The State of Stroke Clinical Research

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Graeme Hankey, MD, The University of Western Australia, Perth, Australia, the 2015 recipient of the David G Sherman Award, gave a historical overview of stroke clinical research and his perspective on future directions in the field.

Many important milestones in stroke treatment and prevention have occurred in the last 25 years (Table 1). A 1988 meta-analysis of 31 randomized antiplatelet trials showed the benefit of antiplatelet therapy in the prevention of subsequent cerebrovascular events. Antiplatelet therapy was the first treatment for stroke, reducing the risk of recurrence by about 25%, noted Prof Hankey.

The results from the ECST trial [ECST Collaborative Group. *Lancet.* 1998] and NASCET trial [Ferguson GG et al. *Stroke.* 1999] of carotid endarterectomy (CEA) were translated into clinical practice immediately, with the number of CEAs rising dramatically. The landmark National Institute of Neurological Disorders and Stroke's (NINDS) tissue plasminogen activator study for acute ischemic stroke demonstrated that intravenous administration with tissue plasminogen activator within 3 hours of stroke onset led to better outcomes [NINDS rt-PA Stroke Study Group. *N Engl J Med*. 1995]. Around the same time, the IST study [International Stroke Trial Collaborative Group. *Lancet*. 1997] showed that aspirin started shortly after ischemic stroke reduced death and disability 6 months later. These 2 trials led clinicians to consider ischemic stroke a medical emergency that needs not only immediate treatment with reperfusion therapy (to reduce case fatality and dependency) but also immediate implementation of secondary prevention (to minimize recurrent stroke).

CAPRIE [CAPRIE Steering Committee. *Lancet.* 1996], ESPS2 [Diener HC et al. *J Neurol Sci.* 1996], and ESPRIT [ESPRIT Study Group. *Lancet.* 2006] provided additional options in secondary prevention of recurrent stroke. The SPARCL trial [SPARCL Investigators. *N Engl J Med*. 2006] was conducted in patients with prior transient ischemic attacks or stroke. Results from this study showed that statins reduced the overall incidence of recurrent strokes. Meta-analyses of blood pressure in stroke trials have demonstrated that every 1 mm Hg reduction in systolic blood pressure is important in reducing the risk of stroke [Rothwell PM et al. *Lancet.* 2011].

More recently, the RE-LY [Connolly SJ et al. *N Engl J Med.* 2009], ROCKET AF [Patel MR et al. *N Engl J Med*. 2011], ARISTOTLE [Granger CB et al. *N Engl J Med.* 2011], and ENGAGE AF-TIMI 48 [Giugliano RP et al. *N Engl J Med.* 2013] trials of new oral anticoagulants have demonstrated that they are at least as effective as warfarin in preventing stroke or systemic embolic events in patients with atrial fibrillation.

The above studies have provided a large body of research for evidence-based stroke treatments, stated Prof Hankey.

However, not all clinical trials have been successful. According to Prof Hankey, >65 unsuccessful randomized clinical trials have been conducted in neuroprotection, enrolling >11 000 patients. Fibrinogen depletion, corticosteroids, food/vitamin supplementation, early percutaneous endoscopic gastrostomy tube feeding, prophylactic antibiotics, lowering blood pressure in acute ischemic stroke, and magnesium in stroke have all yielded negative results. There have also been false positive results in studies of hemodilution, nimodipine, citicoline, and NXY-059. However, it is also possible that trials of anticoagulation in transient ischemic attacks/mild ischemic stroke, early nasogastric tube feeding, normalizing hyperglycemia and body temperature, swallowing therapy, glycerol for brain edema, and methylxanthines were false negatives. These issues have led critics to question both the research methodology and the quality of data, and to call attention to inaccurate results in publications, the selective omission of significant findings, and conflicts of interest in research supported by industry.

Prof Hankey also discussed future opportunities in stroke clinical research. He emphasized the importance of establishing external validity in unstudied populations to determine the generalizability of study findings to other populations with different genomic and risk factor profiles.

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Table 1. Milestones in Evidence-Based Stroke Treatment and Prevention

Acute Treatment	Clinical Trial(s)
Stroke units	SUTC (1997)
Ischemic stroke	
Aspirin	IST (1997)
Thrombolysis and intra-arterial medication	NINDS (1996); MR CLEAN (2015)
Hemicraniectomy	DECIMAL, HAMLET, DESTINY (2009)
Hemorrhagic stroke	
Blood pressure lowering	INTERACT 2 (2013)
Secondary Prevention of Recurrent Stroke	**Clinical Trial(s)**
Atherothromboembolism	
Aspirin	APT (1988)
Carotid endarterectomy	ECST, NASCET (1991)
Clopidogrel	CAPRIE (1996)
Aspirin and extended-release dipyridamole	ESPS2 (1996); ESPRIT (2006)
Statins	LIPID (2000); HPS, SPARCL (2006)
Blood pressure lowering	PROGRESS (2001)
Cardiogenic embolism	
Warfarin	EAFT (1993)
Target-specific oral anticoagulants	RE-LY (2009); ARISTOTLE, ROCKET AF (2011); ENGAGE AF-TIMI 48 (2013)

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Another area identified for improvement is the optimization of translating and implementing important research findings into daily practice.

The efficiency and quality of future research must also be maximized. To do this, clinicians and patients should be consulted when planning research. Relevant, novel study questions should be researched unless the study is replicating an important finding. A review of the relevant evidence should occur to determine the study results' contribution.

The design and statistical analyses of studies should be robust and follow guidelines such as the Consolidated Standards of Reporting Trials guidelines (http://www.consort-statement.org) rather than relying on monitoring later to address and clean up quality concerns. In addition to being valid and reliable, outcome measures need to be patient focused. Bias can be minimized through the use of random and blinded treatment allocation, complete follow-up, and ensuring that personnel assessing outcomes are blinded to treatment assignment. Using multiple centers to optimize patient recruitment and maximize the number of primary outcome events minimizes random error, while building heterogeneity into study designs leads to results that are more generalizable.

Prof Hankey believes that the protocol and statistical analysis plan should be published prior to study conduct. After analyzing the study data, the methods and results should be reported in their entirety so that the study can be reproduced. All study outcome results (not just those chosen post hoc), any negative results, and limitations of the study must be in the publication. Authors should also state what the study adds to current evidence in the literature.

It is also important to share data, protocols, and other materials so that studies can be replicated and externally validated. A collaborative group is far more powerful than working as individuals, emphasized Prof Hankey. Better training of scientists and clinicians in study design, statistical methodology, peer review, and interpretation of research will also benefit the entire research community.