifestyle modification (diet, exercise) are crucial, along with carotid endarterectomy for a few carefully selected patients. But what about doing something about the blood, such as antithrombotic therapy?

Aspirin Works!

A vast amount of randomized data supports the use of antiplatelet drugs to prevent serious vascular events (stroke, MI, and vascular death) in a wide range of patients at high vascular risk (eg, stroke survivors, MI survivors, claudicants). This has been summarized recently by the Antithrombotic Trialists' collaboration.[2] The bottom line is that antiplatelet drugs reduce the odds of such an event by 22%. The effect is more or less identical in patients who have only had a stroke or TIA or if aspirin alone, which makes up two thirds of the data, is considered. Aspirin alone after stroke/TIA reduces the odds of a serious vascular event by 17%.[3] Antiplatelet drugs reduce the risk of not only the composite outcome of stroke, MI, and vascular death but also of each of the 3 components separately, more so for nonfatal than fatal events. Undoubtedly, aspirin works in the secondary prevention of stroke. Furthermore, the cost is minimal, and the risks are low (remember that fatal extracranial and all intracerebral hemorrhages are counted in the composite event outcome).

The Aspirin Dose Is 75 to 150 mg Daily: No More, No Less

There has been long debate about the dose. All agree that to minimize gastrointestinal adverse effects, the dose should be kept as low as possible. But how low can one go and still maintain maximal effectiveness? From the Antithrombotic Trialists' Collaboration, the answer is somewhere between 75 and 150 mg daily. Above that there is certainly no extra benefit, and below that there are not enough randomized patients to be sure if efficacy is compromised. So 75 mg daily is what I use first.

Is Anything Better Than Aspirin?

Yes, anticoagulation is better for patients in atrial fibrillation, if one can deliver the treatment safely.[4] But what about other antiplatelet drugs for patients in sinus rhythm? They are much more expensive, but are they worth it in terms of efficacy or safety? The difficulty is getting enough data to be sure of equivalence between the various options. Even showing superiority requires many thousands of randomized patients.

Clopidogrel and the Thienopyridines

Even the CAPRIE trial, the largest comparative trial by far, could not show a clear advantage of clopidogrel over aspirin.[5] But, by adding in the ticlopidine data in a meta-analysis, it appears that the thienopyridines might have a marginal advantage over aspirin, from a relative risk reduction of serious vascular events by 16% at best to a mere 2% at worst.[6] This corresponds to avoiding 11 (95% CI, 2 to 19) vascular events per 1000 patients treated for about 2 years. Given the width of the CI and how nearly it touches zero difference and the fact that clopidogrel costs about 200 times as much as aspirin, I use clopidogrel only when a patient cannot tolerate aspirin (fortunately, clopidogrel has a quite different adverse effect profile). Clearly clopidogrel works, but the data do not convincingly show that it works better than aspirin.

There is now more interest in whether the addition of clopidogrel to aspirin is better than aspirin alone because their antiplatelet actions are different and may be additive. The combination certainly seems better in the first few months after unstable angina.[7] Trials in stroke patients are clearly needed. The MATCH trial comparison of the addition of aspirin to clopidogrel with clopidogrel alone makes the wrong assumption that the present standard treatment is clopidogrel (www.strokecenter.org). Furthermore, comparing aspirin with no aspirin in the presence of clopidogrel is not very interesting because we already know that aspirin works in the absence of clopidogrel.

Dipyridamole

Dipyridamole alone may have a modest effect on the composite outcome of stroke, MI, and vascular death.[2] Far more interesting is whether the addition of dipyridamole to aspirin is more effective than aspirin alone. From the Antithrombotic Trialists' Collaboration it was not, at least not for all serious vascular events. But there did seem to be more impact on stroke prevention, quite unlike any other drug tested. So why is this the case? There are several possibilities:

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Dr Warlow was on the CAPRIE steering committee and has advised both Sanofi and Boehringer Ingelheim at various times, for which his department received a fee. Dr Warlow has not taken part in any antiplatelet or other drug trial organized by industry.

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(1) The effect is dominated by the results of just 1 trial, the Second European Stroke Prevention Study (ESPS-2), and sometimes a single trial can by chance get the wrong answer.[8] (2) The effect relies on the modified-release formulation of a high dose of dipyridamole (200 mg) combined with a low dose of aspirin (25 mg), given twice a day (Aggrenox in the United Sates, Asasantin in Europe). (3) Dipyridamole was added in the ESPS-2 to a less than maximally effective dose of aspirin, thus providing an advantage for the combination. (4) Dipyridamole lowers blood pressure (since it is a vasodilator) and therefore prevents stroke more effectively than coronary events. Data on blood pressure were collected in ESPS-2 but are not published. (5) Dipyridamole really does reduce vascular events, but any effect on preventing coronary events is offset by cardiac toxicity.

To resolve these uncertainties, we need confirmation from another trial; the ESPRIT trial is in progress for just that reason.[9]

The evidence from randomized trials does not persuade me to combine aspirin with dipyridamole as first-line therapy. Perhaps, if patients declare themselves to be at particularly high risk of stroke (as opposed to a coronary event) by actually having another stroke or TIA while on aspirin, I might add modified-release dipyridamole 200 mg BID to 75 mg aspirin daily (on the basis of incomplete evidence). In North America, where modified-release dipyridamole is not available (for reasons that seem far from scientific), the choice is to add Aggrenox to aspirin or to risk lowering the aspirin dose by substituting Aggrenox.

Other Drugs

There are even fewer data from randomized trials comparing other antiplatelet regimens with aspirin.

Conclusion: Aspirin Still Comes First

Aspirin, 75 mg daily, is still the first antithrombotic drug to use. If the patient cannot tolerate it, I change to clopidogrel 75 mg daily. I might add modified-release dipyridamole (200 mg BID) to aspirin if the patient has an additional ischemic stroke or TIA. However, I would much rather enter my patients, whether or not already on aspirin, into a large trial of aspirin (my standard treatment) versus clopidogrel plus aspirin (expensive but perhaps better than just aspirin) versus dipyridamole plus aspirin (not too expensive and perhaps good for stroke prevention, therefore more cost-effective than the clopidogrel combination). Such a trial would be expensive but not as expensive as drifting into prescribing combination therapy. It is better to put the horse in front of the cart and to seek evidence before changing practice.

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Aspirin Therapy Should Be First-Line Treatment in Secondary Prevention of Stroke—Against

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Patients with transient ischemic attack (TIA) are at high risk for an ischemic stroke,[1] and patients who have already suffered a stroke are at high risk for stroke recurrence. Aspirin leads only to a modest reduction both in the risk of stroke (23%) and in reducing the combined end point of stroke, myocardial infection (MI), or vascular death (18%).[2]

Ticlopidine is more effective than aspirin. A large multicenter trial compared a daily dose of 500 mg ticlopidine and 1300 mg/d aspirin in 3069 patients with TIA or minor stroke.[3] This study was associated with a statistically significant 21% reduction ($P=0.024$) in fatal or nonfatal stroke risk at 3 years in patients who received ticlopidine versus aspirin. The relative risk reduction of the combined outcome of stroke, MI, or vascular death was reduced by 9% in favor of ticlopidine, which was not statistically significant. Ticlopidine, however, can lead to

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neutropenia in up to 0.8% of patients[3,4] and therefore is no longer the drug of choice.

Clopidogrel is an antiplatelet agent that is chemically related to ticlopidine. A pivotal randomized, blinded, international trial, Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE), examined the relative safety and efficacy of daily doses of 75 mg clopidogrel versus 325 mg aspirin in nearly 20 000 patients with stroke, MI, or peripheral arterial disease.[5] The results of the trial showed that clopidogrel was more effective than aspirin in preventing a combined end point of ischemic stroke, MI, or vascular death. The trialists found a significant 8.7% reduction in relative risk ($P=0.043$) for clopidogrel versus aspirin. Although the CAPRIE trial was not powered to detect treatment differences within patient subgroups, a subgroup analysis, which was not part of the original design, was performed. Overall, when the results for these subgroups were examined, there was no significant difference between clopidogrel and aspirin in patients with stroke or MI. There was, however, a significant benefit favoring clopidogrel in patients with peripheral arterial disease.

The combination of aspirin plus slow-release dipyridamole was investigated in the Second European Stroke Prevention Study (ESPS-2).[6] ESPS-2 analyzed 6602 stroke or TIA patients who were randomly assigned to 4 treatment arms: placebo; aspirin alone (25 mg twice daily); extended-release dipyridamole alone (200 mg twice daily); or aspirin (25 mg twice daily) plus extended-release dipyridamole (200 mg twice daily). The trial showed additive effects of aspirin and dipyridamole. The aspirin-plus-dipyridamole regimen of ESPS-2 produced a statistically significant 37% reduction ($P=0.00l$) in risk of fatal or nonfatal stroke over 2 years compared with placebo, similar to the risk reduction of the earlier ESPS-1 trial (38%).[7] Neither aspirin nor dipyridamole or the combination reduced mortality.[8]

Taken together, these study results show that the combination of aspirin plus dipyridamole is superior to aspirin alone in the prevention of stroke after TIA or stroke. The bleeding risk is not higher than with aspirin alone.[6] Therefore, aspirin plus dipyridamole is the first-line treatment for secondary prevention of stroke. Clopidogrel is superior to aspirin for a combined end point of stroke, MI, and vascular death and is first-line treatment for high-risk patients with multiple vascular risk factors (eg, peripheral arterial disease). Whether the combination of clopidogrel plus aspirin is superior to aspirin alone is under investigation (MATCH trial).

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Aspirin Therapy Should Be First Line

Probably, But Watch This Space

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Our protagonists deal with a thorny problem: what should be first-line therapy in the secondary prevention of stroke? They both agree on the evidence: aspirin works, clopidogrel works slightly better than aspirin when a multiple vascular outcome cluster is considered, and dipyridamole seems to have an additive effect to that of aspirin alone for stroke prevention. Warlow points out that the additive benefits of dipyridamole plus aspirin are based

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on a single trial (ESPS2) and that the mechanism of this effect is unclear.

Our practice is to use aspirin alone as first-line therapy but to substitute either clopidogrel (broad-spectrum vascular protection) or add dipyridamole (additive benefits for stroke protection) if a second clinical event has occurred. In aspirin-intolerant patients, we would use clopidogrel. These strategies seem to be generally accepted. However, Diener and other clinicians advocate aspirin plus dipyridamole as first-line therapy for secondary stroke prevention. There is no consensus on this issue, and practice may vary from country to country depending on licensing arrangements. Given the modest benefits of clopidogrel over aspirin in CAPRIE and the encouraging results of the CURE trial in patients with myocardial ischemia, we agree with both contributors that the combination of aspirin plus clopidogrel is potentially more attractive than clopidogrel alone.

Clearly, more evidence is required. We await with interest the results of the MATCH trial, comparing aspirin plus clopidogrel with clopidogrel alone. Warlow suggests the "dream trial" that would compare aspirin alone, aspirin plus clopidogrel, and aspirin plus dipyridamole in a 3-arm design. Interestingly, a 2-arm comparison of these combination therapies is being planned. We also await the results of ESPRIT, which will provide further information about the efficacy of aspirin versus aspirin plus dipyridamole.

While further data will clarify matters, we should not forget that protection against vascular events is still only modest, at approximately 20%. With 80% to go, better strategies are clearly needed. Fortunately, there are a number of newer-generation antiplatelet and antithrombotic agents in the pipeline, some of which are already in phase III trial.

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