Forty Years of Progress in Stroke

Henry J.M. Barnett, MD, FRCP(C), FRCP(UK), FACP

First of all, I congratulate Stroke for being part of such striking advances over the past 40 years and offer the following observations as part of my tribute. Stroke provides an important and unique separate organ for stroke publications. It makes important contributions to the evolution of a new subspecies: “The Stroke Neurologist.” This new world of stroke neurologists is encouraged to gather together and communicate. Peer-reviewed foreign articles have come to wider attention. Major random, controlled trials (RCT) are the backbone of evidence-based medicine.

When they involve stroke, Stroke has provided a venue for original articles, editorials, and reviews relevant to these trials and other important clinical observations emerging in the stroke field. It is increasingly evident that Stroke will need to play an advocacy role to ensure adequate nonindustrial funding for the best of stroke research, including large trials, defensible observations, and basic research on burning issues.

Regarding the future role of Stroke, has the time come to cut the umbilical cord to the American Heart Association? My perception from experience is that this move as evidence of the maturation of this huge subject will enhance solicitation of increased funding for all varieties of stroke research (via memorial tributes, legacies, direct mailings). Of noninfectious diseases, the 3 largest killers on earth are heart disease, cancer, and stroke. In some countries (eg, Russia) stroke is the number 1 cause of death, and in all countries stroke is the number 1 cause of major disability. When Stroke started under American Heart Association funding and supervision, we possessed little knowledge of the risk profile of stroke or anything about its prevention or treatment. All has changed and so, too, must the consideration of an autonomous role for stroke, just as with cancer and heart disease.

Sweeping advances have characterized stroke understanding in the 20th century. At one time I was asked to predict the next 40 years for stroke. The evidence is that I prophesized practically none of the great past advances.

My ancestor, Lord Macaulay, approximately 150 years ago wrote “the highest intellects like the tops of mountains are the first to catch and to reflect the dawn.” Unhappily, I am best at reflecting on the past. Macaulay would have disowned me.

Fortunately for such as me, 60 years ago William Faulkner said in his 1950 Nobel Prize Lecture, “The past is never past. It isn’t even past.” How true this is of even the greatest of medical advances! Medical drama since 4T4, my graduating year, is set out in Tables 1 to 3. The great leaps ahead that I have witnessed are prioritized by their impact on stroke (some moderately large and pivotal). It is apparent that most of them are being revised and restudied and, for some, their priorities have markedly changed.

In the time allotted to this brief introductory lecture, I focus on the pivotal advance of the randomized, clinical trial, the successor to anecdotal and authoritarian dicta based on personal experience. Why is this strategy listed as a pivotal advance? Some of my reasons for trumpeting the RCT as a pivotal advance are published in a recent issue of Stroke. Based on an academic life much occupied with this struggle and using experiences gleaned from a role as Principal Investigator (PI) in 5 major multicenter stroke trials plus parts played in 7 or 8 trials performed by others, I take the liberty of suggesting what follows.

Trials in which stroke is a principal outcome demand a stroke neurologist as “captain on the bridge,” otherwise known as the PI. The roles of this person are vital to the trial’s credibility. Assurance of double-blinding strategies is the top priority of the PI throughout any study. With all appropriate colleagues, the PI must devise a protocol acceptable to the question being asked with as few exclusions as will fit the question being posed. The PI must recruit clinically competent centers and be held responsible for ensuring that all entrants meet the protocol and that the accuracy and completeness of all outcome events pursued with vigor and without any delay. With modern communication technology, delay here is inexcusable because relevant data may be lost. Use of good interaction gives impetus and accuracy to all big trials and decreases loss of patients to long-term follow-up and prevents loss of continuing interest of participants.

A neuroradiologist should centrally report all films because subtle nuances are important. Most neurologists are only amateur radiologists.

Professionals with vested interests are unacceptable in the final design, conduct, and analyses of stroke trials. This proscription includes industry, industry consultants, promotional lecturers, surgeons, or radiologists known to have bias, owners of device or drug patents, or laboratories imaging stroke patients for profit. Statisticians occupy a critical and substantial advisory role. They need to advise in a timely way on the utilization directed by safety stopping rules. It is uncommon for them to possess clinical expertise and, thus, they are not acceptable as a PI.
The ultimate goal of every RCT is a scrupulous database held until analyzed by the academic center with little or no loss to follow-up. To ensure this goal and its perfection, the ideal is that a stroke neurologist be identified and willing to serve faithfully as the main investigator in every center. Large stroke RCT are costly in money and personnel requirements and should be reserved for “burning issues” only. Adequate funding for the full team of personnel needs to be assured in advance. Granting agencies need to be aware of this demand by a believable trial. Aggregating other trials or meta-analyses should not be acceptable as a substitute for the original adequacy in size and quality of the primary trial testing the hypothesis. Trial organization demands that all outcome data are verified and complete before any results are presented.

Aggregation of trials has been a strategy used to strengthen the robustness of conclusions from a single trial. However, there are serious flaws in aggregating trials. RCT are rarely completely comparable in design, details of protocol, and execution. The aggregation will rarely, if ever, serve as adding to the sample size and will flaunt the prime rule of “ceteris paribus” (comparing equals to equals) of the late great Abe Lilienfeld.

There have been notable imperfections in attempts to collate data from RCT seeking benefit for carotid endarterectomy (CE). For example, in the asymptomatic subjects submitted to the 2 large trials, there was investigator discretion in only 1 trial to randomize based on participants’ (notably surgeons’) “wishes.” Different primary outcome events were the objectives in the 2 trials: stroke on the side of the disease and the surgery in the American asymptomatic carotid atherosclerosis study and stroke in any cerebral vascular territory in the Europeans study.

In contrast to the symptomatic trials in which conventional angiography was mandated, neither of the asymptomatic trials using ultrasound alone found it possible to confirm that the stroke risk is linearly related to the degree of stenosis. Both of the asymptomatic trials established a meager 1% absolute stroke risk reduction in stroke at 2 years, with an unacceptably high number needed to be treated. The risk at 2 years without CE is ~2%. Most distressing is that, by Medicare surveys, the surgical skill needed to benefit is found to be commonly lacking. In many states better survival is realized without CE and stroke is more frequent after CE than with medical care alone.

In the symptomatic trials European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial, attempts to aggregate the data from the trials ran into a collection of reasons for failure of ceteris paribus. The 2 trials had different definitions for lacunar stroke. ECST surgeons and physicians were given “discretion” to randomize eligible patients or not and thereby substantially

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### Table 1. Early Medical Advances of Relevance to Stroke

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<th>Some</th>
<th>Moderate</th>
<th>Large</th>
<th>Pivotal</th>
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<tr>
<td>Antiviral agents</td>
<td>Antibiotics</td>
<td>Cerebral angiography and</td>
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<td>Polio vaccination</td>
<td>Heparin</td>
<td>Hultquist &amp; Fisher: postmortem</td>
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<tr>
<td>Smallpox eradication</td>
<td>Risk profile</td>
<td>CT, MRI, and MRA of both</td>
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<td>Doppler ultrasound</td>
<td>Cardiac monitors</td>
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<td>Transcranial Doppler</td>
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<td>Platelet inhibitors</td>
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<td>Risk profile and therapy</td>
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<td>TIA concept</td>
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<td>TIA by cause</td>
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<td>Thrombolysis</td>
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### Table 2. Later Medical Advances of Relevance to Stroke

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<th>Moderate</th>
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<tr>
<td>STA/middle cerebral artery</td>
<td>Rare small vessel disease: CADACL, giant-cell, Moya moya</td>
<td>Biostatistics</td>
<td>Coronary artery bypass graft and coronary stents</td>
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<tr>
<td>CE (asymptomatic)</td>
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<td>Interdisciplinary patient care</td>
<td>Stroke by cause (Harvard Stroke Registry; Framingham)</td>
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<td>Carotid stenting</td>
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<td>Vascular dementia</td>
<td>Cardiac and aortic imaging</td>
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<td></td>
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<td></td>
<td>CE (symptomatic)</td>
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<td>Small-vessel disease: lipohyalinosis and amyloid angiopathy</td>
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<td>RCT and stroke biostatisticians</td>
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<td>Marshaling of active stroke units</td>
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### Table 3. Important Medical Advances Less Relevant to Stroke

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<th>Some</th>
<th>Moderate</th>
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<th>Pivotal</th>
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<tbody>
<tr>
<td>Fiberoptics and flexible endoscopy</td>
<td>Laser surgery</td>
<td>Aneurysm clipping</td>
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<td>Cataract and lens replacement</td>
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<td>Peptic ulcer prescription</td>
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<td>Antirejection drugs</td>
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<td>Prions and slow viruses</td>
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<td>Organ transplantation</td>
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<td>Antiviral agents</td>
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STA indicates superficial temporal artery.
reduced the entry of aged and “severely stenosed” patients. Only North American Symptomatic Carotid Endarterectomy Trial requested bilateral carotid and intracranial views in the angiography. Comments in the aggregate on the effect of anastomotic supply were not available. Unlike North American Symptomatic Carotid Endarterectomy Trial, the ECST investigators lacked funding for cardiac or aortic studies. No stroke by cause could be ascertained. Telephone outcomes were accepted in ECST.

An early ECST report failed to find benefit in stroke-free survival for patients with moderate stenosis. A later report stated that they did find benefit. The lesson here is that all outcomes should be available before any disclosures of results.3,4

There was inequality after randomization to the time to carotid endarterectomy (2 days vs ~2 weeks). This contrarian has some concerns about the indiscriminate use of the technique of meta-analysis. Without doubt it has been a valuable strategy, particularly in population studies. Caution must be exercised in assuring the quality of the individual studies assembled. This rule is frequently breeched. The quality of credible data must not be sacrificed to achieve quantity. The inclusion of small series and unpublished series is a serious worry. Assurance is needed and is often lacking in rigorous, agonizing scrutiny by stroke experts of all outcomes in the pooling. Why rescue them from oblivion?

Important lessons have been learned from a study of the RCT in the antiplatelet field. My comments are abbreviated and center on clopidogrel. Here, serious problems are detectable when comparing aspirin with clopidogrel.5 No significant benefit was found for stroke in the stroke arm of what has become Plavix (Sanofi). The unsatisfactory response to enquiries after publication about the patients entered with stroke was “no subgroup analysis was planned in protocol.” For the readers, the details remained secret. Curiously, nobody repeated separately this negative stroke arm of the trial.

Without previous description of the analysis plans in the missing Methods paper,5 a unique composite of outcomes was submitted in the primary Results section of the final (and only) paper (a composite of 3 disparate vascular systems each of >6000 patients with recent MI, recent stroke, or peripheral vascular disease). A great leap of faith is needed here (“All vascular beds have similar risk of narrowing and response to platelet action and all benefit identically.”).

The PI was a statistician; no stroke neurologist visibly supervised the stroke patients’ entry or outcomes. All data have been held by the company.

Plavix plus aspirin yields unacceptable hemorrhage levels. A recent issue of Lancet featured this risk.6 Aspirin plus Aggrenox (Boehringer Ingelheim) has similar problems.7 No convincing evidence of benefit from any combinations of platelet inhibitors has emerged favoring stroke-threatened patients. There is no advantage for Plavix vs Aggrenox (Boehringer Ingelheim).8 The Food and Drug Administration (on the Internet) has twice warned industry that current advertising of Plavix went beyond their approval for clopidogrel.

This author concludes that it is well past the time for a confirmatory repeat trial of Plavix vs aspirin confined to stroke-threatened patients. Pending this, expensive Plavix cannot be recommended for stroke patients.

The databases of scrupulous trials increase stroke knowledge. Nonscrupulous trials do not even answer the question. A summary style of personal examples and new knowledge coming from RCT are presented.

From the Canadian Aspirin Trial

Mitral valve prolapse came to light as an uncommon but definite cause of stroke. This was soon proven by pathological specimens and was later verified by an Olmstead County prevalence study.9 Three types of emboli (platelet thrombi,
cholesterol crystals, and atheromatous debris) may cause amaurosis fugax and cerebral events (Figure 1).

From the Bypass Trial
Good collaterals predict poor surgical anastomoses. Bilateral carotid, vertebral, and middle carotid artery occlusions may all be compatible with continuing employability (Figure 2).

The “Stump syndrome” was reported as a new entity. Thrombi from an occluded interior carotid artery stump may send emboli via the collateral external carotid artery to cause TIA of eye or hemisphere and also stroke (Figure 3).

The reversal of carotid/middle carotid artery ratio in occidental vs Asian populations was confirmed. Faith may trump fact (witness the attempts to discredit this trial by unconvinced enthusiasts). The trial strengthened our belief in the need for central office reporting of all images.

From North American Symptomatic Carotid Endarterectomy Trial
Sufficient sample size and number of outcomes answered the question of the use and safety of CE in all degrees of stenosis.

Certain subgroups were planned in our Methods description and the investigators’ manual; a few became apparent early and all had full long-term follow-up data recorded. In addition to our main results, we learned risk and benefit increase directly with stenosis (as seen also in the ECST). Near-occlusion patients were described. They had an unexpectedly low medically treated risk and only had a muted reduced surgical benefit. Excessive leukoariosis means high risk for both CE and medical therapy.

The lowest numbers needed to be treated for CE to prevent stroke at 2 years are elderly males and patients with unexpectedly CE with severe signs of renal failure. A patient with contralateral carotid artery occlusion has an increase in 30-day risk but when followed-up to 5 years exhibits benefit. Tandem intracranial stenosis allows benefit. Women with moderate disease and all patients with only amaurosis fugax require other risks to benefit from CE.

In asymptomatic artery (on the other side of the randomizable stenosis with symptoms) with moderate or severe stenosis, 40% of strokes in the control group were not large-artery but were lacunar or cardioembolic. After the first-ever cerebral ischemic event, the next 10 to 14 days have the most serious likelihood of a stroke.

From ACE (Aspirin and Carotid Endarterectomy)
Aspirin is safe during CE. A lower dose (up to 325 m) is better than a higher dose (of 975 or 1200 m). There was a trend favoring 325 m.

The follow-up period was only 90 days. Conclusions about the dose in long-term stroke prevention cannot be made from this trial. It remains speculative because there have been no long-term direct dose comparisons.

Conclusion
This has been a remarkable 40 years in the study of stroke. RCT have shed light on many of strokes “mountain tops” and
have set the stage for evidence-based therapy. However, the job is not finished.

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None.

References
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