Are Two “Antiplatelet” Drugs Better Than One?

Many different processes are involved in platelet activation. Most drugs affect one of these chemical reactions. Theoretically, platelet functions (secretion, aggregation, and adhesion) can be reduced most effectively by using >1 agent or by inhibiting the final step in the attachment of the platelet to fibrin at the level of the glycoprotein IIb/IIIa (GpIIb/IIIa) receptor. Preliminary experience with oral and intravenous GpIIb/IIIa inhibitors has shown that bleeding is an important problem. In MATCH, 2 platelet function inhibitors, clopidogrel and aspirin, did prevent slightly more strokes (but not with statistical significance) but at the price of significantly more excess bleeding. Killing platelets causes bleeding.

What About the Endothelium Platelet Attachment to the Endothelium?

Platelets seem to swim happily in the blood until they reach an area of irregular or damaged endothelium, for example, on the surface of an ulcerated atherosclerotic plaque in a large artery. They then stick to that irregular surface and to each other in an attempt to heal the vascular irregularity. The white platelet–fibrin thrombus can break loose and embolize. The platelet plug also activates the coagulation cascade, promoting the formation of a red erythrocyte–fibrin-rich clot. Perhaps rather than killing the platelet, it might be better to inhibit platelet attachment to the endothelium. Antiplatelet drugs might do this but have not been tested thoroughly for their effect on endothelial–platelet interaction.

Does the Underlying Cardiac-Cervico-Cranial Arterial-Hematological Cause of Brain Ischemia Matter in Trials of Antiplatelet Agents?

Theoretically, antiplatelet agents should work by inhibiting formation of white clots. These tend to form on irregular endothelial surfaces of the cardiac and valvular endocardium and on the endothelial surfaces of the aorta and large neck and intracranial arteries. Anticoagulants inhibit red clots that tend to form in areas of very reduced blood flow. Experience should have taught us that the vascular lesions that cause stroke are very heterogeneous and that one drug or one strategy will not work for all or perhaps most situations. In fact, no single agent has been >25% to 30% effective in stroke prevention in any trial. Arterial lesions were not thoroughly characterized in MATCH, CAPRIE,1 ESPS I2 and ESPS II,3 WARSS,4 or any of the aspirin or ticlopidine trials. Although patients with cardiac lesions that could serve as an embolic source and with severe carotid artery stenosis were exclusions, none of these trials mandated vascular and cardiac studies that documented cardiac status and cervical and intracranial arterial lesions. The MATCH report does not contain information about the evaluations, that is, how many patients had MRIs and thorough vascular testing (magnetic resonance angiography, computed tomography angiography, or neck and transcranial ultrasound) and transesophageal echocardiography.

It is naïve to think that one strategy will prove a panacea. One strategy might work for one situation and another strategy for a different situation. How will we know this without insisting that the cardiac-arterial-blood lesions in the patients are thoroughly studied and that the large trials are powered to include enough patients in each category of interest? Alternatively, only one situation (eg, carotid artery stenosis in the neck, intracranial arterial stenosis, cardiac–origin embolism from atrial fibrillation), could be studied. Knowing that one drug is a bit better than another, or that one drug is 25% better than placebo or another drug among a large group of nondescript, not fully evaluated patients with unknown lesions does not help me or other doctors choose treatment for a patient whose stroke mechanism and cardiac-arterial-blood findings are known unless that particular situation has been tested in trials. Demanding full evaluation will cost more but will provide much more value. False economy is costly.

Why Did MATCH and Other Trials Include so Many “Lacunar” Patients, and What Are the Consequences?

More than half of the 7259 patients in MATCH were thought to have lacunar-small artery type brain ischemia using the TOAST classification. In WARSS, 56% of the 2206 patients...
were classified as “small vessel or lacunar.” Considering that only \( \approx 20\% \) of ischemic stroke patients in the large stroke registries had small artery disease, the proportion of lacunar-type pathology in these 2 very large recent studies is much larger than expected if all stroke types were represented according to the frequency of their occurrence. The vascular pathology (that is, the event in the penetrating artery that precipitates brain ischemia) is least well known in lacunar disease because very few patients die acutely, and the acute vascular pathology is virtually unknown.

Why is there a disproportionate number of small artery disease? Patients may be misdiagnosed as lacunar if intracranial arterial studies are not performed. Atheromatous disease of large arteries can block the origins of penetrators mimicking intrinsic small artery disease. Physicians may not enter patients with carotid artery disease (the most common large artery lesion), and some doctors treat patients with documented large artery disease with anticoagulants and so may not enter the cases. Perhaps the lack of investigations and of MRI data simply fails to identify patients as having important large artery or cardiac lesions. There are too few patients with documented large artery disease in MATCH and WARSS to define the effectiveness of the antiplatelet drugs tested in these trials.

The recurrence rate of stroke in patients during the first and second years after a lacunar stroke is much lower than that found in patients with large artery atherosclerosis and with cardiac and intra-arterial embolism. The relatively short duration of follow-ups in most stroke trials may need to be lengthened to determine the true effectiveness of therapeutic agents in patients with penetrating artery disease.

Are antiplatelets effective in well-documented cases of penetrating artery disease, and are some agents more effective than others? Are white clots the culprits that close the arteries? Instead, are the antiplatelets effective in preventing white clot formation in the large artery plaques and cardiac ischemic lesions that are known to frequently accompany small artery disease in hypertensive patients? Unless patients are evaluated thoroughly, we will not be able to answer these queries.

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**Was the MATCH Protocol Designed Optimally?**

Clopidogrel has been clearly shown in large studies to be effective in patients with coronary artery disease. The data in relation to stroke is less decisive. In CAPRIE, there was a statistically insignificant decrease in the end point stroke in patients treated with clopidogrel. Clopidogrel is by far the market leader among prescribed antiplatelets. Because all patients in MATCH received clopidogrel, and there was no comparator that did not receive clopidogrel, was clopidogrel really fairly tested? Knowledge of the effectiveness of antiplatelets in general now make a placebo group unethical, but why was not an aspirin alone, or an aspirin-modified release dipyridamole group not included in this large trial? Most trials in the United States are company-planned and -directed. In Canada, there is an effective consortium of stroke investigators who work with the various companies to generate trials designed to obtain the most relevant data for patient care. Pharmaceutical companies work with this consortium. The consortium consults on the methods and design of the trials and helps with recruitment of high-quality centers and with analysis. This system is badly needed in the United States and even worldwide.

**References**

Thoughts Evoked by MATCH and Other Trials
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/11/2604