Four Decades of Stroke Prevention Trials

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Medical students in the 1940s observed that stroke victims were regarded as in a hopeless situation. Severely disabled patients with stroke and those in coma from intracerebral clots were confined to Observation Units. What was learned in my early days allowed us to replace this Medical Bedlam with Stroke Prevention and Treatment Units. Stroke neurologists, specialized nurses, and imaging technicians became available to give expert care in these new units. The hopeless era of stroke disappeared. With a growing number of colleagues I was privileged to contribute to this change or watch from the sidelines, as others were involved.

The biggest differences have resulted from epidemiological observations, dramatic scientific breakthroughs, including microbiology, treating infectious disease, pharmacology, and technology, coupled with the advent of rigid clinical trials. The most important may be listed as follows:

- Fleming’s discovery of penicillin eliminated brain abscess and much pneumonia and strokes because of pneumococcal and syphilitic meningo-vascular changes. Streptomycin could cure tuberculous meningitis. Endocarditis with embolic brain infarction was becoming uncommon. I can recall in the mid-1940s, discharging home to their young families, 2 well individuals, 1 recovered from coma because of tuberculous meningitis, the other cured of strep viridans endocarditis. These were pioneering events that before those days were fatal but today we take the cure for granted.

- Confirmation of the risk factors emerged from a combination of research strategies. One of the keys to affirmation of many was the collecting of life-time records of populations as in the Framingham Study1 and the Oxfordshire Stroke Project.2

The Four Horsemen of the Stroke Apocalypse are hypertension, tobacco, diabetes mellitus, and cholesterol excess. Control of all of these has been shown clearly to reduce stroke occurrence. Some important factors cannot be changed (eg, old age, male sex, and heredity) but with these in the patient’s background assiduous management of the risk profile is needed. Clinical trials have been of particular consequence in proving the necessity to regulate blood pressure in all age groups and to maintain normal levels of the low-density lipoprotein fraction of cholesterol.

- Moniz introduced cerebral angiography in 1928 triggering subsequent leaps forward in the ease, safety, and exactitudes of clinical diagnoses. New 3-dimensional imaging of the cerebral arteries from the neck up to the small branches of the Circle of Willis is now feasible. Collateral supply can be identified but not quantified. Soon we will visualize routinely the condition of the penetrating arteries of the basal ganglia/thalamic area and cerebellum and have understanding of and more accurate diagnosis of lacunar stroke.

Moniz must be given credit for first determining the importance of the extracranial arteries in stroke, their importance later being confirmed pathologically by Hultquist in Norway3 and 10 years later by Fisher4 in Montreal. Magnetic resonance imaging (MRI) and computed tomography angiography have become standard in seeking obstructive lesions. Diffusion-weighted MRI of the brain has become essential in deciding on the extent of the early infarction in developing stroke making the early use of thrombolytic agents safer and their use more precise when there has already been infarction.

- Many early trials did not distinguish between causes of the strokes in the subjects entered nor did they identify the causes of the outcome events. Because modern treatment depends on the cause, this has become a sine qua non of a credible trial. The Harvard Stroke registry5 plus the Oxfordshire Stroke Project2 pioneered the quest for answers here. Data emerging from 2 clinical trials (Trial of Organ 10172 in Acute Stroke Treatment [TOAST]6 and North American Symptomatic Carotid Endarterectomy Trial [NASCET])7 were valuable here. The main causes for ischemic stroke are cardioembolism, large artery atherosclerotic disease, spontaneous arterial dissections; and small vessel disease (lacunes).

- The combination of the disciplines of neuroepidemiology, biostatistics, and clinical trial methodology was major factors in advancing stroke research. Introduced in the mid-1940s their scrupulous use has become mandatory in the evaluation of new therapy or even for proof of the value of therapy accepted by custom and traditional wisdom coming from personal experience. Without proper trials regulatory agencies should not authorize the introduction of new therapeutic agents or surgical strategies.
Secondary stroke prevention is by medical or surgical measures and ideally both. Most that have been examined closely by clinical trials will be sketched here:

- Anticoagulants, heparin, and warfarin were introduced in the mid-1940s and were applied for years in stroke prevention without modern methods of scrutiny. The past 15 years have witnessed their careful evaluation in stroke prevention so that with reasonable confidence we can recommend them and identify their application or lack of value. By and large heparin is used as a prelude to launching into longer term warfarin therapy in the following stroke conditions: cardioembolic stroke, when thrombus is visible in an extracranial artery or cardiac chamber; stroke because of cerebral venous or sinus occlusion; and stroke victims (bed-ridden) with evidence of leg-vein thrombotic disorder or pulmonary embolism.

Good trials have denied the superiority of anticoagulants in transient ischemic attack, minor stroke, or progressing stroke. They have been used frequently for victims of stroke because of arterial dissection. The evidence is anecdotal and this use cannot be recommended.

Clinical trials, randomized because of a strict protocol, and followed meticulously by an informed clinician(s), will not be without bias and discipline used as a substitute for a series of clinical observations. Clinical trials are expensive but so too is the use of a strategy or therapy that is based strictly on a disciplined follow-up of a series of patients with defined outcomes. Clinical results can only set the stage for a scientifically disciplined follow-up of a series of patients with defined outcome data. The evidence is anecdotal and this use cannot be recommended.

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The 1960s produced 3 compounds that altered platelet function and were tolerated by humans. The first was dipyridamole. In a small and inadequately designed trial it did not prevent stroke. The next 2, sulfinpyrazone and aspirin, were tested in a factorial design trial (the Canadian aspirin trial as it became known). Sulfinpyrazone alone, despite its attractive platelet inhibitory properties in laboratory testing, was ineffective but in the aspirin-containing arms of the trial a significant benefit was noted (Figure 1). The Canadian trial was positive for aspirin but too small to be definitive. The Bouveri trial in Paris comparing aspirin with dipyridamole and the UK trial run from Oxford by Warlow of 600 versus 300 mg doses of aspirin were confirmatory and the Food and Drug Administration recognized aspirin’s claim as a drug to prevent stroke. It has become the most widely used treatment administered to stroke-threatened individuals. It was marginally better than aspirin alone.

Dipyridamole combined with aspirin and now marketed as Aggrenox is marginally better than aspirin but unless one uses the generic form of dipyridamole the cost is excessive. Claims that the slow-release form justifies the huge cost increase are excessive and unacceptable.

- Amarenco described emboli from plaques in the ascending aorta and these lesions should be considered before deciding on carotid endarterectomy (CE). Amarenco correctly described these lesions as a cause of stroke.

- Clopidogrel now marketed as Plavix has never been shown in sufficiently large enough trials of stroke-threatened patients alone to be any more effective than aspirin. In the Clopidogral versus Aspirin in Patients at Risk of Ischaemic Events trial, clopidogrel benefited patients over aspirin in the one arm of the trial containing patients entered with peripheral vascular disease. Aspirin was significantly superior to clopidogrel in patients who entered with recent myocardial infarction. In the recent stroke arm aspirin was marginally better than clopidogrel. We cannot recommend this expensive drug for any patients presenting with threatening stroke. If aspirin cannot be tolerated or if symptoms recur, the best and only reasonable alternative is aspirin combined with dipyridamole (we suggest a dose of aspirin 325 mg enteric coated form). The latter will be cheaper and equally effective if given in the generic form (suggest 200 mg). The combination with aspirin sold as Aggrenox is not recommended.

- The extremely serious and disturbing concern about Plavix is that the novel way of getting benefit for this drug arose by adding the results of trials of 3 clinically separate events together and coming up with a positive benefit This provoked the company to advertise that the drug should be used for all patients threatening with any of the 3 vascular events. This notion was sprung on the public without this novel and proposed method of analysis appearing in any preliminary Methods article. To this writer this is an unacceptable mode of trial reporting that smacks of statistical juggling. I have had a recent letter from a company official confirming that they never
published a preliminary Methods article. Adding clopidogrel to aspirin has been shown to increase the risk of brain hemorrhage.

- Subarachnoid bleeding from aneurysms and arteriole venous malformations in awkward places (such as the posterior fossa and brain stem) with intracerebral clots is a serious but uncommon cause of stroke. The worst kinds were mastered by Drake and many useful lives spared. Studies are ongoing to decide which incidentally found aneurysm to leave or to obliterate. The fact is that coils have replaced clipping but are used with the knowledge and skill of Drake in the background. His daring explorations of the posterior fossa paved the way for the advances to follow with catheter-injected balloons.

- Two different strategies for cerebral revascularization (by-pass and endarterectomy) were introduced hoping thereby to prevent stroke and improve function after ischemia. Both have been subjected to randomized trials with controls. Both required interdepartmental activity and the large trials recruited patients from multiple centers on multiple continents. Each center required a supervisor and the entire group was under the surveillance of a Study Manager. The study goal and the reason for the large staff were to lose no or few patients to follow-up. No deviations in the protocol were permissible. The only major exception here was the acceptance of a higher cardiothoracic ratio in the Asian patients, which we learned was normal for them. In some countries it was not part of the culture to have all follow-ups done by the study physicians. In this trial, this was mandatory and for all centers, was accepted by all investigators. By rigid adherence to our plan we think that we obtained a final and credible firm answer.

- The Cerebral By-Pass trials (funded by National Institute of Neurological Disorders and Stroke) came about because the delicate procedure of anastomosing the superficial temporal artery to a cortical branch of the middle cerebral artery might improve brain function and prevent stroke. Nine years later, we proved the 2 concepts to be unproven. Two years later, Medicare, Veteran’s Affairs, and large insurers stopped paying for the procedure. Vast sums were spared to already expensive healthcare in many counties. Two other trials attempted to prove our study wrong but failed to obtain a positive result. Clinical research is expensive but more so is the continued application of useless procedures alters inadequate study.

- The challenge to improve carotid artery flow was proposed frequently, but it was eventually stimulated in 1954 by a single case report from Oxford. This local excision by Felix Eastcott rapidly led to the refinement of CE and it became exceedingly popular. After a few years a negative and poorly designed and executed trial was published. This imperfect study failed to deter enthusiasm and after 1 million had been performed, National Institute of Neurological Disorders and Stroke called for a randomized trial hoping to determine who should and who should not be subjected to the procedure and with what upper limits of postoperative cerebral ischemic complications. After The Robarts Institute in London, Ontario, was successful in a competition for required funding, we designed a 5-year trial that eventually needed 11 years to complete. There was a European trial of fairly similar design ongoing under Warlow but with major protocol differences. Both studied the benefit of CE in symptomatic patients with moderately and especially with severe stenosis and we could conclude when the 30-day complication rate does not exceed 6% to 7% that patients with severe stenosis were significantly better than with the best contemporary medical care. Moderately stenosed patients benefited less. Below 50% surgery was accompanied by too many strokes.

- Fox method of measuring the degree of stenosis has been agreed on (Figure 2).

- Patients with the most extreme narrowing (to the point where we named them a new entity [near-occlusion]) do not have greater operative risk, but treated medically) have a good outlook. Treated surgically they have definite but reduced benefit compared with those with stenosis at or >70%. Abundant visible collateral anastomoses have developed slowly as the internal carotid flow has diminished. With Fox, this entity has been reported. We have been unable to quantify the amount of collateral flow. Generous collateral flow is easy to visualize but not to quantify. Luxury collaterals can be counted on when there is occlusion of the internal carotid artery, with few or no symptoms. Bilateral carotid occlusion has been described with little or no cognitive impairment.

- Two randomized trials have examined the potential benefit for subjects with asymptomatic stenosis. Both reported a slight but significant benefit. The results of the trials cannot be equated. One (Asymptomatic Carotid Artery Study [ACAS]) counted only strokes ipsilateral to the most severe stenosis (the operative sides) and the other (Asymptomatic Carotid Surgery Trial [ACST]) counted stroke in any territory supplied by cerebral arteries. It was a mistake to add the results.

- Enthusiasts have used these skimpy data to perform a plethora of operations. This author disagrees with this tendency. Only the subjects at greater than usual risks being identified by Spence and Barnett should be put to the real risk of CE. They will be subjects with enlarging
and possibly ulcerative plaques on serial studies and may exhibit evidence of silent emboli on repeated transcranial Doppler studies of their middle cerebral arteries. We owe these careful early observations to David Spence. Randomized trials are in motion. When told that the institution cannot perform these studies, my suggestion is not to ignore them and get on with a CE but to transfer the patient to a place where they can be done. Patients deserve the best, especially when brain function is threatened. Unhappily, reports indicate that there are many strokes when the procedure is being done with a greater than acceptable operative risk.16

• Reviews and publications of Medicare records by Kresowik19 (a surgeon) and others indicate that in multiple states in the United States, operators are not performing CE in a safe manner. In these areas the operating room must be added as a risk factor for patients with asymptomatic carotid stenosis in controlled trial angioplasty and tenting has proven twice as risky so that it is not a substitute for the hazards of endarterectomy independent auditing is called for.

My final thoughts:

• It was a rare privilege to do clinical research in conjunction with people from so many related departments. As my comments about one of the great scientists of a former era (Isaac Newton) remarked (and I paraphrase), “all of us peered ahead from the shoulders of those who went before.” For me the stimulating innovators to mention starts with James L. Baillie (Ornithological scientist at ROM) who taught me the scientific method and the need for unimpeachable accuracy of all observations, followed by William Boyd (Supreme Pathologist), Fraser Mustard (Platelet Pathophysiologist), David Sackett (master Epidemiologist), Murray Goldstein (Director National Institute of Neurological Disorders and Stroke), Wayne Taylor (Biostatistician), Aaron Fenster (Master of Imaging and computing), and Charles Drake (Neurosurgeon Extraordinaire). This catalogue of names reflects the fact that in so many areas of research a multidisciplinary team is essential. Even a strong leader, no matter how forceful, is dependent on others.

Disclosures

None.

References


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