Should the MATCH Results Be Extrapolated to All Stroke Patients and Affect Ongoing Trials Evaluating Clopidogrel Plus Aspirin?

Pierre Amarenco, MD; Geoffrey A. Donnan, MD

Aspirin alone reduces the risk of recurrent stroke, myocardial infarction (MI), and vascular death by only 13%. Clopidogrel was 8% better than aspirin in the CAPRIE trial and was safer with less gastrointestinal bleeding complications. For these reasons, clinicians anticipated that the combination of clopidogrel and aspirin would be more effective than either drug alone with the hypothesis that bleeding complications would be only modestly increased. Accordingly, many stroke patients were switched to this combination of therapy, mainly in case of recurrent stroke while on a single antiplatelet agent and in patients with high vascular risk. The results of trials showing the efficacy and tolerance of such an approach after percutaneous coronary intervention was reassuring. However, the long-term major bleeding complication rate was unknown except in patients with unstable angina and non-Q wave MI, and the net benefit in stroke patients was hypothetical.

The MATCH Trial

For this reason, the combination therapy had to be tested for safety and efficacy in a stroke population, and this was the purpose of the MATCH trial. MATCH was a secondary prevention trial in patients with ischemic stroke or brain infarction with transient ischemic attack within 3 months of randomization and with 1 of the following entry criteria: diabetes mellitus, past coronary heart disease, recurrent stroke on aspirin, peripheral arterial disease. Aspirin (A) was tested against placebo on the background of clopidogrel (C) in both arms. So it was C+A versus C.

As a consequence of the entry criteria stipulating the presence of multiple vascular risk factors, the MATCH population included 70% diabetic subjects, 54% with lacunar stroke (small vessel disease) plus 10% strokes of unknown cause (both at low risk for recurrence). Only 30% of patients had large artery atherosclerotic disease. Few patients (5%) had a past history of coronary heart disease because most cardiologists had difficulty with the idea that their patients were maintained on a single antiplatelet agent.

The primary endpoint (MI, ischemic stroke, vascular death, and rehospitalization for acute ischemic events) after 18 months was 16.73% in the C arm and 15.70% in the C+A arm, yielding a nonsignificant relative risk reduction of 6.4% (−4.6% to 16.3%) (P=0.244) in favor of C+A. The same pattern was seen in all subgroups, including the large artery atherosclerotic group. On treatment analysis showed a relative risk ratio of 9.5% (−2.0% to 19.6%) favoring C+A (P=0.10).

On the safety side, there was an increase in life-threatening bleeding (any fatal bleeding, symptomatic intracranial hemorrhage, decrease in hemoglobin of >5 g/dL, or significant hypotension with the need of inotropes, or requiring transfusion of more than 4 units of red blood cells or equivalent of whole blood) with 1.3% in the C arm and 2.6% in the C+A arm (absolute difference of 1.26% [0.64 to 1.88], P<0.001); there were 25 symptomatic intracranial bleeds in the C arm and 40 in the C+A arm.

Main Issues Arising From the MATCH Trial

The trial may have been positive if it had A as the comparator (as in the CURE trial); in choosing C, the investigators lost power for the efficacy hypothesis, and they also lost power for the tolerance because the CAPRIE trial clearly showed that there were less life-threatening bleeding complications in the C arm than in the A arm. Thus in MATCH, if A had been the comparator, the absolute difference for life-threatening bleeding complications between A and C+A would have been much lower and possibly not significant.

In MATCH, 70% of the patients had diabetes. In the most recent antithrombotic trialist collaboration meta-analysis, the risk reduction in diabetic patients with a single antiplatelet treatment was 7%, which was not significant (based on 9 trials: 403/2568 versus 426/2558; odds red. 7 [SE, 8], not significant). In other words, the MATCH population consisted predominantly of a patient subgroup (diabetic) in whom antiplatelet agents have never been demonstrated to be efficacious in reducing cardiovascular incidence. Interestingly, we know that in diabetic patients treating blood pressure aggressively yields a 40% reduction in their risk of stroke, and it may be that giving 1 or even 2 antiplatelet agents in addition to blood pressure-lowering drugs results in a ceiling effect.
Fifty-four percent of patients included in MATCH had a lacunar stroke as a qualifying event. It is well-known that this is the group of stroke patients at lowest risk for stroke and MI recurrence. This is emphasized by the relatively low frequency of the hard outcome events (stroke, MI, vascular death) excluding rehospitalizations of only 7% at 1 year.

One could argue that in the group of large atherosclerotic disease (34% of the MATCH population), the results were also neutral; however, the baseline characteristics were such that only 5% of this population had a past history of MI, which is unusual in this population in which we would expect nearer to 30% or 40%. This leads us to conclude that this large atherosclerotic disease group was also unusual. As mentioned, most of the screened patients with past coronary heart disease were in fact not randomized in the trial.

The assumption at the beginning of the study was that A reduces the risk of the primary endpoint by 25%, which was probably an overestimate, given that a meta-analysis found a risk reduction of only 13%.8 Hence, with the sample size calculation based on a risk reduction of 25% for aspirin, and deducting the risk reduction in the clopidogrel group based on the CAPRIE results, does suggest that the study was somewhat underpowered.

Another explanation for the observed outcomes may be the inclusion of many patients (20%) with recurrent ischemic stroke while on aspirin. The investigators probably selected a proportion of patients who were resistant to aspirin and thus reduced the likelihood of benefit. Finally, because the confidence interval was −4% to 16%, MATCH did not exclude a powerful efficacy of C+A over C.

In conclusion, like any clinical trial, the MATCH results only apply to a typical MATCH population. MATCH tells us that there is apparently no net benefit to give C+A in a population of stroke patients with lacunar stroke or diabetic microangiopathy (who are also more prone to bleeding complications). MATCH did not represent the population for whom many of us have been prescribing C+A empirically. More likely, it was typically a patient with carotid or vertebrobasilar stenosis, either extracranial or intracranial, who had a recurrent ischemic event while on a single antiplatelet agent or a patient with severe aortic arch atherosclerosis. These patients were a minority within the MATCH population and the potential effect of C+A may have been diluted. Therefore, MATCH does not give the definitive answer for the population of patients with large atherosclerotic disease in which the risk of hard endpoints is 10% to 15% per year.

What Is Next?
Other secondary prevention trials comparing C+A to antiplatelet monotherapy are ongoing. For example, the CHARISMA trial has a stroke subgroup within a broader vascular group. Other trials, such as C+A versus A in patients with transient ischemic attacks, have very different patient profiles and therefore, perhaps, a very different risk of major bleeding complications.

Patients with ischemic stroke and aortic plaques >4 mm in thickness carry a very high vascular risk despite single antiplatelet therapy.9 The ongoing Aortic arch-Related Cerebral Hazard (ARCH) trial is a prospective, randomized, open-labeled, blinded endpoint evaluation (PROBE) investigator-driven trial comparing the net benefit of C+A over oral anticoagulant with an international normalized ratio (INR) 2 to 3 in patients with an ischemic stroke and plaques >4 mm in the aortic arch or a peripheral embolism with a thoracic aortic plaque >4 mm located upstream the embolized artery. Long-term oral anticoagulant has been chosen as comparator because clinicians previously prescribed warfarin based on frequent superimposed thrombi which at times are mobile in the lumen. C+A have been chosen rather than A or C alone because the risk of the primary endpoint (stroke, MI, vascular death) in observational studies was as high as 26% per year despite a single antiplatelet agent,9,10 WARSS and SPIRIT showed that warfarin was not superior to A in terms of efficacy and net benefit to prevent stroke and death in patients with a noncardioembolic stroke, and a large proportion of these patients with plaques >4 mm in the aortic arch has a past history of MI or percutaneous coronary intervention which is an already established indication for C+A.

The Steering Committee of the ARCH trial considered that the MATCH results should not affect the design of the ARCH trial because patients in ARCH are 100% atherosclerotic patients, 30% to 40% of cases have coronary heart disease, have a risk for hard endpoint of 26% per year—not including rehospitalizations (compared with 7% per year in MATCH)—and we have chosen for the sample size calculation a conservative risk of 14% per year (double compared with the MATCH population), and comparator in ARCH is warfarin, which carries a much higher risk of major bleeding complication than C+A in MATCH (3% per year on warfarin in the real life compared with 1.7% per year in MATCH).

We believe that even patients with lacunar stroke should also be subjected to further clinical trial with combination antiplatelet therapy (C+A) because the confidence intervals for the main outcomes for MATCH were close to significance. As a general principle, it is very important that second trials are conducted in different setting: in this case, comparing C+A to A (not C) in patients with lacunar strokes. Fortunately, the SPS-3 trial is including only patients with lacunar strokes and should continue with the same design. We should not exclude the possibility that further meta-analysis with the MATCH results included may show a net benefit of C+A over A or C.

Conclusion: Do Not Throw the Baby Out With the Bath Water!
Because of the very special population included in MATCH, and because of important positive results in other populations with high thrombogenicity such as percutaneous coronary intervention, the hypothesis of a favorable net benefit of C+A over A or over warfarin still needs to be thoroughly tested in other stroke or high-risk populations. As shown, there are important and substantial differences between the MATCH population and the populations included in other ongoing trials testing C+A (CHARISMA, ARCH, SPS-3, ACTIVATE). Although clinicians should now exercise caution in prescribing C+A in diabetic populations with cerebrovascular disease because of the possibility of an increased risk of
major bleeding, we believe that MATCH did not give a definitive answer for the net benefit of C+ A in secondary prevention of stroke. As is often the case with trials with results of borderline significance, more information is needed!

References
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