
Stroke Prevention — Insights from Incoherence
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If clinical trials were sporting contests, then it would be fair to say that low-dose aspirin plus extended-release dipyridamole (Aggrenox) was the clear favorite against clopidogrel going into the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial (ClinicalTrials.gov number, NCT00153062). The trial, reported on in this issue of the Journal by Sacco et al., tested these two antiplatelet agents for secondary stroke prevention in their first head-to-head contest.

In two previous large randomized clinical trials enrolling patients after stroke (the European Stroke Prevention Study 2 [ESPS2] and the European/Australasian Stroke Prevention in Reversible Ischemia Trial [ESPRIT, NCT00161070]), low-dose aspirin plus extended-release dipyridamole resulted in a substantial and consistent benefit, as compared with aspirin, for preventing recurrent strokes as well as other serious vascular events. Clopidogrel, meanwhile, barely bested aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial — a trial enrolling patients with one of three categories of vascular disease (myocardial infarction, ischemic stroke, and peripheral arterial disease); the margin in the CAPRIE trial was accounted for almost entirely by the subgroup of patients enrolled for peripheral arterial disease, a pathophysiologically homogeneous disorder as compared with ischemic stroke. Indeed, among the more than 6000 patients in the CAPRIE trial for whom ischemic stroke was the qualifying event (i.e., the relevant population for the PRoFESS trial), outcomes were statistically similar between the aspirin and clopidogrel groups, both for recurrent strokes and for the primary outcome of any serious vascular event. On the basis of these results, although aspirin remains the most commonly prescribed antiplatelet agent in patients with stroke and cautious guideline committees have not strongly favored one of these newer agents over the other,5-7 low-dose aspirin plus extended-release dipyridamole became the preferred agent for au courant doctors (ourselves included) determined to select the best of all possible evidence-based antiplatelet regimens for secondary stroke prevention.

The results of these earlier trials involving over 12,000 patients with stroke and measuring the efficacies of low-dose aspirin plus extended-release dipyridamole and clopidogrel against a common control treatment (aspirin) made it possible to indirectly compare the efficacies of these two newer agents even before the results of the PRoFESS trial were known. As shown in Figure 1A, before the PRoFESS trial, the evidence suggested that use of low-dose aspirin plus extended-release dipyridamole might be expected to yield an approximately 14% relative risk reduction in recurrent stroke as compared with clopidogrel. Although this indirect evidence is hardly conclusive, a recently published network meta-analysis of antiplatelet regimens for secondary stroke prevention that included comparisons of five treatment strategies based on data from 24 trials enrolling 42,688 patients yielded similar (and significant) results for the indirect comparison of low-dose aspirin plus extended-release dipyridamole and clopidogrel with regard to the composite outcome of any vascular event (a more common outcome than recurrent stroke, providing more statistical power).8

If indirect comparisons were entirely trustworthy, the PRoFESS trial would have been unnecessary and even unethical, since arguably, equipoise between these agents had already been disturbed. However, the results of the PRoFESS trial show us once again that the compelling logic of the transitive property, so reliable in mathematics, has little authority in the often illogical world of clinical trials.9 Indeed, the trial not only failed to show...
the superiority of low-dose aspirin plus extended-release dipyridamole over clopidogrel, it also failed even to reach the noninferiority margin, despite enrolling over 20,000 patients — meaning, by the investigators’ own unforgiving rules, that we cannot be fully confident that low-dose aspirin plus extended-release dipyridamole is not inferior to clopidogrel.

Interpreting the results of the PRoFESS trial is not easy. First, the failure to demonstrate noninferiority despite essentially identical rates of the primary outcome between the treatment groups is attributable to the extremely stringent noninferiority margin, itself attributable to the fact that the trial was designed under the (apparently mistaken) assumption that low-dose aspirin plus extended-release dipyridamole was in truth superior to clopidogrel. More at issue, how do we interpret the null results of the PRoFESS trial in light of the previous evidence showing clear superiority for low-dose aspirin plus extended-release dipyridamole as compared with aspirin, but not for clopidogrel as compared with aspirin, for secondary prevention of stroke? Logic suggests three nonmutually exclusive solutions: the results of the PRoFESS trial are a statistical fluke, clopidogrel is somewhat better than previous evidence suggests, or low-dose aspirin plus extended-release dipyridamole is somewhat worse than previous evidence suggests. If the third solution is correct, one might wonder whether the winner in this latest battle of the “superaspirins” was aspirin itself.

These possibilities can be formally explored in a network meta-analysis that incorporates the information from the PRoFESS trial together with that from the previous three large trials comparing these agents. Figure 1B shows the result of such a network, which reconciles the different treatment effects internally by estimating a weighted summary for each treatment effect on the basis of both the direct comparison between the two agents of interest and the indirect comparison through the third, reference agent.10

The totality of the direct and indirect evidence across these four large trials would rank low-dose aspirin plus extended-release dipyridamole minimally (and not significantly) ahead of clopidogrel, which itself would rank slightly (and not significantly) ahead of aspirin. An interesting observation is that after including the data from the PRoFESS trial, the superior efficacy of low-dose aspirin plus extended-release dipyridamole as

Figure 1. Relative Risks of Recurrent Stroke from Comparisons among Three Antiplatelet Agents.

Data are shown for low-dose aspirin plus extended-release dipyridamole (ERDP), clopidogrel, and aspirin not including (Panel A) and including (Panel B) the PRoFESS trial. The arrows indicate the direction of the comparison and are weighted by the number of patients; the dashed arrow represents a comparison based on indirect evidence only. The P values and confidence intervals (CIs) are based on a random-effects model, which takes into account inconsistency in the network. The table (Panel C) shows the data we used in the analyses from the four major trials comparing these agents for the outcome of recurrent stroke. Before the PRoFESS trial (Panel A), low-dose aspirin plus ERDP was shown to be clearly superior to aspirin for secondary stroke prevention, whereas clopidogrel was not. Including the results of the PRoFESS study in this network (Panel B) slightly increases the estimated benefit of clopidogrel and slightly diminishes the estimated benefit of low-dose aspirin plus ERDP as compared with aspirin, while increasing the level of uncertainty in the network. CAPRIE denotes Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, ESPRIT the European/Australasian Stroke Prevention in Reversible Ischemia Trial, ESPS2 the European Stroke Prevention Study 2, and PRoFESS Prevention Regimen for Effectively Avoiding Second Strokes.
compared with aspirin does seem somewhat less compelling. This is because the inconsistency between the various trial results in the network is reflected in larger confidence intervals, demonstrating paradoxically that the addition of more data may increase, rather than decrease, statistical uncertainty and reduce clarity about treatment decisions.

Although the inconsistency among trial results should make us examine the trials for differences in design or populations that might support explanatory hand-waving, it is also reasonable to conclude from these comparisons that efficacy should not be the sole, or perhaps even the major, determinant of treatment decisions for antiplatelet therapy after stroke. Low-dose aspirin plus extended-release dipyridamole is difficult for some patients to tolerate, given the common side effect of headache, and it needs to be taken twice a day (vs. once a day for the two other regimens). Also, there were more serious hemorrhagic complications associated with low-dose aspirin plus extended-release dipyridamole than with clopidogrel in the PROFESS trial, though the previous trials suggested both these agents were, to a similar degree, at least as safe as aspirin.4,5 Finally, in resource-limited settings (i.e., just about everywhere), cost is important; aspirin costs pennies per day, whereas low-dose aspirin plus extended-release dipyridamole and clopidogrel cost greater than 100 times that.

Complex though it seems, this discussion of the PROFESS trial has not even considered the results of the other experimental comparison included in this factorial trial, the testing of telmisartan, an angiotensin-receptor–blocking antihypertensive agent, described by Yusuf et al.13 in this issue of the Journal. Despite some evidence from previous trials that inhibition of the renin–angiotensin system may help prevent strokes even independently of the blood-pressure–lowering effect, this aspect of the trial, much like the antiplatelet comparison, was persuasively null.

In the era of comparative effectiveness, when multiple agents are pitted against one another, randomized trials often cannot be understood in isolation. Rather, they need to be interpreted in the context of a sometimes complex network of other similar or relevant evidence.12 The reduction of such complex networks to treatment recommendations is not always straightforward, since different paths within the network may give inconsistent results, and the network may be incoherent.10,13 The at times impossible geometry of such networks might be likened to a zen koan—a statement inaccessible to rational understanding, the contemplation of which may lead to a deeper realization. In the case of PROFESS and the tangle of related trials, enlightenment might be expressed simply, as a haiku: “For stroke prevention, / use an antiplatelet drug. / Treat hypertension.”

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