Cerebrovasc Dis 2014;38:174–175
DOI: 10.1159/000365424

Temporal Changes in the External Validity of Clinical Trials: Asymptomatic Carotid Artery Stenosis

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A well-designed clinical trial has internal validity; i.e., it supports or refutes the efficacy of an intervention in a defined patient population using appropriate methodology to avoid bias and other factors that could skew the results [1]. To be useful for clinical decision-making, a trial must also have external validity [2]. The results should be generalizable to similar populations encountered in clinical practice (i.e., effectiveness). A clinical trial may have both internal and external validity when it is conducted, but secular trends may affect the relative risks and benefits of a therapeutic intervention over time.

Randomized clinical trials found that endarterectomy in addition to best medical therapy in subjects with an asymptomatic carotid artery stenosis reduced the risk of ipsilateral stroke, perioperative stroke or death by about 30% (relative risk, RR = 0.71; 95% CI: 0.55–0.90) over a mean of 3.3 years compared to best medical therapy alone [3]. The absolute benefit, however, was small (3% absolute reduction; 33 patients would need to have the operation to prevent 1 event over this period). There was no benefit for the prevention of any stroke or death (RR = 0.92; 95% CI: 0.83–1.02), and evidence of a benefit in women was lacking (RR = 0.96; 95% CI: 0.64–1.44). In addition to having similar rates of perioperative complications (operation-related complication rate <3%), the application of these results to routine practice assumes that patients receiving medical therapy alone have event rates similar to those experienced by the controls in the clinical trials.

In high-income countries, there was a 37% (95% CI: 19–39) reduction in ischemic stroke-related mortality and a 13% (95% CI: 6–18) decrease in ischemic stroke incidence over the 2 decades between 1990 and 2010 [4]. In the USA, stroke mortality declined by approximately 0.5% per year from the turn of the century until the 1970s, when the rate of decline increased nearly 10-fold to about 5% annually, a benefit attributed in large part to improvements in prevention leading to a lower stroke incidence [5]. As shown in figure 1, the largest randomized clinical trials evaluating the efficacy of carotid endarterectomy in the setting of asymptomatic stenosis had completed subject enrollment between 1 and 3 decades ago. If the rates of stroke and death in patients with an asymptom-

atic carotid artery stenosis declined similarly, then the clinical trials of endarterectomy no longer have external validity (i.e., the efficacy found in these trials would no longer translate into similar clinical effectiveness).

Several previous analyses suggested that the rate of stroke in patients with an asymptomatic carotid stenosis treated with medical therapy alone has substantially declined in recent years and may now be about 1% annually or less, a rate near that in the clinical trial surgical groups [6–11]. The rigorous, evidence-based review by Hadar et al. [12] in this issue of *Cerebrovascular Diseases* is consistent with these prior studies, finding that the incidence of ipsilateral territory ischemic stroke in patients with an asymptomatic stenosis has fallen from 2.3 to about 1 event per 100 person-years ($p < 0.001$; 39% reduction per decade between 1978 and 2009).

As with overall stroke-related mortality, the reduction in stroke incidence in patients with an asymptomatic carotid artery stenosis is at least in part due to the more routine use of medical preventive interventions [13]. In addition to lifestyle measures such as smoking cessation, following a healthy diet and having regular exercise, treatment with platelet antiaggregants, antihypertensives and statins likely contributed to the observed reduction in stroke risk [11]. For example, statin treatment is associated with a slowing of progression or improvement of carotid intimal-medial thickness [14], with carotid plaque stabilization [15] and, possibly, with reductions in carotid stenosis [16, 17]. Aside from the use of aspirin, other medical preventive interventions, particularly antihypertensive treatment and statins, were not mandated in the clinical trials of carotid endarterectomy.

Fig. 1. The period of patient enrollment for the Veterans Administration Cooperative Trial (VA) [20], the Asymptomatic Carotid Atherosclerosis Study (ACAS) [21] and the Asymptomatic Carotid Surgery Trials (ACST) [22] are shown with bars, and the years of the primary reports of the trials' results are shown by asterisks.

Observational studies are subject to a variety of potential biases, but if correct, the reductions in the rate of stroke in asymptomatic patients with carotid artery stenosis may obviate any benefit of endarterectomy (or angioplasty/stenting). This presents a conundrum for those writing clinical guidelines, for which data derived from multiple randomized clinical trials provide the highest level of evidence for informing practice recommendations. Based on the data from the several trials of endarterectomy for asymptomatic carotid stenosis, the 2006 American Heart Association Primary Stroke Prevention Guidelines recommended prophylactic endarterectomy in highly selected patients with high-grade asymptomatic carotid stenosis performed by surgeons with a <3% morbidity/mortality rate (class I: 'the intervention should be performed'; level of evidence A) [18]. Reflecting concerns about changing external validity, the recommendation was downgraded to class IIa ('the intervention is reasonable to perform') in the 2011 Guidelines [19]. Whether even this recommendation is still appropriate can only be addressed through additional randomized trials employing contemporary lifestyle and medical interventions. As discussed by Hadar et al. [12], such trials will need to enroll a large number of subjects to avoid a type II error, given the low rate of events anticipated in the control group.

Until additional data become available, the task of the clinician is to convey these complex issues to patients who are discovered to have an asymptomatic stenosis of a carotid artery. Dealing with uncertainty is never easy, especially if a proposed intervention may entail a risk that could outweigh its benefit.

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