Stroke in the patient with coronary heart disease

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Abstract

Coronary heart disease (CHD) and stroke frequently coexist, partly because they share many risk factors. After myocardial infarction (MI), there is a significant risk of mural thrombus formation, left ventricular aneurysm, impaired left ventricular function and atrial fibrillation; all these increase the risk of stroke. The risk of neurological deficit after cardiac surgery is higher in those patients who have already had a stroke. Cognitive decline after cardiac surgery is common: it may follow a pattern of early improvement but later decline. Lipid-lowering therapy has been shown to reduce non-fatal stroke in patients at risk of developing or with coronary artery disease. Clopidogrel with aspirin may be of benefit in patients with unstable angina and non-ST elevation MI. Antihypertensive treatment and stopping smoking are helpful. The HOPE trial results showed a powerful and preventative role for ACE inhibitors.

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Key words: stroke, coronary heart disease, cardiac surgery, risk factors, cognitive decline.

Introduction

Coronary heart disease (CHD) and stroke are two of the most common causes of mortality and morbidity in developed countries. Many risk factors are shared, hence CHD and stroke frequently coexist. Ischaemic stroke has a cardiac basis in approximately one third of cases. In many instances there may be more than one potential cause for stroke, for example the patient may have both atrial fibrillation and carotid artery disease. More than 20% of patients with a recent transient ischaemic attack (TIA) and ipsilateral carotid artery disease also have a potential cardiac source of embolus.[1]

Coronary artery disease may be silent and will not have been previously diagnosed in many patients with stroke, purely by virtue of its frequency in the older population. Patients with overt coronary artery disease and patients at significant risk of its development should be receiving appropriate risk factor assessment and modification. In many instances, this would reduce the risk of stroke in addition to its effects on the heart (see below).

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Predisposing factors in the coronary heart disease patient

There are several important cardiac lesions that may predispose to stroke, although some of them – for example, valvular heart disease and endocarditis – are not specific to the patient with coronary heart disease. The consequences of coronary artery disease, such as impaired left ventricular function and rhythm disturbance, increase stroke risk further. Moreover, standard treatments for coronary heart disease, as in coronary artery bypass surgery and thrombolysis for acute myocardial infarction, may give rise to stroke. Increasingly aggressive thrombolytic and antiplatelet regimes, developed in an attempt to improve further coronary artery patency rates for the treatment of acute coronary syndromes, have to be balanced against any increased risk of stroke from the treatment itself.

Post-myocardial infarction

Following myocardial infarction (MI), there is a significant risk of mural thrombus formation,[2] which predisposes to cardioembolic stroke. The incidence is highest in extensive Q-wave anterior infarcts. Current treatment strategies, encompassing aggressive thrombolysis and early initiation of ACE inhibitors to prevent and reduce left ventricular (LV) dysfunction, have reduced the inci-

dence of mural thrombosis. Echocardiographic evaluation of post-MI patients in the GISSI-3 study revealed LV thrombus in 5.1% patients overall.[3] Thrombus was detected in 11.5% of patients with anterior infarcts, compared with 2.3% of patients with infarcts elsewhere. If LV thrombus is left untreated, neurological symptoms may develop in up to 15% of patients.[4] A meta-analysis revealed an odds ratio of 5.5 for embolism following LV thrombus formation detected echocardiographically.[5] Formal anticoagulation markedly lowers this risk and is generally given for up to six months, hence covering the first three to four months when the risk of embolic stroke is highest.

Left ventricular aneurysm

Development of a left ventricular aneurysm following MI is a risk factor for stroke since aneurysms frequently contain thrombus. Effective thrombolytic and ACE inhibitor therapy has halved the incidence of post-MI aneurysm formation. Formal anticoagulation effectively reduces the risk of embolism, at least in the early stages.[6] With time, persistent thrombus organises and stabilises, so the risk of embolism falls.

Impaired left ventricular function

Although stroke is generally an early complication of myocardial infarction, impaired left ventricular function post-MI is an additional risk factor for subsequent stroke (figure 1); the risk increases as left ventricular ejection fraction (LVEF) falls.[7] In an observational study of 2,231 patients with left ventricular dysfunction post-MI who were enrolled in the SAVE trial, Loh *et al.* found a 4.6% stroke rate during a mean of 42 months follow-up. The estimated five year stroke rate was 8.1%, and some 96% of cases were due to ischaemic infarction. The greatest predictor of stroke was LVEF: for every decrease of five percentage points in the ejection fraction, there was an 18% increase in the risk of stroke. There was an 81% reduction in the risk of stroke with anticoagulation, emphasising the benefit of formal anticoagulation in these patients.

Atrial fibrillation

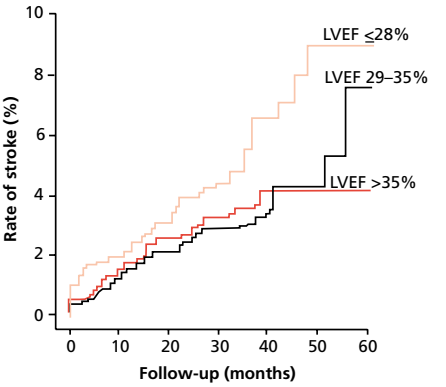
Atrial fibrillation is a well-recognised risk factor for cardiac embolism. Atrial arrhythmias, of which atrial fibrillation is the most common, occur in up to 20% of acute infarcts, typically within the first 72 hours. Acute MI patients in GUSTO-1 who were in atrial fibrillation at the time of randomisation had an increased in-hospital ischaemic stroke rate of 1.8%, compared to a 0.5% rate in patients who were not in atrial fibrillation.[8]

Persistent atrial fibrillation, for example in the cardiac patient with impaired left ventricular function and secondary mitral regurgitation, is an important risk factor for stroke. Increasing atrial size, spontaneous contrast and low left atrial appendage peak flow velocity identify high-risk patients.[9] Atrial fibrillation develops commonly after cardiac surgery and may contribute to the incidence of peri-operative stroke.[10]

Atherosclerotic disease of the aortic arch

Coronary artery disease is frequently associated with other vascular disease, such as peripheral vascular disease and carotid artery disease, which may be clearly obvious through symptoms and signs. Disease of the thoracic aorta has received less attention, partly because it is less frequently imaged and partly because the link with symptoms and signs is less easily made. Atherosclerotic disease of the aortic arch is an important predisposing factor for stroke, especially when there are ulcerated plaques or plaques $\geq$ 4 mm thick.[11] The same study also showed that plaques $\geq$ 4 mm thick identified patients at increased risk of any vascular event (not just stroke), including myocardial infarction and sudden death.

Figure 1. Cumulative rate of stroke in the SAVE trial according to the left ventricular ejection fraction (LVEF)



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Neurological complications from coronary artery bypass surgery

Neurological complications following cardiac surgery account for a significant proportion of peri-operative morbidity and mortality. Patients often fear these complications more than the risk of peri-operative infarction, or even cardiac death. A major stroke is readily identified but more subtle alterations of cognitive function, which occur frequently, are often missed by the clinician and are rarely diagnosed outside the context of a clinical trial.

The incidence of stroke following cardiac surgery ranges from < 1 to 6% of patients.[12] Risk factors include older age, previous stroke or pre-existing cerebrovascular disease, atherosclerotic disease of the aorta or carotid arteries, peripheral vascular disease, hypertension, diabetes and atrial fibrillation. The risk is greater in patients undergoing heart valve (open chamber) surgery than in patients having coronary artery bypass grafting (closed chamber surgery).[13] Intra-operative stroke in cardiac surgery results from either hypotension and hypoperfusion or from embolism. Air embolism, for example from cannulation sites, or embolism from aortic debris at the time of aortic cross-clamping and release, can be readily detected using transcranial Doppler monitoring of the middle cerebral artery. Retinal artery embolism occurs frequently but clinically important abnormalities of vision

are, fortunately, rare. Importantly, the mortality from stroke post-CABG is high (~20%), compared with a 2–4% mortality for all CABG patients.[14]

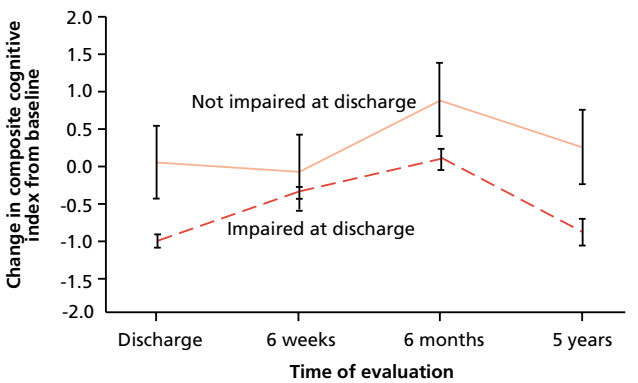
The risk of neurological deficit after cardiac surgery is higher in patients who have already had a stroke. In one prospective study of 1,000 patients undergoing cardiac surgery, 7.1% patients had had a stroke.[15] In this group there was a significantly higher incidence of focal deficit after bypass, including a new stroke in 8.5%, re-emergence of a previous deficit in 26.8% and worsening of previous deficits in 8.5%. Of note, the last two presentations were not associated with new abnormalities on imaging of the brain. One-month mortality was far higher in patients with prior stroke (7%) than in those without prior stroke (0.7%).

Recent stroke is an important risk factor for further stroke after cardiac surgery. Consequently, surgery on the heart should be deferred for several months where possible to reduce the risk of further stroke.

Cognitive decline has increasingly been recognised following cardiac surgery – it is thought to be due to cerebral emboli and alterations in cerebral blood flow. Despite improvements in anaesthetic, surgical and bypass techniques, the incidence of cognitive decline after surgery has changed little in the last two decades. However, the prevalence may increase since elderly patients, who are at greater risk of developing cognitive defects, are more frequently being offered cardiac surgery relatively late in life.

Persistent cognitive defects, including disturbances of memory and attention, occur in 20–40% of patients following cardiac surgery.[16] Transient defects occur in up to 60–80% of patients and generally improve with time. However, recent work suggests that the improvement seen in the early months after surgery may itself be transient, and may be followed by a deterioration in cognitive function. Newman *et al* studied 261 patients undergoing CABG and showed that 53% had cognitive decline at discharge.[17] At six weeks 36% had decline, falling to 24% at six months but rising later to 42% at five years (figure 2). The pattern of early improvement followed by later decline was best predicted by the presence of early post-operative cognitive decline at the time of discharge. Whether this later decline is linked to events at the time of surgery or simply reflects an older population with an inherently higher risk of cognitive decline is unknown.

Figure 2. Composite cognitive index as a function of cognitive impairment at discharge



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Coexisting carotid artery disease

Coexisting carotid artery disease, which is not uncommon in patients with coronary artery disease, increases the risk of perioperative stroke. Significant bilateral carotid disease increases the risk to about 20%. Some centres advocate simultaneous carotid endarterectomy and coronary artery bypass grafting.[18] Others recommend a staged procedure, with the more severely diseased carotid artery operated upon first. The severity of the carotid artery disease and whether or not ipsilateral stroke has previously occurred should be considered but there are no randomised trials to guide our strategy. The role of carotid artery stenting in this situation is unknown. Pre-operative carotid Duplex imaging should be undertaken in all cardiac patients with a carotid bruit (although this is an unreliable sign), in patients with a previous stroke or TIA, and ideally in patients with peripheral vascular disease. Minimally invasive and off-pump surgery offer the prospect of fewer neurological sequelae.

The association between stroke and coronary artery disease was shown again in a recent prospective study of carotid artery ultrasonography and the subsequent risk of MI or stroke.[19] O'Leary *et al* examined the common and internal carotid arteries of 5,858 subjects, aged > 65 years and without known cardiovascular disease, using high resolution ultrasonography with clinical follow-up over a median period of 6.2 years. The relative risk of MI or stroke increased significantly with increasing intima-media thickness, even after adjustment for traditional risk factors.

Risk of cardiac events in atypical TIA

Some symptoms do not totally fit the criteria for a neurological event. In a prospective study of 572 such patients compared with typical TIA or stroke patients, the hazard ratio for stroke was 0.6 (5.6% *vs.* 9.4%) whereas the hazard ratio for a major cardiac event was 1.4 (8.4% *vs.* 5.9%).[20] The differences could not be explained by differences in baseline cardiovascular risk factors. The authors hypothesise that brief symptoms, such as dizziness and giddiness, may be due to cardiac arrhythmias and postural hypotension.

The effects of treating coronary risk factors on stroke incidence

Lipid-lowering agents

In contrast to coronary artery disease, there is no direct link between an adverse cholesterol profile and stroke risk. Part of the explanation is that, unlike coronary heart disease, not all strokes are due to atheroma. Recent large-scale trials of lipid-lowering therapy in patients at risk of developing or with overt coronary artery disease, however, have demonstrated a reduction in non-fatal stroke with treatment. In the 4S secondary pre-

vention trial, lipid lowering reduced the risk of non-embolic stroke and TIA by 37%.[21] Progression of carotid wall thickening, a predictor of stroke, in asymptomatic patients and in patients with coronary artery disease is slowed when plasma low-density lipoprotein (LDL) concentrations are reduced by 25% or more.[22] There has been concern that low cholesterol levels may be associated with haemorrhagic stroke, but the recent LIPID secondary prevention trial of pravastatin in patients with myocardial infarction or unstable angina[23] showed no significant effect on the incidence of haemorrhagic stroke.

All patients below the age of 75 who are recovering from a stroke, with carotid atheroma as the cause or with known coronary artery disease, should be considered for statin treatment. There are inadequate data to guide management in older patients.

Preliminary findings have been reported from the Heart Protection Study (HPS)[24] showing treatment with simvastatin was associated with a significant reduction in the incidence of stroke in patients who were at high risk of vascular events. No adverse effect on the development of haemorrhagic stroke was observed in the study.

Antiplatelet agents

The effectiveness of aspirin in stroke prevention has been recognised since the 1970s. Aspirin, which is the most widely tested antiplatelet drug, reduces vascular events (vascular death, non-fatal stroke and non-fatal myocardial infarction) in doses from 75 mg to 325 mg/day. There is no convincing evidence that higher doses are more effective, although side-effects are inevitably more common.[25] Clopidogrel is at least as effective as aspirin for the prevention of ischaemic stroke, myocardial infarction and vascular death in patients with recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral vascular disease.[26] The side effect profile is similar to aspirin but it is a more costly drug.

The latest data from the CURE study[27] indicated that treatment with clopidogrel, in addition to aspirin, in patients with unstable angina and non-ST elevation MI reduced the risk of death, non-fatal MI and stroke by > 20% (median follow-up nine months). The benefit was seen in all prespecified subgroups tested, opening up a new and effective therapeutic strategy in this large group of patients.

Antihypertensive therapy

The benefit from lowering blood pressure is significantly greater for the prevention of stroke than for coronary artery disease. The size of the benefit was convincingly shown in the North Karelia and Kuopio provinces of Finland[28] where, over a 20 year period, stroke mortality fell by 66% in men and by 60% in women, primarily due to reductions in diastolic blood pressure and smoking.

The PROGRESS trial (see editorial pages 131–4) has shown that treatment with a combination of perindopril and indapamide prevents stroke recurrence even in patients without high blood pressure. This was shown after a four-year follow-up where the incidence of stroke recurrence was reduced by 28% in the drug treatment group versus the placebo group.

Table 1. The effect of ramipril on outcome (myocardial infarction, stroke and death) during the five year follow-up period in the HOPE study

Outcome	Ramipril (n=4,645)	Placebo (n=4,652)	Relative risk (95% CI)	p value
Myocardial infarction, stroke or death from cardiovascular causes	651 (14.0%)	826 (17.8%)	0.78 (0.70–0.86)	<0.001
Death from cardiovascular causes	282 (6.1%)	377 (8.1%)	0.74 (0.64–0.87)	<0.001
Myocardial infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70–0.90)	<0.001
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56–0.84)	<0.001
Death from non-cardiovascular causes	200 (4.3%)	192 (4.1%)	1.03 (0.85–1.26)	0.74
Death from any cause	482 (10.4%)	569 (12.2%)	0.84 (0.75–0.95)	0.005

Key: CI = confidence interval

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Similarly, non-fatal myocardial infarction was reduced by 38% with antihypertensive treatment.

Stopping smoking

Although there are no randomised trials to guide us, observational studies suggest that smoking increases the risk of stroke and TIA by at least 50%.[29] The risk of stroke rises with the number of cigarettes smoked. The increased risk is rapidly reversible with the risk of stroke falling to that of non-smokers within five years of quitting; the risk of coronary heart disease falls similarly.[30]

Angiotensin-converting enzyme (ACE) inhibitors

The recently published HOPE trial has shown a powerful and preventative role for ACE inhibitors, irrespective of left ventricular function.[31] Patients with evidence of coronary artery disease, stroke or peripheral vascular disease, and patients with diabetes mellitus and at least one other vascular risk factor were randomised to treatment with ramipril 10 mg/day or placebo. The trial was terminated early because of the difference in outcome between the two treatment arms (table 1). Treatment with ramipril was associated with a risk reduction of 25% for cardiovascular death, 20% for myocardial infarction and 32% for stroke. The reduction in overall events was greater than could be expected from the reduction in blood pressure, suggesting another mechanism of action by the ACE inhibitor.

Summary

The patient with coronary heart disease has a significant risk of stroke, partly by virtue of several risk factors common to both conditions, but also as a consequence of the disease process

Key messages

- Coronary heart disease and stroke frequently coexist
- The consequences of coronary artery disease, such as impaired left ventricular function and rhythm disturbance, increase stroke risk further
- Neurological complications after cardiac surgery account for much morbidity and mortality
- The risk of stroke is increased as a complication of therapeutic interventions such as thrombolysis

itself (eg. the development of atrial fibrillation following acute myocardial infarction) and as a complication of therapeutic intervention (eg. following thrombolysis or as a result of bypass surgery). Closer working links between cardiologists and neurologists can only enhance delivery of care to cardiac patients.

Editors' note

This is the ninth article in our stroke series. Previous articles are:

- Cerebrovascular disease (editorial) (*Br J Cardiol* 2001;**8**:482)
- The epidemiology of stroke (*Br J Cardiol* 2001;**8**:507-13)
- The pathophysiology of stroke (*Br J Cardiol* 2001;**8**:586-9)
- Acute management of stroke (*Br J Cardiol* 2001;**8**:654-7)
- Prevention of vascular disease following acute ischaemic stroke (*Br J Cardiol* 2001;**8**:704-11)
- Stroke rehabilitation (*Br J Cardiol* 2002;**9**:23-30)
- Prognosis, outcome and recurrence of stroke (*Br J Cardiol* 2002;**9**:103-5)
- PROGRESS in the secondary prevention of stroke (*Br J Cardiol* 2002;**9**:131-4)

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