Stroke is a coronary heart disease risk equivalent: implications for future clinical trials in secondary stroke prevention

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With an estimated 1 million cases per year in Europe, 1.2 million in North America, and 10 millions in the rest of the world, the burden of stroke is enormous. Stroke includes brain haemorrhage, transient ischaemic attacks (TIAs), and cerebral (brain) infarction (each of these causes accounting for approximately 15, 15, and 70% of cases, respectively). Overall, a quarter of all stroke patients has a history of a symptomatic coronary event. These patients are prone to recurrent coronary heart disease (CHD) events. In the PROGRESS trial, in the subset of patients with recent stroke and a history of CHD, the risk of a new CHD event was as high as the risk of a new stroke, but in the remainder of stroke patients without overt CHD, the risk of CHD events or pre-symptomatic CHD has not been well evaluated.

The main modifiable risk factors in stroke patients include hypertension, diabetes, atrial fibrillation, cigarette smoking, hypercholesterolaemia, obesity, physical inactivity, and alcohol consumption. These factors increase the risk for other vascular disease, including CHD, except perhaps atrial fibrillation. As a consequence, stroke is usually part of a global disease. The REACH registry has shown that 40% of 19,000 stroke patients have one or two other locations of vascular disease such as coronary artery disease (CAD) and peripheral arterial disease.

After a stroke/transient ischaemic attack, patients are at high risk of short-term non-fatal stroke and of long-term fatal coronary heart disease

Patients with stroke are at high risk of having another major vascular event such as stroke, myocardial infarction (MI), or vascular death. Observational studies and clinical trials have shown that during the 2 years following a stroke, the next most common event is having another stroke. However, the risk of MI is far from negligible, and the risk of another stroke decreases after 2 years to a level similar to that of patients with asymptomatic carotid disease, whereas the risk of MI increases continuously over time. It has been exemplified in endarterectomy trials. Consequently, the 5 year most common cause of death after a stroke is MI. There are twice as many MI deaths after a stroke as deaths from another stroke.

In 2003, the National Cholesterol Education Program-Adult III (NCEP-III) recommendation recognized stroke of carotid origin and carotid atherosclerosis as 'CHD risk equivalents', because the 10 years risk of CHD in these patients is >20%. This statement pointed out the need for developing strategies and effort to detect and prevent CAD complications in patients with a stroke associated with carotid artery disease. In stroke registries, atherothrombotic disease accounts for 9–20% of all cases of stroke, and the majority are of carotid origin. A carotid stenosis of any degree is observed in up to 45% of patients with stroke.

Recent advances in the neuropathology and epidemiology of stroke as well as data from recent clinical trials have confirmed and strengthened the view of stroke of carotid origin as a CHD risk equivalent and form the purpose of this editorial. They also provided evidence that this should be extended to stroke patients without carotid artery disease or without history of CAD.

Coronary heart disease is highly prevalent at autopsy in patients with stroke/transient ischaemic attack

In the Multiple Atherosclerosis Site in Stroke autopsy study, 75% of 392 patients with fatal stroke had coronary plaques (80% in ischaemic and 68% in haemorrhagic stroke patients), and 40%
had coronary stenosis $>50\%$. Compared with patients who had died from other neurological diseases (such as multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, brain tumours, and degenerative diseases), and after adjustment on age, gender, risk factors, and heart weight, there was a significant 3.7-fold increase in the prevalence of coronary plaques, a 2.6-fold increase in the prevalence of coronary stenoses, and a 2.3-fold increase in the prevalence of MI (two-third being only an autopsy finding). The prevalence of coronary plaques, coronary stenosis, and MI was 79.1, 45.5, and 45.7%, respectively, in the presence of plaques in any segment of extra- and intracranial brain arteries, and was as high as 50.7, 17.4, and 23.2%, respectively, in the absence of brain artery plaques (Figure 1). These data show that the burden of CAD is very high in stroke patients even in the absence of brain artery plaques or known CHD.

### Recent studies confirmed 10-year incidence of coronary heart disease in patients with stroke/transient ischaemic attack is 20%

A meta-analysis of 65,996 individuals with stroke followed a mean of 3.5 years in eight observational population-based cohorts, 25 randomized controlled trials, and six single-centre hospital-based cohorts, found that the risk of MI after a stroke was $\sim2\%$ per year. The time course of risk was linear, therefore 10 years of risk projected to 20%. In the recent REACH registry, 18,957 patients with stroke have been included once stabilized, meaning that most of them were included well after the first 6 months following the qualifying stroke event. According to either the absence of other vascular beds involved, association with CAD, or with both CAD and peripheral arterial disease, the 1 year risk of non-fatal MI and vascular death was 1.9, 3.6, and 5.4%, respectively. Therefore, even in the group with no known CAD or peripheral arterial disease, the risk projected at 10 years (since it is known to be linear) is close to 20%. In the Northern Manhattan population-based epidemiological study (NOMAS study) the risk at 6 months, 1 year, and 5 years in patients with a first ever stroke have been recently reported. The 5 year risk of MI was 9.8%, which is in keeping with CHD-risk equivalence.

### Secondary prevention trials should not only focus on the first 2–3 years

Because the next most common event within 3 years after a stroke is having another stroke, most of the recently published or ongoing clinical trials in secondary prevention of stroke focused, by design, on the prevention of recurrent stroke as primary end-point. This puts an emphasis on outcomes during the next 5 years, but may have led to the wrong perception that MI is not an important event, or trial end-point, after a stroke. Because many studies have relatively short follow-up, of $<3$ years, they likely did not capture late events, such as the continuously increasing 10 year risk of MI. For example, in the ESPRIT and ESPS-2 trials, the risk of stroke was significantly reduced by 23% with the treatment with combination of low-dose aspirin/dipyridamole, but there were no clear evidence that the agent tested had an effect on the 5–10 year risk of CHD. None of the major antiplatelet trials could show a significant reduction in major coronary events (MACE) in patients with stroke likely because they did not accrue enough MACE. This was likely because these trials lasted only 18–36 months and were not powered enough to capture the CHD risk in stroke patients.

### Two long-term (4–5 years) secondary prevention trials showed reduction in coronary heart disease events

Antihypertensive trials in patients with stroke, such as PROGRESS which lasted for 4 years, could show a benefit on MACE reduction [118 vs. 158 fatal or non-fatal MACE, 0.74 (0.58–0.94)]. In the SPARCL trial, performed in patients with recent (≤6 months) stroke or TIA, the 5 year risk of any CHD event was 10% in the placebo group and was reduced by 42% (27–54%) in the atorvastatin 80 mg/day group. Since patients with a past history of CAD were excluded from SPARCL for ethical reasons, this trial demonstrated that stroke with no known CHD is a CHD risk equivalent and that this risk can be substantially reduced by atorvastatin therapy.

Stroke/TIA patients are at high long-term risk of major coronary events. Future secondary stroke prevention trials should assess that the drug under investigation not only reduces the risk of having another stroke, but also reduces the risk of MACE. This is important when comparing therapeutic strategies after stroke.

**Conflict of interest:** none declared.
References


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