Evolution of Evidence-Based Medicine in Stroke

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Abstract

The introduction and evolution of evidence-based stroke medicine has realized major advances in our knowledge about stroke, methods of medical research, and patient outcomes that continue to complement traditional individual patient care. It is humbling to recall the state of knowledge and scientific endeavour of our forebears who were unaware of what we know now and yet pursued the highest standards for evaluating and delivering effective stroke care. The science of stroke medicine has evolved from pathophysiological theory to empirical testing. Progress has been steady, despite inevitable disappointments and cul-de-sacs, and has occasionally been punctuated by sensational breakthroughs, such as the advent of reperfusion therapies guided by imaging.

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Introduction

In the early 1980s, I aspired to be a clinical neurologist. My training prioritized clinical expertise, emphasizing proficiency in the diagnosis, management, and care of individual patients. By the mid-1980s, I began to appreciate that caring for individual patients and being an effective

clinical neurologist also involved understanding the patient's background, personality, and priorities; their prognosis; and the potential benefits, risks, and costs of treatments that may alter the prognosis [1]. A landmark book by Sackett et al. [2] introduced me to clinical epidemiology, as opposed to “dry” epidemiology, and described how the principles of epidemiology could be applied to individual patients.

Evidence-Based Medicine

Sackett et al. [3] promoted the practice of “evidence-based medicine” as the judicious application of the best available external evidence, obtained by systematic research, to complement individual clinical expertise in making informed decisions about individual patient care. They [3], and others [4], emphasized that neither evidence nor individual clinical expertise alone were enough and that the best external evidence was determined by the clinical question. The accuracy of a diagnostic test required cross-sectional studies of patients with the disease, the prognosis required observational studies of inception cohorts that were followed up completely, and the effect of treatments (beneficial and harmful) required a systematic review of experiments, ideally randomized controlled trials (RCTs), and if no RCTs available, the next best external evidence [3].

In the mid-1980s, the principles of epidemiology were also being applied prospectively to populations to study the incidence, causes, and outcome of stroke [5, 6]. The causes of stroke were numerous, and the outcome of stroke was variable; two-fifths of cases died, one-third remained functionally disabled, and one-quarter were functionally independent at 6 months after stroke [5, 6]. The outcome was influenced by several prognostic factors, of which treatment was only 1 factor (Table 1) [5, 6]. There were few, if any, effective treatments for stroke. The implications of these fundamental observations were several.

Matched Controls Were Needed to Distinguish Treatment Effects from Natural History

First, the variable natural history of stroke suggested that recovery could occur spontaneously, unrelated to any treatment [6]. Therefore, any assessment of the effect of a treatment would require comparison with an otherwise identical group of untreated controls to distinguish a treatment effect and its size (signal) from the expected prognosis (background noise).

Treatment Effects for Stroke Were Likely to Be Mild or Moderate Overall

Second, because the outcome after stroke was not always fatal or disabling, any effect of treatment on the outcome was not likely to be so dramatic (e.g., signal-to-noise ratio >10, as with antibiotics for bacterial septicaemia) that moderate biases could be ruled out as an explanation [7]. The aetiological heterogeneity of stroke also meant there was unlikely to be a single “magic bullet” for stroke, in the same way that there was no single antibiotic for all infections, and no single treatment for all cancers. Hence, an effective treatment given to all stroke patients was likely to have only a mild or moderate overall effect (i.e., less than a 2-fold difference in the incidence of the outcome between using and not using the treatment) [7].

Moderate Biases Needed to Be Distinguished from Moderate Treatment Effects

Third, the significant effect of several prognostic factors, independent of treatment, on outcome after stroke (Table 1) meant that imbalance in prognostic factors between treated cases and untreated controls could underestimate or nullify a moderate true effect of a treatment (false negative or type 2 error) or erroneously conclude a moderate false effect (false positive or type 1 error). All potential prognostic factors would therefore need to be

Table 1. Prognostic factors that may influence the outcome of patients with stroke

Systematic
Patient
Age
Sex
Ethnic background
Socio-economic and employment status
Residence (urban, rural, or remote)
Pre-stroke function
Co-morbidities (e.g., atrial fibrillation, heart failure, diabetes, prior stroke, and smoking)
Disease (Stroke)
Diagnostic criteria – validity
Coding – accuracy
Pathological type (ischaemic vs. haemorrhagic stroke)
Severity
Time since stroke onset
Treatment
Treatments and adherence to them
Quality of care
Outcome
Definition (e.g., disability, handicap, recovery, and recurrent stroke)
Diagnostic criteria
Adjudication
Coding – accuracy
Timing of when outcome measured
Follow-up duration and completeness
Random
Chance factors

measured, and adjusted if unbalanced, in comparisons of the outcome between cases and controls, before a causal association could be inferred between treatment and outcome. Other potential sources of bias would also need to be minimized, and other aspects of an association between 1 variable (e.g., treatment) and another variable (e.g., outcome) would need to be considered, before deciding whether an association was causal (Table 2) [8]. Hill [8] considered the strongest of these was an experiment, whereby an action (e.g., treatment) reduced or prevented the associated events. However, it took time for methodologically reliable experiments of treatment effects (e.g., RCTs) [9] to become de rigueur in stroke medicine [10].

Methods of Evaluating Treatment Effects

Observational Epidemiology – The Example of Carotid Endarterectomy

Observational cohort and case-control studies [11], driven by pathophysiological concepts, were the mainstay of evaluating interventions to prevent and treat stroke [10]. For example, the safety and effectiveness of

Table 2. Reasons for an association between 2 variables (e.g., treatment and outcome)

Systematic error (bias)
Selection bias (systematic pretreatment differences in comparator groups)
Performance bias (systematic differences in care, besides the treatment being evaluated)
Detection bias (systematic differences in outcome assessment)
Attrition bias (systematic differences in withdrawals from treatment groups and completeness of outcome data)
Reporting bias (selective reporting of some, but not other, outcomes depending on direction of the results)
Random error (chance)
Impact of the play of chance on outcome among those exposed and not exposed
Determined by the number of relevant outcome events in the study
The potential error can be quantified by means of a CI, which indicates the range of effects statistically compatible with the observed results
Can prevent real effects of treatment being detected or their size being estimated reliably
Causality (truth)
Bradford Hill Criteria [8]
Temporal relation
Treatment precedes effect
Strength of relation
High correlation or risk ratio (relative risk) of the association
Plausibility
Based on current understanding of disease mechanism
Helpful but not mandatory
Consistency
Across settings and methods
Coherence
Consistent with knowledge of related treatments
Dose-response relation
Biological gradient
Specificity
Treatment causes the effect and little else
Experiment
Does preventive action prevent the disease?
Analogy
None of my 9 view points (criteria) can bring indisputable evidence for, or against, the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect [8]?
NB. Tests of significance: No formal tests of significance can answer those questions (about cause and effect). Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that, they contribute nothing to the “proof” of our hypothesis [8]

CI, confidence interval.

carotid endarterectomy were initially assessed by comparing the outcome of patients who had undergone carotid endarterectomy, usually as part of their hospital care, with the outcome of others who had not (literature, historical, or concurrent controls) [12]. The numerical method was used to compare number of outcome events (strokes) in each group over the average follow-up period, rather than actuarial life tables or the Kaplan-Meier method of survival analysis [10, 12]. Poor risk patients were less likely to be selected for surgery than good risk patients (indication bias), so patients in surgical series had more favourable outcomes. A range of statistical strategies (e.g., multivariable regression and propensity-score matching) could adjust for imbalance between the surgical and non-surgical groups in measured confound-

ing factors but could not remove, with certainty, residual confounding (due to differences between patient groups in unmeasured confounding factors or measured confounding factors that were misclassified or imprecisely measured); confounding by indication (inability to know and adjust for reasons why some patients received the treatment whereas others did not), or reverse causality bias (when the probability of the outcome was causally related to the exposure). Invariably, patients who were treated non-randomly were likely to be systematically different from untreated controls in ways that were not measurable with the data collected, introducing systematic bias into estimates that were wrong, and we could not be sure just how wrong, qualitatively or quantitatively.

Table 3. Strategies to minimize systematic and random errors

Minimization of systematic error – good study design
Selection bias
Proper randomization
Random sequence generation
Allocation concealment
Performance bias
Blinding of participants and investigators to allocated treatment
Detection bias
Blinding of the outcome assessor to allocated treatment
Attrition bias
Complete follow-up of all outcome data
Reporting bias
Reporting of all outcomes
Other bias
Analysis by allocated treatment (including all randomized patients: intention to treat)
Pre-specification of primary outcome (preventing data dredging or “p-hacking”)
Chief emphasis on results in overall population (without undue data-dependent emphasis on particular subgroups)
Systematic review of all relevant studies (without undue data-dependent emphasis on particular studies)
Minimization of random error – large numbers of outcome events
Large numbers of participants with major outcomes (with streamlined methods to facilitate recruitment)
Systematic search and review of all relevant studies (yielding the largest possible number of participants with major outcome events)

In the same issue of *Stroke* in 1984, Warlow [12] and Barnett et al. [13] independently called for a good study design to minimize systematic error (bias) and large numbers of primary outcome events to minimize random error (chance) in order to reliably determine the true effect of carotid endarterectomy (Table 3) [14, 15]. The most efficient method of minimizing systematic error is by concealed randomization (to ensure comparability between treatment groups) and blinded outcome evaluation [14, 15]. Other fundamentals are good adherence to assigned treatment, complete ascertainment of outcomes, and unbiased statistical analysis.

RCTs – Carotid Endarterectomy, Anticoagulation, Antiplatelet Therapy

Carotid Endarterectomy

The first RCT of carotid endarterectomy, conducted between 1962 and 1968 in 24 US centres under the leadership of Bill Fields [16], was an astonishing effort but the results were inconclusive. The sample size was too small ($n = 316$ patients with TIA and carotid stenosis) to reliably detect or exclude a moderate but clinically worthwhile benefit of surgery; 43% of the patients had experienced only vertebrobasilar TIA (i.e., asymptomatic carotid stenosis); the results for patients with carotid TIA (i.e., symptomatic carotid stenosis) were not reported; completeness of follow up in each group was not known; the major end point (stroke) was not evaluated “blind” to the allocated treatment; and it was not clear whether the pa-

tients were analysed (by intention to treat) in the groups to which they were randomized [16].

Uncertainty about the safety and efficacy of carotid endarterectomy polarized opinions and led to wide variations in surgical policy and practice around the world. In contrast to the UK, carotid endarterectomy became one of the most commonly performed vascular procedures in the USA [12]. Inconsistency between rigorous regulatory requirements for licensing drugs and unregulated uptake of surgical procedures was also exposed [12]. The uncertainty became such a burning issue that it prompted the launch of the European Carotid Surgery Trial (ECST) in 1981 and North American Symptomatic Carotid Endarterectomy Trial (NASCET) in 1987 [17, 18]. Their interim results, published in 1991, resolved uncertainties about the overall balance of benefits and harms of carotid endarterectomy for symptomatic, extracranial carotid stenosis [17, 18]. Moreover, because both trials shared similar methods and friendly collaboration, it was possible to test hypotheses generated from 1 trial in the other independent trial. The individual patient data were pooled to develop and externally validate risk models which enable more precise targeting of carotid revascularisation to patients most likely to benefit, such as those with recent or recurrent symptoms of thromboembolism from an irregular or ulcerated atherosclerotic plaque [19, 20].

The ECST and NASCET also illustrated how different trial designs could realize similar and complementary re-

sults. The ECST had a simple design with few key data requirements recorded on single page forms at baseline and follow-up. Entry was based on the “uncertainty principle,” whereby patients were enrolled only if the clinician was substantially uncertain which trial treatment would be most appropriate for their patient [17, 21]. The uncertainty principle enabled clinicians to provide information and obtain informed consent in a manner similar to routine clinical practice. It facilitated recruitment of a wide range of patients because clinicians had different “grey areas” of uncertainty; for example, some were uncertain about the benefits of carotid endarterectomy in patients with 0–50% stenosis, others were uncertain about 30–70% stenosis, and others were uncertain about 50–99% stenosis. Hence, the ECST could determine the effectiveness of carotid endarterectomy for all degrees of symptomatic carotid stenosis [17].

Anticoagulation

In the early 1960s, Hill et al. [22, 23] led 2 RCTs of anticoagulation (phenindione) to prevent recurrent stroke in >14-day survivors of presumed ischaemic stroke. The first trial enrolled 142 patients and suggested an adverse effect of anticoagulation in hypertensive patients [22]. The second trial enrolled 131 non-hypertensive patients and reported that anticoagulation increased fatal stroke (possibly haemorrhages) but not non-fatal stroke [23]. Despite several shortcomings of these trials [24], anticoagulation was generally rejected for acute/subacute ischaemic stroke until 35 years later, when a sufficiently large trial showed that early anticoagulation with unfractionated heparin (5,000 or 12,500 IU bd) reduced recurrent ischaemic stroke by about 9 (95% confidence interval [CI]: 4–13) per 1,000 patients treated but increased haemorrhagic stroke by about 9 (6–11) per 1,000 patients, with no net reduction in recurrent stroke (odds ratio [OR]: 0.97; 0.85–1.11) or death or dependency (OR: 0.99; 0.93–1.04) [25].

By contrast, long-term oral anticoagulation for preventing stroke in patients with atrial fibrillation was evaluated systematically by several, well-organized clinical trials in the late 1980s/early 1990s [26–30]. Adjusted-dose warfarin (international normalized ratio [INR]: 2.0–3.0) and antiplatelet therapy were shown to reduce stroke by about two-thirds and one-fifths, respectively, compared to the control [30]. Adjusted-dose warfarin (INR 2.0–3.0) was substantially more efficacious than both antiplatelet therapy alone and the combination of antiplatelet therapy plus low-intensity, fixed-dose warfarin (INR 1.2–1.5) [26–30]. Later, 4 very large RCTs showed non-inferiority

of 4 direct oral anticoagulants compared to adjusted-dose warfarin for stroke prevention in atrial fibrillation [31].

Trials of long-term oral anticoagulation for preventing stroke in patients with TIA or minor ischaemic stroke of presumed arterial (non-cardiac) origin were less successful. The first large trial in 1,316 patients was stopped prematurely because high intensity oral anticoagulation (INR: 3.0–4.5) caused an excess of intracranial haemorrhages compared to aspirin 30 mg daily [32]. A follow-up trial found that medium-intensity oral anticoagulation (target INR: 2.0–3.0) reduced ischaemic events (HR: 0.73, 0.52–1.01) but also increased major bleeding (HR 2.56, 1.48–4.43) which offset any benefit on the primary composite outcome (HR: 1.02, 0.77–1.35) compared to aspirin (30–325 mg daily) [33]. A post hoc subgroup analysis of 1,032 patients with non-lacunar, non-cardioembolic, ischaemic stroke in the COMPASS trial now raises the hypothesis that adding low-intensity anticoagulation (rivaroxaban 2.5 mg bd) to aspirin 100 mg daily may be more effective than aspirin alone in preventing recurrent stroke and be acceptably safe [34].

Antiplatelet Therapy

The first RCT of antiplatelet therapy (dipyridamole) to prevent stroke was reported in 1969 [35]. Soon after, Bill Fields [36] led the first double-blind RCT of aspirin for secondary stroke prevention between 1972 and 1975. Among 178 patients with carotid territory TIAs, aspirin significantly reduced the composite of death, cerebral or retinal infarction, or TIA during the first 6 months follow-up but not individual end points. In 1978, the Canadian Cooperative Study reported that among 585 patients with “threatened stroke” (406 men and 179 women), aspirin reduced the risk of stroke or death by 31% ($p < 0.05$) compared to the placebo [37]. Aspirin was also reported to be effective in men (risk ratio [RR] = 0.52, $p < 0.005$) but not women (RR: 1.42, $p = 0.35$); the subgroup interaction p value was < 0.003 . The conclusion that aspirin was effective for men but not women, based on an underpowered subgroup analysis, became an entrenched belief for more than a decade until the publications of the Antiplatelet Trialists’ Collaboration (APT) [38, 39].

The January 30, 1988, issue of the *BMJ* contained the first results of the APT [39] and the interim results of the UK-TIA aspirin [40]. The UK-TIA aspirin trial reported that among 2,435 patients with TIA or minor stroke, aspirin reduced the odds of stroke, myocardial infarction (MI), or death compared to the placebo (18%; 95% CI: 2–31%) but not disabling stroke or vascular death (7%; 95% CI: 26% reduction to 18% increase). The authors la-

Table 4. Taxonomy of the hierarchy of evidence for treatment efficacy and safety [41]

Randomized trials
1. Systematic review and meta-analysis of multiple, congruent, very large, mega-trials
2. Single, very large, mega-trial
3. Meta-analysis of multiple, congruent small-moderate size trials
4. Meta-analysis of multiple, mostly congruent small-moderate size trials
5. Single small-moderate size trial
Observational data
6. Systematic review and meta-analysis of large and propensity-weighted or multivariate-adjusted studies
7. Meta-analysis of small or unadjusted studies
Physiologic data
8. Studies in humans
9. Studies in other species
Authority
10. Expert opinion

mented, “Having spent nearly 10 years designing, funding, conducting, and analysing this study, we are frustrated to conclude that its results cannot stand alone” [40].

Limitations of Single RCTs

In addition to suboptimal sample size, other drawbacks of single RCTs were limited generalizability (external validity) and poor reporting [41]. However, although the population of stroke patients studied in any RCT will not be representative of all stroke patients, the proportional effects of the treatment observed in the RCT should be similar, and therefore generalizable, in different stroke populations, unless there is good reason to expect otherwise. If so, the absolute effects of a treatment in local stroke populations can be estimated reliably by applying the proportional effects observed in the RCTs to the absolute risks/incidence of the relevant outcomes recorded in observational studies of local stroke populations [14]. Reporting of RCTs has improved substantially since journals mandated adherence to the Consolidated Standards of Reporting Trials (CONSORT) statements, which provide guidance and checklists for ensuring complete and transparent description of methods and findings [42, 43].

Systematic Reviews and Meta-Analyses of RCTs – To Identify Moderate Treatment Effects

In order to improve precision of the results from single RCTs, without introducing bias, Richard Peto, Tom Chalmers, and Iain Chalmers developed a method of systematically reviewing and collating all related trials in a given field and combining the differences between the treatment group and the control group from each trial into a meta-analysis that produced a summary of the

overall effect of interventions from several similar studies [10, 44, 45]. The key assumption was that if a treatment had any definite effect on the incidence or outcome of disease, then the direction of the effect would be similar under different circumstances (i.e., *qualitatively* similar; positive or negative), whereas the magnitude or size of the effect would be likely to vary (i.e., be *quantitatively* different) due to clinical and statistical heterogeneity among the trials. The results were graphically represented as “forest plots” with each line depicting the 95% CI of the RR (or OR) of the outcome for each trial, the square on each line representing the point estimate of the RR (or OR), the size of the square being proportional to the power of the trial, and the overall summary estimate of the RR and its CI at the bottom of the figure [46]. The 95% CI expressed the range of values that is likely to contain the true effect of the treatment in the trial population, with some degree of uncertainty [47, 48]. It implied that if the RCTs were to be repeated over and over among random samples from the same population, then 95% of the calculated intervals would contain the true estimate of the treatment effect. The CI is preferred to *p* values because estimates of treatment effects/differences derived from controlled comparisons are always subject to some uncertainty (because of both the quality of the data and the play of chance), and the CI captures the degree of statistical uncertainty surrounding the estimate of the treatment effect. Clinicians can then judge whether the likely range of effects would be clinically important or not. In contrast, the *p* value gives just 2 options – to reject any differences that are not significant or accept those that are, and definitive statements that “no difference exists between treatments” may not be correct [48].

The systematic review and meta-analysis by the APT of 31 RCTs of prolonged antiplatelet therapy in 69,671

Table 5. Evolution of evidence-base strategies to treat acute stroke and prevent recurrent stroke

	Year of initial or important year
Acute treatment	
Organized care in stroke units [52, 53]	1993, 2012
Graduated compression stockings [55]	2014
Ischaemic stroke	
Thrombolysis [60, 61]	1995
Aspirin [25]	1997
Decompressive hemicraniectomy [59]	2007
Aspirin + clopidogrel [55, 62]	2013
Endovascular thrombectomy [59, 60]	2015
Extending time window and perfusion imaging for EVT [56]	2018
Extending time window and perfusion imaging for thrombolysis [56]	2019
Aspirin + ticagrelor [62]	2020
Haemorrhagic stroke	
Surgery [55]	2005, 2013
Blood pressure-lowering [55]	2013
Secondary prevention	
Atherothromboembolism	
Aspirin [37–39]	1978, 1988
Carotid endarterectomy [17, 18]	1991
Clopidogrel [72]	1996
Aspirin + extended release dipyridamole [55]	1996, 2006
Blood pressure-lowering [76]	2001
Cholesterol-lowering [77, 78]	2002, 2006
Cilostazol [55]	2010
Extracranial carotid stenting [55]	2011
Pioglitazone [55]	2016
Cardiogenic embolism	
Anticoagulation with warfarin [29]	1993
Anticoagulation with direct oral anticoagulants [31]	2009
Patent foramen ovale closure [61]	2017

patients showed that antiplatelet therapy reduced the odds of major vascular events by $23\% \pm 2\%$ (standard deviation) ($2p < 0.0001$) compared to control [39]. With an overall treatment effect of >10 times the standard deviation (z value >10), there was sufficient statistical power to undertake reliable and meaningful pre-specified subgroup analyses and show more definitively that antiplatelet therapy reduced the odds of major vascular events consistently among men ($24 \pm 2\%$) and women ($20 \pm 5\%$) [39]. The findings from the APT changed policy and practice, extending antiplatelet therapy to women, as well as men, at high vascular risk [39]. The contrast in conclusions from subgroup analyses in the smaller Canadian Cooperative Study [37] and the larger APT [39] was an early lesson in the potential perils of subgroup analysis, as described in a superb three-part series by Rothwell et al. [20, 49, 50].

The systematic review and meta-analysis of RCTs has since become the tip of the pyramid (highest tier) of the hierarchy of evidence and grading systems for rating the level (quality) of the evidence and class (strength) of recommendations for interventions (Table 4) [41, 51]. Its

methodology was soon embraced by stroke clinicians and revealed the benefits of stroke units [52, 53] and decompressive surgery for space-occupying hemispheric infarction [54]. It has subsequently been utilized to more precisely evaluate the effects of other treatments for stroke [55, 56], including thrombolysis [57, 58], endovascular thrombectomy [59, 60], patent foramen ovale closure [61], and dual antiplatelet therapy [62] (Table 5).

Limitations of Systematic Reviews and Meta-Analyses

Limitations of systematic reviews and meta-analyses include potential for publication bias, study quality bias, heterogeneity between studies, reporting bias, poor reporting, and outdated reviews [41, 63–65]. Publication bias arises if studies showing no significant treatment effect (“negative” trials) were less likely to be published, and included in meta-analyses, than “positive” trials, leading to overestimation of the true treatment effect in meta-analyses [63]. Publication bias can be detected sometimes by asymmetrical funnel plots (scatter plots) of effect size against sample size (precision) of the individual studies [66]. Registration of trials (e.g., <https://clinicaltrials.gov/>)

now enables reviewers to identify all trials and flag trials where no results were published.

Inclusion of poor quality studies, as assessed by high risk-of-bias judgements (for sequence generation, allocation concealment, blinding, and incomplete data) [64], in systematic reviews has been associated with exaggerated estimates of treatment effects [67], emphasizing the importance of assessing the methodological quality of the trials included in a meta-analysis [64] and conducting a sensitivity analysis of the results according to methodological quality. Systematic reviews may also be biased by selective inclusion and reporting of outcomes and analyses [65]. Selective inclusion occurs when there are multiple estimates of treatment effect in a trial and the choice of estimate is based on the statistical significance, magnitude, or direction of the results. Selective reporting occurs when only a subset of outcomes and analyses are reported, based on the results, rather than reporting all protocol-defined outcomes.

Reporting of systematic reviews and meta-analyses has improved following consensus recommendations in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [68]. The need to regularly update systematic reviews to incorporate the results of recent RCTs led to the Cochrane Collaboration (<https://www.cochrane.org/>) and Library (<https://www.cochranelibrary.com/>) [69, 70] and a stroke review group within it, which has informed evidence-based stroke medicine for >25 years [71].

Mega-Trials – To Identify Moderate Treatment Effects

Another strategy to improve precision in evaluating treatments with likely moderate, but clinically important, effects has been to conduct very large mega-trials. One of the first mega-trials was the CAPRIE trial which showed that, among 19,185 patients with previous atherosclerotic ischaemic stroke ($n = 6,431$), MI ($n = 6,302$), or peripheral arterial disease ($n = 6,432$), long-term clopidogrel reduced the incidence of ischaemic stroke, MI, or vascular death by 8.7% (95% CI 0.3–16.5%; $p = 0.043$) compared to aspirin [72]. The CAPRIE trial also produced another controversy from subgroup analysis. Although only powered to reliably detect (or exclude) the mild observed treatment effect in the whole study cohort, and not each of the 3 clinical subgroups, it was reported that clopidogrel reduced the relative risk of the primary outcome by 7.3% (95% CI: –5.7 to 18.7%) and 23.8% (8.9–36.2%) in patients with prior stroke and peripheral arterial disease, respectively, but increased the relative risk by 3.7% (22.1 to –12.0%) in patients with prior MI [72]. As a test of het-

erogeneity of these 3 treatment effects was statistically significant ($p = 0.042$), it was suggested “that the true benefit (of clopidogrel) may not be identical across the 3 clinical subgroups” [72]. Consequently, clopidogrel was considered by many cardiologists to be no more effective than aspirin for patients with MI and not used by cardiologists until 15 years later, when the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial showed that adding clopidogrel to aspirin in 12,562 patients with acute coronary syndromes reduced the composite of stroke, MI, or cardiovascular death by 20% (10–28%) [73]. Clopidogrel is now one of the most widely used drugs in cardiology.

The first mega-trials in acute stroke treatment were the International Stroke Trial [25], which enrolled 19,435 patients from 467 hospitals in 36 countries, and the Chinese Aspirin Stroke Trial [74], which enrolled 21,106 patients from 413 Chinese hospitals. They collectively showed that aspirin, started within 48 h of ischaemic stroke onset, prevented 10 (standard deviation 3) deaths or recurrent strokes per 1,000 during the first few weeks ($2p = 0.001$) [25, 74]. They lay the foundations (methodology, infrastructure, and networks) for subsequent large trials of stroke treatments [75].

In 2001, the PROGRESS trial reported that, among 6,105 patients with prior stroke or TIA, a perindopril-based antihypertensive regimen lowered blood pressure by 9/4 mm Hg and reduced stroke risk by 28% (95% CI: 17–38%) compared to placebo [76]. The proportional reductions in stroke risk were consistent in hypertensive (relative risk reduction: 32%) and non-hypertensive (relative risk reduction: 27%) participants (p for homogeneity = 0.7), but the absolute risk reductions were greater in hypertensive participants (5.2% [11.1% active vs. 16.2% placebo]) than in non-hypertensive (2.4% [9.1% active vs. 11.5% placebo]) because hypertensive patients are generally at higher absolute risk of stroke than non-hypertensive patients. The following year, the Heart Protection study reported that, among 3,280 participants with prior ischaemic stroke, simvastatin 40 mg daily reduced the risk of major vascular events by 20% (95% CI: 8–29%) compared to placebo. Again, the proportional reduction in risk of one-fifth was consistent, irrespective of baseline blood cholesterol concentration, but the absolute risk reduction was higher among participants with higher blood cholesterol concentrations [77]. The SPARCL trial replicated these results in 4,731 patients with prior stroke or TIA; atorvastatin 80 mg daily reduced the risk of major cardiovascular events by 20% (95% CI: 8–31%) compared to placebo [78].

Smaller RCTs – To Identify Large Treatment Effects

Although large RCTs were needed to reliably identify and distinguish moderate treatment effects of medical (drug) therapies for stroke from moderate biases and random errors, smaller RCTs proved sufficient to reliably identify larger treatment effects of surgical and other mechanical interventions for stroke that clearly exceeded any potential moderate errors [17–19, 59–61]. For example, endovascular thrombectomy for acute ischaemic stroke caused by anterior-circulation large-artery occlusion had such a dramatic treatment effect in reducing death and dependency (mRS >2) at 90 days (47% control vs. 30% thrombectomy; RR: 1.56; 95% CI: 1.38–1.75) in a total of 1,771 patients enrolled in 7 RCTs that single RCTs with as few as 70 randomized patients had sufficient statistical power to report a statistically significant treatment effect of thrombectomy (71% control vs. 40% thrombectomy; RR: 1.79; 1.13–2.82) that was consistent with the other 6 trials [59]. Closure of a patent foramen ovale in patients aged <60 years with cryptogenic ischaemic stroke also had a dramatic treatment effect, substantially reducing recurrent ischaemic stroke compared to antiplatelet therapy alone (1.3% PFO occlusion plus antiplatelet vs. 10% antiplatelet; OR: 0.12; and 95% CI: 0.04–0.27) [61]. The astonishing effectiveness of these mechanical interventions, or “plumbing” procedures, is a salutary reminder of potential power of investing in simple clinical innovation and technological advances to further reduce the burden of stroke [79].

Neutral and Negative Trials

Between the mid-1980s and mid-2000s, many positive results in pre-clinical studies of stroke therapies failed to translate to positive results in large clinical RCTs, and some therapies were even harmful [80, 81]. Reasons included poor pre-clinical experimental design, conduct, delivery, and clinical oversight. The Stroke Therapy Academic Industry Roundtable (STAIR) responded by publishing standards for preclinical drug development [82] and recommendations for advancing the development of acute stroke therapies [83]. They have facilitated improvements in RCT design and delivery, including pre-registration of trials, stratification and minimization at randomization, blinding of treatment and outcomes, and analysis by ordinal logistic regression.

Unpublished Trials

A substantial body of evidence relevant to stroke practice and research remains unpublished. A systematic review of 940 completed trials of pharmacological interven-

tions for acute ischemic stroke (1955–2008) found that 125 trials (19.6%, 95% CI: 16.5–22.6%), involving 16,058 patients, were completed but not published in full [84]. Investigators have a responsibility to ensure that the full methods and results of their RCTs are reported and publicly available within a reasonable interval of trial completion.

Current Status and Future Directions

Now that the rationale and methods for robust clinical trials are accepted, their conduct has been discouraged and compromised by increasing rules, regulation, bureaucracy, governance, complexity, and costs. The intention of research regulation and governance – to protect research participants (their safety, tissues, and data) and improve the reliability of the results – is imperative. Further, it is accepted that regulation and governance is an important way of setting and monitoring quality standards. However, approval systems have been complex, rules and regulations have been interpreted and enforced inconsistently, and assessment of studies has not always been proportionate to the risks of the research to participants [85]. Excessive attention to rules, rather than scientific principles, may neither improve patient safety nor study quality [14, 86].

Potential solutions are to simplify, centralize, and harmonize the application process consistently across regulatory bodies and countries, tailor regulatory and governance requirements in proportion to potential harms to the patients, and encourage research centres to network and collaborate in their endeavours to deal professionally and efficiently with regulations and integrate research with clinical practice [85, 87, 88]. The Clinical Trials Transformation Initiative has developed a framework of principles for building quality into the scientific and operational design of clinical trials so that trials are feasible to conduct, participants are safeguarded, important errors are prevented rather than remediated, and results are reliable [89, 90]. Opportunities to improve the quality and efficiency of RCTs also include ensuring trial guidelines are based on scientific principles, accessing established registries and electronic health-care records to recruit a broad range of patients rapidly, and implementing interactive electronic case report forms and digital technologies (e.g., smartphones and telehealth) to facilitate real-time monitoring and improve protocol adherence, completeness of follow-up, and trial quality [14, 91].

Conclusion

The introduction and evolution of evidence-based stroke medicine has realized major advances in our knowledge about stroke, methods of medical research, and outcomes for patients that continue to complement traditional individual patient care. It is humbling to recall the state of knowledge and scientific endeavour of our predecessors who were unaware of what we know now and yet pursued the highest standards for evaluating and delivering effective stroke care. The science of stroke medicine has evolved from pathophysiological theory to empirical testing. Progress has been steady, despite inevitable disappointments and cul-de-sacs, and has occasionally been punctuated by sensational breakthroughs, such as the advent of reperfusion therapies guided by imaging. My account of the evolution of evidence-based stroke medicine is a personal reflection that is far from comprehensive but is in the spirit of celebrating 30 years since the publication of the first issue of *Cerebrovascular Diseases* and the honour of contributing to it [92].

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Conflict of Interest Statement

Prof. Hankey trained in neurology and stroke medicine at the Royal Perth Hospital, Mayo Clinic, and University of Edinburgh. He is a senior advisory board member of *Cerebrovascular Diseases* and a member of the Cochrane Stroke Review Group. He reports personal honoraria outside the submitted work from the American Heart Association (honoraria for serving as the associate editor of *Circulation*), AC Immune (Chair, Data Safety Monitoring Committee, of ACI-24-701 and AC-35-1201 trials of immune therapies for Alzheimer's disease), Bayer (lecturing at sponsored scientific symposia and consulting on advisory boards about stroke prevention in atrial fibrillation), Bristol Myers Squibb (Executive Steering Committee of the now ceased PARFAIT trial of a PAR4 antagonist for acute TIA and minor ischemic stroke), and Medscape (consulting about physician education regarding thrombosis and antithrombotic therapy).

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