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REVIEW ARTICLE

Carotid Artery Disease and Stroke During Coronary Artery Bypass: a Critical Review of the Literature

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Objectives: *to determine the role of carotid artery disease in the pathophysiology of stroke after coronary artery bypass (CABG).*
Design: *systematic review of the literature.*
Results: *the risk of stroke after CABG was 2% and remained unchanged between 1970–2000. Two-thirds occurred after day 1 and 23% died. 91% of screened CABG patients had no significant carotid disease and had a <2% risk of peri-operative stroke. Stroke risk increased to 3% in predominantly asymptomatic patients with a unilateral 50–99% stenosis, 5% in those with bilateral 50–99% stenoses and 7–11% in patients with carotid occlusion. Significant predictive factors for post-CABG stroke included; (i) carotid bruit (OR 3.6, 95% CI 2.8–4.6), (ii) prior stroke/TIA (OR 3.6, 95% CI 2.7–4.9) and (iii) severe carotid stenosis/occlusion (OR 4.3, 95% CI 3.2–5.7). However, the systematic review indicated that 50% of stroke sufferers did not have significant carotid disease and 60% of territorial infarctions on CT scan/autopsy could not be attributed to carotid disease alone.*
Conclusions: *carotid disease is an important aetiological factor in the pathophysiology of post-CABG stroke. However, even assuming that prophylactic carotid endarterectomy carried no additional risk, it could only ever prevent about 40–50% of procedural strokes.*

Key Words: Stroke; Coronary bypass; Carotid artery disease.

Introduction

Despite being a proven treatment for ischaemic heart disease,[1] stroke remains a major cause of morbidity and mortality after coronary artery bypass (CABG). Extracranial carotid disease has been implicated in the aetiology of post-CABG stroke and vascular surgeons are increasingly asked to consider staged or synchronous carotid endarterectomy (CEA) in patients with carotid and coronary artery disease. Because there are no conclusive data to determine whether either strategy is appropriate, there remains unease regarding advice to give patients and colleagues alike. The purpose of this review is to provide as much information as possible regarding the prevalence, timing, fatality and patho-physiology of post-CABG stroke, with particular emphasis on the role of carotid artery disease.

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Materials and Methods

A literature review was undertaken as to the role of carotid artery disease in the aetiology of stroke following coronary artery bypass. Studies were identified by manual journal reviews (*European Journal of Vascular and Endovascular Surgery*, *Journal of Vascular Surgery*, *Stroke*, *Annals of Thoracic Surgery*, *Journal of Thoracic and Cardiothoracic Surgery*), cross-referencing and an electronic PUBMED search using the advanced search option. Search terms included "carotid artery", "stroke", "coronary artery bypass" and "ultrasound". Studies were included if published in English language journals between 1970–2000 and provided information regarding; (i) prevalence of stroke within 30 days of CABG, (ii) timing and fatality of post-CABG stroke, (iii) the relationship between carotid bruit and neurological status in predicting peri-operative stroke risk, (iv) Duplex ultrasound and CT scan/autopsy findings in patients suffering post-CABG stroke, (v) the distribution of carotid disease in CABG patients and (vi) the risk of stroke ipsilateral to a carotid stenosis in CABG patients. Series documenting stroke after valve

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Table 1. Risk of stroke following coronary artery bypass.

Parameter	No of studies	CVA/CABGs*	Risk (95% CI)†	Heterogeneity
Overall	59	3259/190 449	1.7% (1.5–1.9)	$\chi^2=657$, df=58, $p<0.0001$
Prospective	33	2122/106 211	2.0% (1.7–2.3)	$\chi^2=312$, df=32, $p<0.0001$
Retrospective	26	1137/84 238	1.7% (1.1–1.6)	$\chi^2=223$, df=25, $p<0.0001$
1971–1985	18	666/45 486	1.5% (1.2–1.7)	$\chi^2=93$, df=17, $p<0.0001$
1986–2000	41	2593/144 963	1.8% (1.5–2.0)	$\chi^2=534$, df=40, $p<0.0001$

* Number of strokes during CABG.
† Overall risk +95% confidence intervals.

replacement were excluded as were repeat studies from individual centres unless the study periods did not overlap.

A statistician (ZM) performed all statistical analyses. The risks of stroke were combined across studies allowing for extra-binomial variation to account for the heterogeneity of risk.[2] Overall risks with 95% confidence intervals (95% CI) were calculated. The odds ratio from different studies were pooled using the Mantel–Haenzel method and 95% confidence intervals (95% CI) determined.[3] Differences between studies for stroke risk were measured using the standard chi-squared or Fisher's Exact Test. Where necessary, smaller studies were combined to make statistical analysis valid. Heterogeneity between odds ratios in different studies was evaluated using a chi squared test.[4]

Incidence of stroke following CABG

Establishing the true incidence was confounded by; (i) study type (retrospective, prospective), (ii) date of publication and hence the effect of changes in surgical, anaesthetic and ITU practice (iii) the changing patient population (recent studies have older and more high risk patients and those unsuitable for coronary angioplasty), (iv) heterogeneous definitions of operative stroke (focal versus non-focal symptoms, deficits lasting >24 h, deficits persisting at seven days, permanent versus transient, in-hospital versus 30 day) and (vi) the type of assessor (neurologist, physician, anaesthetist or surgeon).

Not withstanding these limitations, Table 1 summarises the incidence of stroke after CABG.[5–63] For the purposes of this study, the definition of stroke included patients with unilateral or bilateral hemispheric events lasting more than 24 h and/or coma within 30 days of operation, but not those with post-operative confusional states. It is accepted that an indeterminate number of the latter may have also suffered a stroke. The risk of stroke following 190 449 CABGs was 1.71% (95% CI 1.5–1.9). The incidence was significantly higher in prospective[5–37] as opposed to retrospective[38–63] studies (2.0% (95% CI 1.7–2.3) versus 1.4% (95% CI 1.1–1.6), $p<0.0001$). There was no evidence that the risk of stroke had changed over the last three decades. The risk of stroke in 144 963 patients undergoing CABG between 1986–2000 was 1.79% (95% CI 1.54–2.04) versus 1.46% (95% CI 1.2–1.7), $p=0.076$) in 45 486 patients undergoing CABG between 1970–1985.

Stroke risk increased with age. For those <50 years the risk was <0.5%,[10,15,39,51] increasing to 1–1.5% for patients aged 50–60,[7,10,15,29,39,52] 2–3% for those aged 60–70,[7,10,15,29,35,39,51] 4–7% for those aged 70–80[7,10,15,39,51] and 8–9% for those over 80 years of age.[5,7,10,14,15,51,64] The association with age is important as the proportion of patients undergoing CABG aged >70 years has increased significantly over the last decade.[65] However, age is a confounding variable because of its association with an increasing incidence of carotid and aortic arch disease.

Timing of operation related stroke

Most authors defined intra-operative stroke as being apparent following attempts to wean the patient from the ventilator. Others included any stroke occurring within the first 24 h. Both, of course, will include an unknown proportion of patients with immediate post-operative rather than true intra-operative events but this cannot, currently, be avoided. For the purposes of this review, an operative stroke was defined as being "early" if it occurred within 24 h of completion of the procedure and "late" if it occurred any time thereafter (up to 30 days).

Thirteen series documented the timing of 484 strokes following 36 797 CABGs.[7,16,26,37,38,40,45–48,50,53,57] A relative minority (38.3% (95% CI 30.3–46.3) occurred <24 h of surgery. The majority 61.7% (95% CI 53.7–69.7) happened sometime in the post-operative period, usually the first seven days. This suggests that the majority of strokes can not simply be ascribed to an adverse intra-operative event (low flow, hypotension and carotid embolism).

Mortality of operative stroke

The lack of standardised criteria for defining stroke severity (e.g. the Rankin Classification or the Oxfordshire Handicap Score[65,66]) precluded interpretation of disabling as opposed to non-disabling stroke after CABG. Although some authors differentiated between permanent/transient strokes or major versus minor events, the heterogeneity of definitions did not permit valid statistical analysis. Only 26 series documented the mortality associated with operation related stroke.[5,6,8,10,11,15,17,18,19,24,26,28,32,35,37,39,40,45–48,50,53,54,56,67] The overall case fatality following post-CABG stroke was 23.1% (95%CI 19.5–26.7).

Aetiology of post-CABG stroke

Following CEA, it is possible to determine the likely cause of any operation related stroke.[68] Intra-operative stroke (apparent upon recovery from anaesthesia) follows embolisation of luminal thrombus or haemodynamic failure during carotid clamping.[68,69] Post-operative stroke follows endarterectomy site thromboembolism, intracranial haemorrhage or the hyperperfusion syndrome. Once the principal causes are known, steps can be taken to prevent them.[68]

Similar analyses have not been possible following CABG. Although the onset of post-operative stroke is usually easy to diagnose, there are no monitoring or quality control techniques for reliably diagnosing stroke during CABG. Second, the potential causes of stroke after CABG are much greater than following CEA alone and a number of CABG patients remain ventilated for up to 12 h after the procedure. Confusional states are not uncommon following recovery from anaesthesia and may be difficult to interpret. Most importantly, few patients suffering a stroke after CABG undergo the sort of investigation that would normally follow stroke after CEA (CT scan/autopsy, extracranial Duplex assessment, transcranial Doppler evaluation, neurological assessment) in order to determine the likeliest cause and most appropriate management.

Univariate analyses have identified numerous factors associated with an increased risk of stroke after CABG including; age, prior stroke/TIA, prolonged cardiopulmonary bypass, aortic arch disease, carotid artery disease, peripheral vascular disease, the use of alpha adrenergic drugs, previous carotid endarterectomy, the presence of a carotid bruit, recent myocardial infarction, left mainstem coronary artery disease, redo cardiac surgery, diabetes, smoking, ventricular thrombus, hypotension, pre-operative hypertension, pulmonary disease, post-infarction angina, cardiac failure, diuretic use and impaired renal function. The heterogeneity of these factors suggests that the causes of post-CABG stroke are multi-factorial and inter-linked. For example, increasing age is a risk factor for cardiac disease, pre-existing cerebrovascular disease, carotid stenosis and aortic arch atheroma. A history of recent myocardial infarction or cardiac failure will predispose towards an increased risk of arrhythmia, hypotension, mural thrombus, cardiac embolisation and prolonged cardiopulmonary bypass.

Much of the debate regarding the aetiology and prevention of operative stroke has focussed on the relevance of carotid artery disease. However, as is often the case with controversial issues, personal interpretation of the data tends to be "selective" and clinical practice tends to reflect a combination of personal dogma and training experience. In order to evaluate the principal issues objectively, the next sections will analyse the evidence regarding the relationship between stroke and pre-operative neurological status, the patterns of carotid disease in patients suffering a stroke after CABG, the findings at CT scan or autopsy and its ability to predict the likely cause of stroke and the frequency and associated peri-operative stroke risk of severe carotid artery disease in patients undergoing CABG.

Pre-operative neurological status

The prevalence of carotid bruit in 18 175 patients undergoing CABG was 9.93% (95% CI 7.85–12.01). The risk of operative stroke in patients with a bruit was 5.6% (95% CI 3.7–7.5) compared to 1.6% (95% CI 1.1–2.2) in those with no bruit. This equates to an almost fourfold excess risk (Odds Ratio 3.6 (95% CI 2.8–4.6) $p<0.0001$). However, most studies demonstrating a positive correlation between bruit and post-CABG stroke failed to document whether the stroke was ipsilateral to the bruit. Second, we have no way of knowing, although it was frequently implied, that the most likely explanation was a co-association with underlying carotid disease. This was not simultaneously evaluated in the majority of studies. The simplest explanation may be that a carotid bruit is an important marker for advanced vascular disease generally and carotid and aortic arch disease in particular. Katz has shown that a carotid bruit was the only significant pre-operative predictor for severe aortic arch atheroma.[72]

Table 2. Prevalence of preceding stroke/TIA and its association with stroke risk after CABG.

Reference	No with Preceding TIA/CVA	Peri-operative stroke risk	
		Preceding TIA/CVA	Neurologically asymptomatic
Tuman[5]	88/2000	9/88	47/1912
Berens[9]	138/1087	7/138	30/949
Roach[10]	175/2108	18/175	48.1933
D'Agostino[15]	171/1835	17/171	28/1664
Salasidis[19]	28/387	0/28	24/387
Taylor[26]	11/453	4/11	7/442
Martin[48]	36.1669	0/36	13/1633
Adebo[95]	4/400	2/14	2/348
Overall risk	6.8%	8.5%	2.2%
95% CI	4.3–9.2%	4.9–12.0%	1.9–3.1%
Heterogeneity	<0.0001	0.2191	<0.0001

Table 3. Patterns of carotid disease in 111 patients with operative stroke.

Reference	Bilateral <50% stenosis	Unilateral 50–99% stenosis	Bilateral 50–99% stenosis	Occln + <50% stenosis	Occln + >50% stenosis	Bilateral carotid occlusions
Mickleborough[6]	0	1	0	2	3	1
Barmes[11]	2	1	2	0	0	0
D'Agostino[15]	24	10	8	1	2	0
Schwartz[17]	7	1	3	1	0	0
Hirotani[35]	8	3	5	0	0	0
Hise[47]	2	0	1	2	0	0
Dashe[54]	7	5	3	2	0	0
Gerraty[78]	2	0	0	0	0	0
Safa[79]	0	1	0	0	0	0
Breslau[80]	1	0	0	0	0	0
Total	53 (48%)	22 (20%)	22 (20%)	8 (7%)	5 (4%)	1 (1%)

Overall, 6.8% (95% CI 4.3–9.2) of CABG patients reported a prior stroke or TIA. Nine series compared the stroke risk in 7187 neurologically asymptomatic patients with 665 patients describing a history of TIA or stroke (Table 2). The risk of peri-operative stroke in patients with a prior stroke/TIA was 8.5% (95% CI 4.9–12.1) as compared to 2.2% (95% CI 1.4–3.1) in neurologically asymptomatic patients. This represents a near fourfold excess risk of peri-operative stroke (Odds Ratio 3.6, 95% CI 2.7–4.9, $p<0.0001$).

This relationship persisted when patients with a history of TIA or stroke were differentiated. Patients presenting with a prior TIA were significantly more likely to suffer an operation related stroke than those who were neurologically asymptomatic (Odds Ratio 3.35, 95% CI 2.38–4.71, $p<0.0001$). CABG patients who described a history of stroke were significantly more likely to suffer a further stroke than those who were either neurologically asymptomatic or had previously suffered a TIA (Odds Ratio 3.6, 95% CI 3.0–4.3, $p<0.0001$. Two other studies suggested that patients with a history of stroke had a 13–44% risk of further stroke after surgery.[75,76] These were not included in table 3 because the authors either failed to include the remaining patients in the series for comparison or compared stroke risk with independently selected controls.

Neurological status is clearly an important predictor for stroke after CABG. These findings could mean that symptomatic patients (who are more likely to have intracranial disease, hypertension, diabetes, pre-existing areas of infarction and/or a compromised ischaemic penumbra at the time of CABG) are more vulnerable to falls in cerebral perfusion pressure during cardiopulmonary bypass or particulate emboli from the aortic arch or carotid arteries. As has been observed in patients undergoing discrete CEA, the margin for technical error in these high risk patients may be reduced or non-existent.[77]

Carotid disease in patients suffering an operative stroke

Ten series (Table 3) documented patterns of carotid disease in 111 patients suffering a post-CABG

Table 4. Patterns of carotid disease in CABG patients with:
(a) Unilateral post-operative carotid infarction on CT/autopsy.

Reference	Ipsilateral 0–50% stenosis	Ipsilateral 50–99% stenosis	Ipsilateral occlusion
Mickleborough	0	1	3
D'Agostino[15]	9	7	1
Schwartz[17]	2	4	1
Hirotani[35]	4	4	0
Dashe[54]	1	4	2
Hise[47]	1	1	1
Gerraty[78]	2	0	0
Safa[79]	1	0	0
Total	20 (41%)	21 (43%)	8 (16%)

(b) Bilateral post-operative arotid infarction on CT scan.

Reference	Bilateral <50%	Unilateral 50–99%	Bilateral 50–99%	Occlusion + <50% stenosis	Occlusion + >50% stenosis	Bilateral occlusion
Mickleborough[6]	0	1	0	0	0	1
D'Agostino[15]	2	2	1	0	0	0
Dashe[54]	5	1	1	0	0	0
Total	7 (50%)	4 (29%)	2 (14%)	0)0%)	0 (0%)	1 (7%)

stroke.[6,11,15,17,35,47,54,78–80] Overall, 53 stroke sufferers (48%) had either normal carotid arteries or stenoses <50%, 22 (20%) had unilateral 50–99% stenoses, 22 (20%) had bilateral 50-99% stenoses, eight (7%) had occlusion with a contralateral stenosis <50%, five (4%) had an occlusion with a contralateral stenosis of 50–99%, while only one (1%) had bilateral carotid occlusions. Table 3 does not, however, provide information as to whether the stroke occurred ipsilateral to the stenosis or occlusion. In order to evaluate the aetiology further, data regarding the patterns of ipsilateral and contralateral carotid disease were analysed in patients with unilateral and bilateral carotid territory infarction on CT scan or autopsy. Eight series (Table 4) documented the extent of carotid disease ipsilateral to 49 cases of unilateral carotid territory infarction on CT scan/autopsy. Overall, 20 (41%) had a normal carotid artery or a stenosis <50% ipsilateral to the infarct. Twenty-one (43%) had an ipsilateral 50–99% stenosis and eight (16%) had ipsilateral carotid occlusion. There was no information as to whether the occlusions were recent or chronic. Three studies (Table 4) evaluated the patterns of carotid disease in 14 patients with bilateral carotid territory infarction on CT/autopsy. Seven (50%) had no evidence of significant carotid artery disease, four (29%) had a unilateral 50–99% stenosis, two (14%) had bilateral 50–99% stenoses and one had bilateral carotid occlusion. Only 3/14 (21%) had significant bilateral disease.

Table 5. CT scan/autopsy findings in 214 patients suffering a stroke after coronary artery bypass surgery (derived from refs 6, 11, 15, 17, 35, 45, 47, 48, 54, 81, 82).

Single vascular territory		(128)
Anterior circulation*	95	
Posterior circulation†	26	
Watershed‡	7	
Multiple vascular territories		(49)
Bilateral anterior circulation	12	
Bilateral anterior and posterior circulation	20	
Unilateral anterior and posterior circulation	5	
Bilateral watershed‡	7	
Multiple (non-specified)	5	
No recent infarct demonstrated		(37)

* Anterior circulation includes anterior and middle cerebral artery territory lesions.
† Posterior circulation refers to infarcts in the vertebrobasilar artery territory.
‡ Watershed refers to infarcts found in the vascular zones.

CT scan/autopsy findings following operative stroke

Eleven studies[6,11,15,17,35,45,47,48,54,81,82] documented the CT scan/autopsy findings in 214 patients suffering a stroke after CABG (Table 5). No new infarct was demonstrated in 37 (17%) of patients. This probably reflects the timing of the CT scan after the acute event. Of the 177 patients with a new area of infarction, 128 (72%) involved a single vascular territory, while 49 (28%) involved multiple vascular territories. Of the 128 patients with single territory infarction, 95 (74%)

involved the territory supplied by the internal carotid artery (anterior cerebral artery, middle cerebral artery), while 26 (20%) were located in the territory supplied by the vertebrobasilar and posterior cerebral arteries. Seven patients (5%) had unilateral watershed infarcts on CT scan/autopsy. Of the 49 patients with multiple infarctions, 25 (51%) had infarcts in both the anterior and posterior circulations.

The patterns of infarction in Table 5, taken in context with the patterns of vascular disease in Tables 3 and 4, provide valuable information regarding the role of carotid disease. Fifty-six of the 177 patients (32%) with infarction could not have suffered a stroke due to carotid disease alone (isolated posterior territory infarction ($n=26$), bilateral anterior and posterior infarctions ($n=20$), unilateral anterior and posterior infarction ($n=5$), multiple territory infarction ($n=5$)). If one now extrapolates patterns of carotid disease in patients with unilateral carotid territory infarction from Table 4, a further 39 patients (41% of 95) would not be expected to have significant carotid disease. Finally, the data suggests that 9/12 patients with bilateral anterior territory infarction will not have bilateral severe carotid disease. The available data from the CT scan or autopsy studies suggest that primary carotid thrombo-embolic disease alone was not responsible for up to 59% (104/177) of strokes.

This assumes that all 14 patients with watershed infarction on CT or autopsy had appropriate unilateral or bilateral carotid disease. If they did not, then up to 67% of operative strokes (118/177) were not due to carotid disease alone. It has always been assumed that watershed infarction follows profound hypotension or haemodynamic failure in the presence of severe extracranial carotid disease.[83] However, recent research suggests that watershed infarctions can be embolic and may occur in the absence of significant extracranial carotid artery disease.[84]

One important study was not included in the above analyses because the authors did not differentiate between anterior/posterior territorial infarctions in individual patients.[85] Barbut found that the mean number of infarcts detected by neuroradiologists in each patient suffering a post-CABG stroke was five. Up to 80% of stroke victims had at least one area of infarction in the posterior circulation.

Prevalence of carotid disease in CABG patients

Numerous studies have found that patients with significant carotid disease have an increased risk of stroke after CABG. This indirect evidence has, thereafter, been used to develop protocols for recommending CEA in selected patients undergoing CABG. The observation that patients aged >60 with a carotid stenosis >75% have a 15% stroke risk after CABG, compared with 0.6% in similarly aged patients with no stenosis,[56] has been pivotal in recommending synchronous carotid and cardiac revascularisation.[86] The fact that no patient numbers for this subgroup were quoted in Faggioli's paper seems to have been overlooked, but were almost certainly very small. It has also become customary to justify CEA in neurologically asymptomatic CABG patients through extrapolation of the findings of the Asymptomatic Carotid Atherosclerosis Study.[87] As a consequence, much of the current debate is not so much whether patients with co-existent carotid disease actually require prophylactic endarterectomy, but whether the procedure should be synchronous or staged. The following sections will concentrate on (i) the difficulties in interpreting the published data regarding the incidence of carotid disease in patients undergoing CABG, (ii) the risk of stroke (overall) in patients with carotid disease and, (iii) the risk of stroke ipsilateral to a severe carotid stenosis or occlusion.

It was difficult to establish the true prevalence of carotid disease in patients undergoing CABG and thereafter to determine its role in the aetiology of perioperative stroke. The reasons are multifactorial but must be borne in mind when interpreting the data. First, there have been a number of techniques for imaging the carotid arteries over the last 20 years (contrast angiography, MRA, Duplex ultrasound, Doppler ultrasound), a wide range of reported disease subgroups (>50%, >60%, >70%, >80%) and multiple criteria for defining patterns of disease. Many of the published series have combined occlusion with stenosis (termed "carotid stenosis >50%") and the implications of this will be discussed. Second, many of the published series are retrospective and most of the prospective screening studies have excluded patients with urgent cardiac symptoms. The latter will include a greater proportion of patients with left main stem disease who harbour a higher incidence of occult carotid artery disease.[9,15] Thirdly, the yield of any screening programme will inevitably reflect the population under investigation. The prevalence of stenosis will be highest in populations comprising older patients and those with a history of cerebrovascular events and lowest in asymptomatic, younger individuals. The final problem was the tendency for some screened patients with severe carotid disease to undergo prophylactic CEA, thereby confounding meaningful interpretation of stroke risk in the remaining patients.

Table 6. Patterns of caotid disease in patients undergoing CABG.
(a) Stenosis >50% or occlusion

Reference	Bilateral <50%	Unilateral 50–99%	Bilateral 50–99%	Occln + <50%	Occln + 50–99%	Bilateral occlusion	Symptom status
Berens[9]	901	113	35	10	9	0	Asymp + symp
Schwartz[17]	452	67	42	13	8	0	Asymptomatic
Brener[22]	3894	49	10	29	5	3	Asymptomatic
Riccotta[46]	1516	175	57	18	12	1	Asymp + symp
Breslau[80]	84	10	6	1	1	0	Asymp + symp
Risk	90.8%	5.5%	2.2%	0.9%	0.5%	0.05%	
95% CI	83.4–97.8	1.1–9.9	0–4.5	0.6–1.3	0.1–0.9	0.0–0.1	
Heterogeneity	$p<0.0001$	$p<0.0001$	$p<0.0001$	$p=0.0141$	$p<0.0001$	$p<0.6275$	

(b) Stenosis >80% or occlusion

Reference	Bilateral <80%	Unilateral 80–99%	Bilateral 80–99%	Occln + <80%	Occln + 80–99%	Bilateral occlusions	Symptom status
Berens[9]	1022	35	11	13	6	0	Asymp + symp
Schwartz[17]	524	25	12	14	7	0	Asymptomatic
Salasidis[19]	344	14	2	14	2	1	Asymp + symp
Safa[79]	1012	71	17	6	0	0	Asymptomatic
Hill[92]	184	14	0	0	2	0	Asymp + symp
Hines[89]	1618	44	9	0	5	0	Asy,p + symp
Risk	93%	4.0%	1.0%	0.9%	0.4%	0.02%	
95% CI	91.4–95.7	2.7–5.4	0.5–1.5	0.0–1.89	0.1–0.8	0.0–0.1	
Heterogeneity	$p<0.0001$	$p<0.0001$	$p=0.0066$	$p<0.0001$	$p=0.0044$	$p=1.00$	

The prevalence of stenosis increased with age. CABG patients aged <60 years had a 4% prevalence of detecting a >50% carotid stenosis, rising to 11% in patients aged >60 and 15% in those aged >70.[9] Notwithstanding the problems regarding ultrasound criteria for diagnosing carotid disease, Table 6 summarises patterns of bilateral disease in patients undergoing CABG whose carotid arteries were screened pre-operatively with Duplex ultrasound. In practice, about 95% will be neurologically asymptomatic. Overall, 91% of the CABG patients (95% CI 83–98) did not have a 50–99% stenosis or occlusion. One in 20 (5.5%, 95% CI 1.1–9.9) had a unilateral 50–99% stenosis, 2% (95% CI 0–4.5) had bilateral 50–99% stenoses, while 1.5% had carotid occlusion $\pm$ a contralateral stenosis. Data regarding the prevalence of 80–99% stenosis or occlusion are detailed in Table 6. Overall, only 6% of CABG patients would be expected to have an 80–99% carotid stenosis or occlusion.

What is the risk of stroke in CABG patients with carotid artery disease? Although some have found no statistical association,[11] a larger number have observed that a "severe stenosis" or "stenosis >50%" was associated with a significantly increased risk of operative stroke.[6,15,19,28,35,46,54] However, few have documented neurological status, nor if the data discriminated between a severe stenosis (50–99%) and occlusion and, finally, whether the stroke was actually ipsilateral to the stenosis.

Most data are derived from patients with asymptomatic carotid disease. Few CABG patients with symptomatic, severe carotid disease have not been subjected to synchronous or staged CEA. There is also no accepted definition of "previously symptomatic". Does this only include patients with symptoms <12 months of CABG or any time in the past? Intuitively one feels that symptomatic patients with severe carotid disease represent a high-risk subgroup undergoing CABG. This is borne out in one of the few available studies that documented the incidence of post-CABG stroke in 229 patients screened for symptom status and carotid artery disease.[15] The incidence of operative stroke in asymptomatic patients with a unilateral stenosis was 2.9% (4/137), which increased to 6.7% (3/45) in asymptomatic patients with bilateral disease. Symptomatic patients with unilateral stenoses had an 18% risk of stroke (5/28) increasing to 26% in those with bilateral disease (5/19).

The second problem relates to data misinterpretation when occlusions are included within the category "stenosis >50%". Ten series compared the stroke risk in 7685 CABG patients with no carotid disease against 980 patients with a 50–99% stenosis or occlusion (Table 7). The stroke risk in patients with no significant carotid

Table 7. Stroke risk in CABG patients with "severe" carotid disease.

Author	Risk of peri-operative stroke	
	<50% stenosis	50–99% or occlusion
Berens[9]	23/901	14/186
Barnes[11]	4/284	1/40
D'Agostino[15]	24/1017	21/262
Schwartz[17]	7/452	5/130
Ivey[21]	0/66	3/19
Brener[22]	74/3894	9/96
Hirotani[35]	11/410	5/62
Dashe[54]	4/145	10/79
Faggioli[56]	5/432	14/88
Breslau[80]	1/84	0/18
Overall risk	2.0%	8.4%
95% CI	1.7–2.3	6.0–10.7

Table 8. Stroke risk in CABG patients with a <50%, 50–99% carotid stenosis or occlusion differentiated.

Author	Risk of peri-operative stroke		
	<50% stenosis	50–99% stenosis	Occluded carotid
Schwartz[17]	7/452	4/109	1/21
Ivey[21]	0/66	0/16	3/3
Brener[22]	74/3894	3/59	6/37
Hirotani[35]	11/410	5/46	0/16
Dashe[54]	4/145	8/54	2/23
Breslau[80]	1/84	0/16	0/2
Iverall risk	1.9%	6.7%	11.5%
95% CI	1.5–2.3	2.5–10.8	0.0–23.9

disease was 2.0% (95% CI 1.7–2.3) which increased to 8.4% (95% CI 6.0–10.7) in patients with "a carotid stenosis >50%". This represents a fourfold excess risk of stroke in patients with significant carotid disease (Odds ratio = 4.3, 95% CI 3.2–5.7, $p<0.0001$).

However, patients with occlusion cannot undergo CEA. If the data are reanalysed so as to differentiate between patients with (i) no carotid disease, (ii) a severe (50–99%) stenosis or (iii) occlusion (Table 8), the highest risk is now observed in those with occlusion. Patients with no significant carotid disease had a 1.9% (95% CI 1.5–2.3) risk of stroke increasing to 6.7% (95% CI 2.5–10.8) in those with a 50–99% stenosis. The highest peri-operative stroke risk (11.5%, 95% CI 0.0–23.9) was observed in CABG patients with carotid occlusion. Thus patients with a 50–99% carotid stenosis were almost four times more likely to have a peri-operative stroke than patients with no significant disease (Odds Ratio 3.6, 95% CI 2.0–6.5, $p<0.0001$). CABG patients with carotid occlusion were more likely to suffer a stroke than patients with a 50–99% stenosis (Odds Ratio 1.5, 95% CI 0.6–3.7, $p=0.3394$), but this did not reach statistical significance. CABG patients with carotid occlusion were seven times more at risk than patients with no carotid disease (Odds Ratio 6.66, 95% CI 3.73–11.90, $p<0.0001$).

Unfortunately, these data still tell us nothing about the risk of ipsilateral stroke nor whether stroke risk was influenced by the presence of bilateral carotid disease. Table 9 summarises the stroke risk in screened CABG patients, not undergoing prophylactic CEA, in whom the bilateral status of the carotid arteries was documented pre-operatively. There was insufficient data to perform a similar analysis for patients with >80% stenoses. As can be seen, in this predominantly asymptomatic population, the risk of stroke was lowest in patients with no evidence of significant carotid artery disease (1.8% (95% CI 1.4–2.2)). Stroke risk increased to 3.2% (95% CI 0.0–6.5%) in patients with a unilateral 50–99% stenosis, 5.2% in patients with bilateral 50–99% stenoses (95% CI 0.0–10.8) and 7–11% for patients with unilateral carotid occlusion.

Although the data from Tables 7–9 suggest an association between significant carotid disease and post-CABG stroke, it still does not tell us anything about the laterality of the event. The key unanswered question, therefore, remains "what is the risk of ipsilateral stroke distal to a carotid stenosis or occlusion during CABG?" Although 21 studies examined the relationship between carotid disease and post-CABG stroke, six Duplex screened selected subgroups of the overall CABG population,[6,21,54,82,88,89] ten did not analyse the rate of ipsilateral stroke in all patients with stenosis

Table 9. Risk of stroke in duplex screened patients undergoing CABG (excluding those submitted to synchronous or staged (CEA).

Reference	Bilateral <50%	Unilateral 50–99%	Bilateral 50–99%	Occlusion +<50%	Occlusion +50–99%	Bilateral occlusion	Symptom status
Schwartz[17]	7/452	1/67	3/42	1/13	0/8	0/0	Asymp
Breslau[80]	1/84	0/10	0/6	0/1	0/1	0/0	Asymp + symp
Brener[22]	74/3894	3/49	0/10	4/29	1/5	1/3	Asymp
Total	82/4430	4/126	3/58	5/43	1/14	1/3	
Risk	1.8%	3.2%	5.2%	11.6%	7.1%	33%	
95% CI	1.4–2.2	0.0–6.5	0.0–10.8	2.1–21.2	0.0–19.7	—	
Heterogeneity	$p=0.5551$	$p=0.5057$	$p=1.000$	$p=1.000$	$p=0.4286$	n/a	

Table 10. Stroke/TIA risk ipsilateral to carotid artery disease.
(a) Ipsilateral to 50–99% stenosis or occlusion*

Reference	Normal of <50% stenosis	50–99% stenosis	Occlusion	Event reported	Symptom status†
Breslau[80]	1/179	0/23	0/2	CVA only	A+S
Brener[22]	75/7866	2/74	6/40	TIA/CVA	A+S
Schwartz[17]	2/984	4/159	1/21	CVA only	Asymp only
Total "events"	78/8143 (1.0%)	6/256 (2.3%)	7/63 (11%)		

(b) Ipsilateral to 80–99% stenosis or occlusion*

Reference	Normal or stenosis	80–99% stenosis	Occlusion	Event reported	Symptom status
Salasidis[19]	6/714	2/20	2/18	TIA/CVA	A+S
Schwartz[17]	4/1087	2/56	1/21	CVA only	Asymp only
Total "events"	10/1801 (0.6%)	4/76 (5.3%)	3/39 (8%)		

* Refers to the number of at risk arteries rather than patients.
† A+S = neurologically asymptomatic and symptomatic CABG patients screened.

or occlusion[9,11,35,43,46,56,90–92] and one combined stenosis with occlusion.[15]

Table 10 summarises the risk of operative stroke or TIA per ipsilateral carotid artery in the four available studies. This method of interpretation corrects for the fact that each CABG patient has two carotid arteries, most of which have no significant disease. Unfortunately, even these studies were difficult to interpret reliably. Three screened neurologically asymptomatic and symptomatic patients[19,22,80] while one screened asymptomatic patients only.[17] Two[19,22] performed combined CEA-CABG on selected patients, leaving the remainder for analysis. Finally, two[19,22] combined post-CABG stroke with TIA, while two reported the incidence of stroke but not TIA.[17,80]

Notwithstanding these limitations, the data from table 10 suggests that the risk of stroke/TIA increases with the severity of the ipsilateral stenosis. However, an alternative interpretation might be that even though the stroke/TIA risk increased with the degree of ipsilateral stenosis, 86% of all observed cerebral events[78–91] occurred ipsilateral to a hemisphere without a 50–99% stenosis or occlusion and only 7% of strokes/TIAs occurred ipsilateral to a surgically remediable lesion.

Summary and Recommendations for Future Studies

The risk of stroke after CABG is about 2% and has not changed appreciably over the last three decades. Two thirds of strokes occur after the first 24 h and one quarter will die. Factors predictive of an increased risk of post-CABG stroke include (i) the presence of a carotid bruit, (ii) neurologically symptomatic as opposed to asymptomatic patients and (iii) the presence of severe carotid artery disease.Severe carotid disease does appear to be an important risk factor for post-CABG stroke. Most of the data are derived from asymptomatic patients and there is little information regarding stroke risk in symptomatic patients. The risks increase for asymptomatic patients with bilateral as opposed to unilateral disease and for the more severe degrees of unilateral stenosis. The maximum risk was observed in patients with carotid occlusion. The actual risk of stroke ipsilateral to a carotid stenosis was difficult to determine and certainly warrants further study.

However, the data also suggest that carotid disease may only be responsible for a relative minority of all post-CABG strokes. Firstly, 50% of patients suffering a stroke will not have significant carotid disease on subsequent investigation. Second, when the distribution of infarcts from CT scan/autopsy are correlated with underlying carotid disease, up to 60% could not be attributable to carotid disease alone.

Evidence that aortic arch embolisation may be an important cause of stroke in the remaining 60% comes from a number of sources. Firstly, studies[93] have shown that the largest number of cerebral emboli detected during CABG occur immediately following aortic cross clamping (i.e. when they must be particulate) and again following aortic clamp removal (when the emboli can be either gaseous or particulate). Secondly, the risks of post-CABG stroke correlate closely with the presence or absence of moderate/severe aortic

atheroma. Severe aortic arch disease has been defined as aortic wall thickening >5 mm, plus, either marked calcification or protruding/mobile atheroma or ulcerated plaque with overlying thrombus or circumferential involvement.[94] Patients with severe aortic disease have a 5–19% risk of peri-operative stroke as compared with 0–2% in patients with no significant aortic arch disease.[6,10,28,38] The prevalence of aortic arch disease increases with age from 9% in patients aged 50–59 years, 18% in patients aged 60–69 years, 22% in patients aged 70–79 years, peaking at 33% in patients aged over 80 years.[94] This parallels the increase in the incidence of carotid disease with age and recent studies suggest that patients with a combination of carotid and aortic arch disease have a significantly higher risk of stroke (14%) as compared to those with no evidence of aortic or carotid disease (0.9%).[13] The only clinical predictor of severe aortic arch disease is a carotid bruit.[72]

The review suggests that prophylactic CEA could only ever prevent 40% of post-CABG strokes. However, this review also suggests that before implementing radical changes in practice (particularly as a randomised trial remains unlikely) authors are asked to clearly document the following parameters in future studies. Indeed, in some centres, this information may already be available but unpublished.

1. The status of the carotid arteries (and preferably the aortic arch) and CT scan/autopsy findings ipsilateral to the hemisphere involved in a post-CABG stroke.
2. The timing of onset and its relationship to the presence or absence of ipsilateral carotid and aortic arch disease.
3. Clear documentation of the 30-day mortality, ipsilateral stroke rate and any stroke rate in screened patients undergoing CABG, supplemented by death + ipsilateral stroke rate, and death + any stroke rate.
4. Publication of databases which have screened the prevalence of aortic and carotid artery disease prior to CABG and the ensuing ipsilateral/any stroke risk.
5. The risk of stroke relative to age group and degree of carotid stenosis/aortic arch disease.

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