Indirect comparisons of CAPRIE, ESPS-2, and MATCH trials led many stroke experts to favor the combination of aspirin and extended-release dipyridamole (ASA/ERD) over clopidogrel as the preferred antiplatelet therapy for secondary stroke prevention.\textsuperscript{1–3} The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study, a 2×2 factorial, double-blind, event-driven, active and placebo-controlled study of ASA/ERD versus clopidogrel, and the angiotensin receptor blocker, telmisartan, versus placebo in 20,332 patients with a recent ischemic stroke was performed to evaluate the 2 antiplatelet agents directly. No clear winner can be declared, but ASA/ERD, the presumptive favorite, has been bruised and clopidogrel’s role in stroke prevention has been partly restored. A rematch between these rivals appears unlikely.

PRoFESS demonstrated that the risks of recurrent stroke or the composite of stroke, myocardial infarction, or vascular death are similar with ASA/ERD and clopidogrel.\textsuperscript{4} However, increased risks of nonfatal hemorrhagic stroke and side effects leading to discontinuation of therapy were seen with ASA/ERD. Treatment with either ASA/ERD or clopidogrel did not seem to afford neuroprotection. Disability due to stroke and cognitive decline was not different between the 2 antiplatelets.\textsuperscript{5} There was no interaction between the treatment benefit of the antiplatelets and telmisartan in any outcome measure.

A few editorials have already attempted to explain “What went wrong with PRoFESS?” and how to interpret its results.\textsuperscript{6,7} They elegantly discussed the stringent choice of the noninferiority margin for the study and design modifications after the first 2027 subjects were randomized based on the results of the MATCH study.\textsuperscript{3} Future meta-analyses and post hoc subgroup analyses will certainly follow. PRoFESS is the largest secondary stroke prevention trial to date and was overall well designed. Although antiplatelets are definitely effective in reducing the risk of stroke recurrence, their benefit is modest as evident from earlier trials. It is therefore possible that PRoFESS was unable to detect small differences, if there were any, of an already modest benefit between ASA/ERD and clopidogrel, especially on the background of other stroke preventive therapies such as antihypertensives and statins. Similarly, the lack of neuroprotective effects, if there were any, may be related to the fact that the time from stroke onset to randomization was delayed (median, 15 days).

Like any other stroke trial, PRoFESS shares many of the shortcomings of its predecessors and leaves us with many unanswered questions. More than 50% of the qualifying strokes in PRoFESS were thought to be due to small vessel occlusions. The rate of stroke recurrence after a lacunar stroke is much lower than that in patients whose initial stroke is due to large artery atherosclerosis or embolism.\textsuperscript{8} This, together with the short follow-up period, (mean, 2.5 years), translated into a modest number of primary events, which hindered assessment of the true effectiveness of the therapeutic intervention(s) in PRoFESS. This is best illustrated by telmisartan, whose trends toward benefit only appeared during the latter part of the follow-up period. PRoFESS confirms what we have learned from prior studies; longer follow-up is required.

Is it possible that various antiplatelets may have differential effects in preventing vascular events based on the underlying stroke mechanism? For example, could ASA/ERD be more effective in patients with small vessel occlusions, whereas clopidogrel is more effective in large artery atherosclerosis? The benefit of clopidogrel in CAPRIE was largely accounted for by its effectiveness in patients with peripheral arterial disease.\textsuperscript{1} In PRoFESS, ASA/ERD was slightly more effective than clopidogrel in reducing the risk of recurrent strokes in patients who had lacunar strokes, whereas clopidogrel was more effective in patients whose strokes were attributed to large artery atherosclerosis. Although subgroup analyses may be appropriate for hypothesis generation and future study, one should not solely base treatment decisions on such observations. Future studies should be powered to answer the question of whether there is a differential effect of various antiplatelets among patients...
with different stroke etiologic mechanisms or be restricted to a homogeneous population of patients with stroke.

Twenty-nine percent of the patients taking ASA/ERD and 23% of those taking clopidogrel prematurely discontinued their antiplatelet regimen during PROFESS, indicating that approximately 28% of the patients were not on the intended treatment at the end of the study. What happened to these patients? Were they switched to another agent? Reporting on-treatment versus intent-to-treat analyses could help shed more light on the PROFESS results.

Some of PROFESS’ results are difficult to interpret. The rates of hemorrhagic events, whether minor or major, were 5.3% in the ASA/ERD group versus 4.9% with clopidogrel. These rates are higher than the ones reported in ESPS-2, ESPRIT, CAPRIE, and even MATCH.1–3,9 The increased rate of hemorrhagic complications in PROFESS with either antiplatelet agent may be attributed to higher participation of Asian patients in PROFESS. Asian patients are particularly prone to hemorrhagic strokes and may be more susceptible to the antiplatelet effects of ASA/ERD and clopidogrel predisposing them to higher risks of bleeding complications.10 Is it possible that higher rates of hemorrhagic strokes with ASA/ERD versus clopidogrel in PROFESS are ethnically dependent? Exploratory analyses of PROFESS data are warranted to address this intriguing possibility given its potential therapeutic implications.

It was not all bad news for ASA/ERD; PROFESS provided evidence for ASA/ERD against those who questioned its use in cardiac patients. Not only were the rates of myocardial infarction and vascular death similar in ASA/ERD- and clopidogrel-treated patients, but ASA/ERD was associated with a significant reduction in the risk of new or worsening congestive heart failure as compared with clopidogrel.

PROFESS indicates that we still have options. Any antiplatelet is appropriate and the decision of which agent to use in individual patients with stroke will depend on several factors, including cost, tolerance of adverse effects, compliance, and concomitant cardiovascular risk factors. In this regard, the once-per-day dosing, more favorable tolerability and compliance profile, near-term availability of generic preparations, and wider use among patients with cardiac comorbidities and those undergoing arterial angioplasty and stenting would have to make one ponder if clopidogrel is the undeclared winner of PROFESS.

For those who remain skeptical of the marginal superiority of clopidogrel over aspirin in CAPRIE,1 I pose the following question. If ASA/ERD is significantly better than aspirin alone (ESPS2), but has similar efficacy to clopidogrel (PROFESS), does this imply that clopidogrel is better than aspirin and should be the first-choice antiplatelet for stroke prevention? What have we really learned from PROFESS?

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References

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