Antiplatelet Agents in Secondary Prevention of Stroke
A Perspective

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Background and Purpose—Antiplatelet agents are widely used in the secondary prevention of stroke and other vascular events. The purpose of this review is to give a perspective of the factors involved in clinical practice for selecting antiplatelet drugs appropriate to the patient population.

Summary of Review—Aspirin remains the most popular drug, because it is modestly effective (≈25% risk reduction); however, it has undesirable side effects that are sometimes serious. The nonaspirin compounds are marginally more effective but are much more expensive and subject to commercial pressures from industry. A completely new look at these compounds is necessary, rather than spending more precious resources on “drug wars” that are expensive in time and money.

Conclusion—A “polypill” has been previously proposed, and possibly a combination of drugs targeted at the major vascular risk factors that is given to patients within 24 hours of initial stroke symptoms and to clearly defined patient populations may prove a solution. (Stroke. 2005;36:2034-2036.)

Key Words: antiplatelet agents ■ stroke management

The first attempts in stroke prevention began 50 years ago by carotid surgery and anticoagulants, but being based largely on intuitive ideas, lacking proper scientific methodology, and accompanied sometimes by serious complications, they received a generally lukewarm reception. Advances in methodology and statistics, and patient groups numbered in thousands rather than dozens, encouraged early clinical scientists to generate convincing evidence that some strokes could be prevented in patients who had already experienced cerebrovascular events. The advent of evidence-based science, which, at times becomes an unforgiving and dogmatic task master, also had an enormous impact in further shaping this process. Unfortunately, tempted by huge profits, the intervention of pharmaceutical companies has proven a mixed blessing, because they have provided the funding and administration for large-scale trials but at the potential cost of distorting the science of stroke prevention.

Current, informative, and detailed publications of secondary stroke prevention by antiplatelet drugs are available elsewhere, and this review represents a perspective from a clinician closely involved in the treatment and prevention of stroke. Major current questions that are pertinent to the daily use of available antiplatelet drugs include their degree of effectiveness, whether we are giving them to the right patients, and just how significantly drug companies influence our perception and judgment when we prescribe these drugs.

How Effective Are Present Antiplatelet Drugs?
The early aspirin trials clearly established that this cheap and almost universally available drug has a significant impact in preventing vascular sequelae in patients after cerebral ischemic events. It remains the most widely used antiplatelet agent, but its preventive effect is modest, at most a 25% relative risk reduction for all vascular end points, according to a substantial metaanalysis of the Antithrombotic Trialists, and only 13% in cerebral ischemic events. Unfortunately metaanalyses are subject to their own problems in attempting to homogenize data from different trials, but, in any case, the demonstrated impact was certainly only minor.

Attempts to retain the same prophylactic effect as aspirin, but without its occasional serious side effects of gastric irritation, led to a search for alternative antiplatelet drugs. The first of these aspirin competitors was ticlopidine, which also proved to have its own toxicity, including disabling diarrhea and neutropenia, and this was soon replaced by clopidogrel, a similar thienopyridine derivative but strikingly free of any significant side effects. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study of clopidogrel versus 325 mg of aspirin, tested in nearly 20 000 patients, showed a relative risk reduction of 8.7% but with an absolute risk reduction of only 0.5%.

These risk reduction figures can be very deceptive. For instance, using the data from the North American trial of
carotid endarterectomy in asymptomatic patients, carotid surgery reduced the annual incidence of stroke by 50%, from 2% to 1%. A relative risk reduction of 50% after surgery would be viewed much more favorably by the patient than the absolute risk reduction of only 1%; yet surely this figure reflects far more realistically the true state of affairs? The second European Stroke Prevention Study, using a combination of extended release dipyridamole and 50 mg daily of aspirin, similarly showed a relative risk reduction of stroke of 23% but an annual absolute risk reduction of only 1.5%.

Therefore, with all its shortcomings, aspirin has an established, though weak, secondary prevention effect on subsequent vascular events, and the newer compounds have only minimal additional prophylactic effects. No stroke prevention drug has yet appeared with a fraction of the effectiveness as carotid surgery in symptomatic patients with high grade stenosis, with its 16% absolute risk reduction.

**Are We Giving Them to the Right Patients?**

Increasing emphasis on trials conforming to evidence-based medicine has become a mixed blessing, more because of faulty extrapolation than faulty calculation. Data must be interpreted only within the confines of the original trial itself, and any extrapolations must be viewed critically. For instance, trial patients are always highly selected, a bias that may flatter a therapeutic strategy, whether surgical or medical. A therapeutic effect is more likely to be detected in patients at high risk of vascular events, but, conversely, those with minor clinical disabilities are more likely, and more able, to comply with long-term attendance. This may result in artificial “lacunarization” of drug trial populations because lacunar strokes are a large part of any stroke group. More relevant, the immediate days, and even hours, following transient ischemic attack (TIA) or stroke are a high-risk period for further events, but most published trials allow delays of up to 3 months for patient entry; therefore, missing this high-risk period of therapeutic potential. Antiplatelet trials must start in the emergency or casualty room as soon as possible after the event, not months later in the outpatient department.

Also, once the trial results are in the public domain, the drug is usually given indiscriminately to all patients who might remotely respond, irrespective of the original guidelines. This dilutes any potential therapeutic effects and, at the same time, exposes patients unnecessarily to possible adverse side effects.

Future trialists should also consider the role of recent discoveries such as “aspirin resistance,” a combination of noncompliance and unexplained, irreversible persisting platelet activation. Cerebral “microbleeds” demonstrated by gradient echo technology on MRI scanning in patients taking aspirin may play a predictive role in subsequent cerebral hemorrhage, data only now available by advances in neuroimaging.

“Brain attacks” are not comparable to “heart attacks” because, unlike myocardial ischemic events, stroke is a variegated entity, and the pathogenesis and therapeutic potential in cardiogenic and lacunar strokes are entirely different from those of cerebral vasculitis. These completely different cerebrovascular pathogeneses behave differently and should be treated separately. However, ever since the successes of the earliest aspirin trials in TIAs and stroke, aspirin has been the usual prophylaxis in all types of ischemic stroke, regardless of origin.

**How Serious Is the Influence of Pharmaceutical Companies on Medical Prescribing?**

The search for better antiplatelet drugs has led to fierce competition in the pharmaceutical industry, resulting in the current “antiplatelet wars.” In turn, with so little from which to chose among therapeutic effects in the nonaspirin compounds, industry has wooed the medical profession to tip the balance in their favor 1 way or another. There has been a proliferation of inducements, from the humble T-shirt to all-expense-paid world trips, for physicians to prescribe, attend conferences, or, if influential, advise their colleagues about the chosen drug. These inducements also include grants for research and sponsorship of meetings. Industry spends $12 billion annually on payments to physicians.

This, combined with uncertainty of the extent of this problem, has alarmed many neutral medical bodies, such as the National Institutes of Health, where the director, Elias Zerhouni, recently announced a 1-year moratorium on any employees accepting paid consultancy work from industry. In 2002, the American Medical Association, the American College of Physicians, and the Accreditation Council for Continuing Medical Education issued guidelines defining the acceptable relationship of physicians to pharmaceutical companies. Abridgements of anti-“kick back” statutes have sometimes resulted in criminal prosecution.

Much of industry research never sees the light of day, raising concerns about the concealment of negative data or even hazardous side effects that force trials to be aborted prematurely by the company. This has led to calls for the registration of all drug and devices trials, including proposed methodology, to be made available for public scrutiny, before the first patient is enrolled. A comprehensive public trials registry, compiled by the US Food and Drug Administration and the National Institutes of Health, already exists, but these are trial results. Industry has also recently established a voluntary electronic database of trial results through the Pharmaceutical Research and Manufacturers of America. The influential international committee of medical journal editors plans to institute a policy this year in which trials will be published only if they have been previously entered in a public registry at or before patient enrolment. However, mandatory registration of all publicly and privately funded trials would be more reassuring, and legislation is presently in the planning stages in the US Senate.

**Future Directions for Antiplatelet Drugs**

Wald and Law evaluated published meta-analyses (by 2003) to devise a single composite pill, a “polypill” that would simultaneously reduce 4 major cardiovascular risk factors: raised low-density lipoprotein, high blood pressure, platelet aggregability, and raised blood homocysteine levels. The pill would consist of a statin, an antihypertensive agent,
aspirin, and folic acid and would be targeted toward everyone aged >55 years and those with previous “cardiovascular disease.” Although a flurry of hostile correspondence followed in the journal in which this report was published, a visit to any acute coronary or acute stroke unit today will demonstrate that this policy is largely in general use, by coincidence if not by design. Yusuf\textsuperscript{20} calculates that over the past 25 years, the beneficial effects of aspirin, lipid-lowering drugs, angiotensin-converting enzyme inhibitors, and $\beta$-blockers in high-risk patients, when used together, could prevent 2-thirds to 3-quarters of future vascular events.

Aspirin remains the most widely used antiplatelet drug for secondary stroke prevention at present, despite a frequent gastrotoxicity problem. Presently available nonaspirin alternatives are much more expensive and of marginal extra benefit. Clopidogrel is an effective substitute when aspirin is contraindicated and is at least as effective. The dipyridamole–aspirin complex (Aggrenox, Asasantin) has been tested in only 1 trial, is marginally more effective than aspirin, but its aspirin content reduces its potential extra protective effect to that of aspirin alone as a result of intolerance. Post hoc metaanalyses\textsuperscript{21} are interesting but subject to errors and do not have the conviction of evidence-based randomized trials.

A totally new antiplatelet drug is needed with a major preventive effect on vascular outcomes. The present “drug wars” are divisive, time consuming, and expensive; however, the “winning” drug is unlikely to show more than a minor effect on absolute risk reduction. A major collaborative effort of industry has better potential, with trials designed at targeting clearly defined diagnostic groups, not just “ischemic stroke.” Most important of all, patients with TIAs and minor stroke must be entered into trials urgently, because the most dangerous period is in the first 48 hours. The potential of combination therapy, (a polypill), should be explored for immediate administration in the emergency or casualty room. Industry will clearly continue to play a pivotal role but needs not competition between companies would be infinitely more productive even if not likely or even practical in the immediate future. Mandatory regulation reimbursement to physicians from industry would limit the chances of prescribing expensive drugs that are of little therapeutic value or are even hazardous.

However, the relationship between medical investigators and pharmaceutical companies is symbiotic. Industry funds approximately 60% of biomedical research, 70% of clinical trials, and 50% of continuing medical education programs in the US.\textsuperscript{16} We need each other.

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