Upper age limits for randomized controlled trials for stroke (and other conditions) have been common. Reasons have included historical precedent, risk management by pharmaceutical companies, fears of unacceptable side effects, and practical issues of consent, recruitment, and follow-up. The FAST-MAG trial (Field Administration of Stroke Therapy-Magnesium) was no exception, but the age limit of 95 years provided an opportunity to study the effect of including older people (those aged ≥80 years) in this important trial of prehospital magnesium for stroke. Their results are important and illustrate some important aspects of modern stroke care. First, 29% of the trial population were aged ≥80 years, matching the epidemiology of stroke in developed nations. We cannot continue to exclude one-third of the people with the disease in question. Second, the baseline characteristics illustrate that older people were different from younger people in important clinical variables. They were more likely to be white and female (because of the longevity of this demographic) and had significant differences in risk factors. Fewer smokers (perhaps because of a survival bias of those who do not smoke), fewer diabetics for similar reasons, but also reflecting the increased prevalence of diabetes mellitus and obesity in younger people.

What effect will differences in age have on acute stroke trials? In general, treatment effects rarely change direction with age, that is, a beneficial treatment at younger age is usually beneficial at older age but with some provisos. The relative risk reductions tend to diminish (because of increased noise from inevitable comorbidity) and absolute risks tend to increase (as poor outcome becomes increasingly common), as seen in the response to thrombolysis for myocardial infarction where the absolute benefits are similar between old and young. But myocardial infarction is largely a homogeneous pathology; stroke is far more complicated. Close inspection of the baseline characteristics of the older FAST-MAG participants reveals striking differences in atrial fibrillation (34% versus 12% for old and young, respectively). This will inevitably lead to different stroke subtypes, as cardioembolic stroke, for example, will be more common in the older patient. So we cannot necessarily assume that a stroke treatment will have a similar benefit in younger people and older people because the mix of underlying stroke type (hemorrhage, large artery, small vessel, cardioembolic, and other determined) will be different. Accurate stroke subtyping by anatomic, etiologic, and imaging criteria will be critical to understand acute stroke treatment effects across the age span.

The high rate of thrombolysis treatment for the older patients in FAST-MAG (29%) probably reflects organized stroke care in the recruiting region of the trial and reliable trial data for this age group. As noted by Sanossian et al, few older people were included in the NINDS trial (National Institute of Neurological Disorders and Stroke), and the ECASS trial (European Cooperative Acute Stroke) had an age limit of 80 years. The lack of patients aged >80 years in the early pivotal trials led to an age limit of 80 years for the European license for alteplase. The IST-3 trial (Third International Stroke) was designed to provide new evidence for older people and succeeded in recruiting >1600 patients (more than half of the trial participants) aged >80 years. This was largely because of the trial being based in the United Kingdom (with a tradition of geriatricians providing acute medical care including stroke), inclusion of geriatricians in the research team, and the track record of the IST collaborative group completing large-scale trials with no upper age limit. The subsequent individual patient meta-analysis of alteplase confirmed that thrombolysis was an effective treatment for older people. The endovascular trials narrowly escaped repeating old mistakes with key trials having no upper age limit.

Removal of the upper age limit is merely the start, as the other big issue is frailty. With every medical success, we add to the future queue of the frail elderly. In developed nations, the care of the frail older people has become routine hospital business, but the evidence base is poor. Because chronological age is a poor discriminator of frailty, other measures have been developed, and trialists have started measuring frailty at trial baseline, and this should become as routine as recording other basic demographic characteristics. In the SPRINT trial (Systolic Blood Pressure Intervention Trial) of intensive blood pressure lowering for vascular prevention, a frailty index based on cumulated deficits was generated. The frailty index predicted poor outcomes and thus had internal validity, but frailty (within this selected trial population) did not have the expected interaction with the intensive blood pressure.
lowering.22 Such general frailty indices may be of most importance when dealing with treatments or interventions that could have general effects (or side effects) as in SPRINT. More sensitive measures of frailty for acute stroke may include chronic brain imaging signs, such as brain atrophy, lacunes, and white matter hyperintensities of presumed vascular origin, perivascular spaces, cerebral microbleeds, and previous stroke (infarction or hemorrhage).7,23–25 This, and other examples of the successful use of a frailty instrument in nonstroke medicine,26 will provide the reliable evidence that interventions will be beneficial for older people, whether frail or not.

**Disclosures**

None.

**References**


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http://stroke.ahajournals.org/content/47/11/2679