

IS CANADIAN CARDIAC SURGEONS' MANAGEMENT OF ASYMPTOMATIC CAROTID ARTERY STENOSIS AT CORONARY ARTERY BYPASS SUPPORTED BY THE LITERATURE? A SURVEY AND A CRITICAL APPRAISAL OF THE LITERATURE

Louis P. Palerme, MD; Andrew B. Hill, MD; Daniel Obrand, MD; Oren K. Steinmetz, MD

OBJECTIVE: To document and compare the management of asymptomatic carotid stenosis (ACS) by Canadian cardiac surgeons at coronary artery bypass grafting (CABG) against a critical literature analysis.

DESIGN: A multiple choice survey and a structured literature review.

DATA SOURCES: Seventy-seven surgeons and 272 publications selected from the English literature between 1980 and 1997. Search terms used were "carotid," "coronary bypass," and "cardiac surgery."

STUDY SELECTION: Five natural history studies were identified, and 58 studies were found that had objective documentation of ACS of 50% or more before cardiac surgery, and both operative stroke and mortality data reported for CABG with and without carotid endarterectomy (CEA).

DATA EXTRACTION: Natural history and outcome studies were independently rated against published guidelines. Outcome data were independently pooled and compared. Data discrepancy was resolved by consensus. Survey results were tabulated for simple descriptive statistics.

DATA SYNTHESIS: No methodologically sound natural history studies were found to document an increased risk of stroke from ACS after CABG. There were no randomized controlled studies to guide treatment recommendations. Pooled data for stroke or death did not support CEA for risk reduction from ACS at CABG (relative risk 0.9, $p = 0.5$). Ninety-four percent of surgeons believed that the literature is insufficient to support the routine use of CEA to reduce the risk of stroke from ACS after CABG. Despite this, 20% of surgeons advocated CEA for this purpose.

CONCLUSION: The management of ACS at CABG by the majority of Canadian cardiac surgeons is consistent with the results of the literature review; however, significant management variation exists.

OBJECTIF : Documenter la prise en charge de la sténose asymptotique de l'artère carotide (SAAC) par les chirurgiens cardiologues du Canada au moment d'un pontage aortocoronarien (PAC) et la comparer à une analyse critique de la littérature scientifique.

CONCEPTION : Questionnaire à choix multiples et recension structurée de la littérature scientifique.

SOURCE DES DONNÉES : Soixante-dix-sept chirurgiens et 272 publications en anglais parues entre 1980 et 1997. On a utilisé, comme termes de recherche, les mots «carotid», «coronary bypass» et «cardiac surgery».

SÉLECTION D'ÉTUDES : On a trouvé cinq études d'antécédents naturels et 59 études qui documentaient de façon objective une SAAC, dont 50 % ou plus avant une chirurgie cardiaque, ainsi que des données sur l'accident vasculaire cérébral opératoire et la mortalité signalées pour un PAC avec et sans endartérectomie (EAC).

EXTRACTION DES DONNÉES : On a évalué les antécédents naturels et les études de résultats indépendamment en fonction de guides publiés. On a regroupé de façon indépendante et comparé les données sur les résultats. Les écarts entre les données ont été réglés par consensus. On a regroupé en tableaux les résultats des questionnaires pour établir des statistiques descriptives simples.

From the Division of Vascular Surgery, Faculty of Medicine, McGill University, Montreal, Que.

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Correspondence to: Dr. Andrew B. Hill, Division of Vascular Surgery, Ottawa Hospital — General Site, 501 Smyth Rd., Ottawa ON K1H 8L6; fax 613 737 8617, ahill@ogh.on.ca

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SYNTHÈSE DES DONNÉES : On n'a trouvé aucune étude d'antécédents naturels solide sur le plan méthodologique pour documenter un risque accru d'accident vasculaire cérébral causé par une SAAC après un PAC. Il n'y avait pas d'étude contrôlée randomisée pour guider les recommandations sur le traitement. Les données regroupées sur l'accident vasculaire cérébral ou la mort n'appuyaient pas l'endarterectomie carotidienne pour réduire le risque causé par une SAAC au moment du PAC (risque relatif, 0,9, $p = 0,5$). Même si 94 % des chirurgiens étaient d'avis que la littérature scientifique ne suffit pas pour appuyer l'utilisation de routine de l'endarterectomie carotidienne dans le but de réduire le risque d'accident vasculaire cérébral causé par une SAAC après un PAC, 20 % des chirurgiens préconisaient malgré tout l'endarterectomie carotidienne à cette fin.

CONCLUSION : La prise en charge de la SAAC au moment du PAC par la majorité des chirurgiens cardiologues du Canada est conforme aux résultats d'une analyse de la littérature scientifique, mais il existe toutefois d'importantes variations dans le traitement.

Neurologic complications after coronary artery bypass grafting (CABG) remain a significant clinical problem. The incidence of stroke reported in the contemporary cardiac surgery literature ranges from 2% to 5%.^{1,2} In addition, minor neuropsychiatric complications may also be present in up to 50% of patients.^{1,2} This is particularly relevant when one considers the large number of CABG procedures performed yearly and the significant morbidity and mortality that follows a stroke. Unfortunately, modification of the absolute risk is difficult because the understanding of etiology and prevention of such events remains incomplete.

The etiology of stroke after cardiac surgery is multifactorial. Potential mechanisms include embolization from atherosclerotic lesions of the aortic arch, carotid arteries and intracerebral circulation, occlusion of carotid artery stenosis, embolization from the bypass pump, cerebral hypoperfusion, stroke due to hypertension and intra-cerebral hemorrhage associated with the use of systemic anticoagulation.³⁻⁷ A great deal of attention, however, has been given to the potential relationship between carotid artery stenosis and stroke after cardiac surgery. Patients presenting for CABG have a significant risk of coexisting carotid artery lesions, which can be found preoperatively by duplex ultrasonography. In addition, carotid endarterectomy (CEA) has at least the potential to reduce the speculated risk of stroke from carotid artery

stenosis after CABG. Unfortunately, the independent contribution that carotid artery stenosis makes to the incidence of stroke after CABG has not been well defined. This is particularly true for asymptomatic carotid artery stenosis (ACS). Not all patients who suffer stroke after cardiac surgery have coexisting ACS, and not all patients with ACS suffer stroke after cardiac surgery.

Carotid endarterectomy performed at the time of CABG was first reported by Bernhard and associates⁸ in 1972. Since then, a proliferation of publications has resulted in conflicting results and management recommendations. A consensus statement from a multispecialty task force has addressed this controversy. Based on available literature, the task force recommended CEA at the time of CABG only for significant symptomatic carotid artery stenosis. The optimal management of significant asymptomatic stenosis at the time of CABG remained poorly defined.⁹

The recent publication of the Asymptomatic Carotid Atherosclerosis Study has resulted in controversy as a result of the proliferation of CEA for ACS.^{10,11} Although the study did not address ACS at the time of CABG, following that publication we surveyed Canadian cardiac surgeons concerning their beliefs and management of ACS at the time of CABG. The results of the survey are discussed in the context of a critical analysis of the English literature concerning ACS, CABG and stroke published since 1980.

METHODS

The survey

An anonymous survey, available in French and English, was mailed to all members of the Canadian Society for Cardiovascular and Thoracic Surgery in February 1996. Members were identified from a current mailing list supplied by the Society. Not all members of the Society practised cardiac surgery; consequently, to provide an estimate of how well the responding cardiac surgeons represented the population of Canadian cardiac surgeons, we asked each member to provide the number of CABG procedures that he or she performed over the previous 12 months. This number was then compared to published data concerning the total number of CABG procedures in Canada per year. One hundred and eight completed questionnaires were returned in stamped, addressed envelopes that were supplied with the survey. Seventy-seven of the 108 respondents were cardiac surgeons who were currently performing CABG. These 77 cardiac surgeons make up our study group.

The survey comprised 11 multiple-choice questions concerning etiology, evaluation and potential intervention for stroke occurring after CABG.

Critical appraisal of the literature

We reviewed the English language medical literature since 1980. Our literature search consisted of computer-

ized searches of the National Library of Medicine databases, using Internet GratefulMed, a review of journal references, and recommendations from medical colleagues. Query terms included in our computer search were: carotid, cardiac surgery, and coronary bypass. This search yielded 272 papers for review.

Natural history studies: ACS, CABG and stroke

We searched for natural history studies. To be included in our review, published studies had to be prospective cohort studies that considered ACS, CABG and stroke. Any such study had to meet the following criteria to be included for review: carotid artery stenosis of 50% or greater as demonstrated by an objective study (either Doppler scanning or angiography); ACS must be documented before CABG; the cardiac surgery should be limited to CABG without additional procedures; no patient with ACS should be removed from the study population by undergoing CEA at CABG during the study period; stroke and mortality data should be available for all study patients after CABG and there should be no recorded symptoms that could be attributed to the carotid artery stenosis (asymptomatic stenosis) as defined by criteria from the North American Symptomatic Carotid Endarterectomy Trial.¹² The quality of the studies that met these inclusion criteria was then evaluated against published guidelines for literature reporting natural history.^{13,14}

The influence of CEA on the relative risk of stroke and death from carotid artery stenosis after CABG

There are no randomized controlled studies available to evaluate the potential for CEA to reduce the potential risk of stroke from ACS after CABG. There-

fore, we attempted to estimate what that potential might be by combining stroke and mortality data for all patients from any published study (prospective and retrospective) that reported these data for patients with carotid artery stenosis who underwent CABG with or without simultaneous CEA.

The patients were pooled from studies that met the following inclusion criteria: publication in the English literature since 1980; objective documentation of 50% or greater carotid artery stenosis recorded before cardiac surgery; stroke and operative mortality data available for all patients after CABG and if CEA is performed, then it should be at the same time as CABG. Data were recorded and analysed for any carotid artery stenosis of 50% or greater (symptomatic and asymptomatic) and for ACS alone that was 50% or greater.

From these pooled patient populations we calculated the relative risk of stroke, death, and stroke and death for the patients with carotid artery stenosis who underwent CABG with and without CEA. Based on the result of this pooled analysis, we graded the clinical recommendation that could be made concerning the potential role of CEA to reduce any potential risk from carotid artery stenosis after CABG.^{15,16}

Two of the authors (L.P.P. and A.B.H.) independently evaluated each paper found in the search for inclusion in the reviews. The reported morbidity and mortality figures were recorded independently by each author. The results of each independent review were then compared, and any discrepancy was resolved before the final data entry and analysis.

Statistical analysis

Information from the survey is reported with simple descriptive statistics. Pooled data from the critical review were entered on a database and

analysed with a statistical software package (NCSS 97 8). Two-way contingency tables were analysed using Fisher's exact test (2-tailed). The relative risk of stroke, death and the combined risk of stroke and death are reported for each analysis.

RESULTS

The survey

The surgeons

The Canadian Society for Cardiovascular and Thoracic Surgery is not exclusive to cardiac surgeons. Seventy-seven (71.3%) of the 108 surgeons who responded to the survey currently perform CABG. These cardiac surgeons were distributed among all 9 provinces where CABG is performed in Canada (Table I). The 2 most populous provinces, Ontario and Quebec, accounted for 50 (65%) of the 77 respondents performing CABG surgery. Seven surgeons (9%) responded from the Maritime provinces and the remaining 20 surgeons (26%) responded from western Canada.

The procedure

The 77 responding cardiac surgeons reported that they performed a total of 12 115 CABG procedures in 1995. During the 1994/95 fiscal

Table I

Distribution of the 77 Canadian Cardiac Surgeons Who Responded to the Survey

Province	No. of respondents
Newfoundland	1
Nova Scotia	3
New Brunswick	3
Quebec	18
Ontario	32
Manitoba	3
Saskatchewan	4
Alberta	6
British Columbia	7

year, 15 816 CABG procedures were performed in Canada.¹⁷ Consequently, the responders in this survey would perform approximately 77% of all CABG procedures in Canada. The number of reported yearly procedures per surgeon averaged 157, ranging from 115 in western Canada, 171 in Ontario and 128 in eastern Canada to 192 in Quebec.

The etiology of hemispheric stroke after CABG

When questioned on the primary etiology of hemispheric stroke (in contrast to diffuse cerebral injury) after CABG, 56 (73%) of the 77 reported that embolization from atherosclerotic disease of the aortic arch is the most common cause. Only 8 (10%) believed that ACS is the most common cause. These 8 surgeons performed approximately 1300 CABG procedures per year (11% of all reported cases). The remaining surgeons (17%) listed other potential etiologies as the primary cause of hemispheric stroke (Fig. 1).

CEA for ACS and CABG

Although only 10% of surgeons believed that ACS was the primary mechanism for hemispheric stroke after CABG, even more believed that the presence of ACS was an indication

for prophylactic CEA to reduce the risk of such stroke. Twenty percent of the surveyed surgeons believed that CEA is indicated for this purpose. These surgeons were responsible for approximately 2095 of the patients who undergo CABG in Canada (17.3% of all CABG patients accounted for in the survey). All surgeons who believe in CEA for ACS at CABG felt that the carotid artery stenosis should be at least 70% or greater before the patient should be considered for treatment. The degree of stenosis that was thought to be clinically important was ACS of 70% or greater, 80% or greater and 90% or greater among 28%, 38% and 34%, respectively, of these cardiac surgeons. The remaining 80% of cardiac surgeons reported that they did not believe that CEA is indicated for this purpose.

Screening for ACS before CABG

Although only 20% of Canadian cardiac surgeons believed that CEA is indicated for ACS to prevent hemispheric stroke after CABG, 30% (23 of 77) routinely screened for ACS before CABG. These surgeons were responsible for 3490 (28.8%) patients of the total 12 115 patients. The preferred method for carotid artery screening, when performed, was duplex ultrasonography for 92% of surgeons (71 of 77).

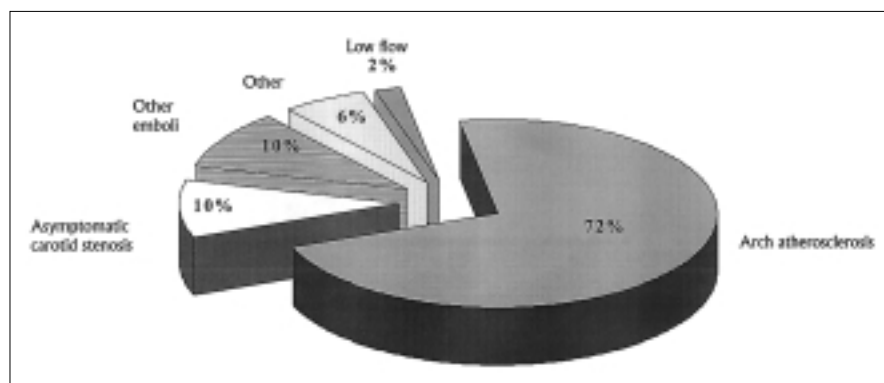


FIG. 1. The causes of hemispheric stroke after coronary artery bypass grafting as estimated by responding cardiac surgeons.

Opinion of Canadian cardiac surgeons concerning the available clinical literature

We attempted to clarify how the responding surgeons arrived at their beliefs concerning ACS, CEA, stroke and CABG. Those who believe that CEA is indicated for ACS at the time of CABG indicated that the following best supported their position: clinical literature (32%), personal experience (44%), expert opinion (12%) and other sources (12%). Those who do not believe that CEA is indicated for ACS at the time of CABG indicated that the following best supported their position: clinical literature (or lack of adequate literature) (71%), personal experience (19%), expert opinion (7%) and other sources (3%).

CRITICAL ANALYSIS OF THE LITERATURE

Natural history studies

From the 272 papers identified by the computer search and our other enquiries, we identified 5 prospective natural history (cohort) studies published since 1980 that met our criteria for inclusion in the review (Table II¹⁸⁻²²). A relationship between hemispheric stroke after CABG and ACS was not demonstrated in 4 of these studies.^{18,19,21,22} One study did report such a relationship.²⁰ In this study, the relative risk of ipsilateral hemispheric stroke after CABG was 8.7 for ACS of 50% or greater ($p = 0.002$). The relative risk of stenosis without occlusion was 4.6 ($p < 0.05$).

We evaluated the 5 studies¹⁸⁻²² against methodologic criteria for the critical assessment of an article on prognosis (Table III).^{13,14} All studies had significant problems with these criteria. All demonstrated the creation of an inception cohort; however, the referral patterns for assembling the patient cohorts were not well described in any study. All provided follow-up data on all patients entered in

the study; however, the follow-up interval was not uniform. One study followed up patients for at least 30 days,¹⁸ 2 studies specified follow-up until hospital discharge^{20,22} and 2 studies did not specify the follow-up period.^{19,21} Only 1 study reported to use objective outcome criteria for stroke.²² This study was also the only one that reported blinded outcome assessment. None of the studies made statistical adjustment for extraneous prognostic factors. This is particularly relevant for the study by Schwartz and colleagues,²⁰ which documented a significant association between carotid artery stenosis and stroke with univariate analysis. Whether or not this association would persist after statistical adjustment for other prognostic factors can only be speculated. Consequently, we were unable to find methodologically sound studies to document an independent risk of stroke after CABG that could be attributed to ACS.

Carotid endarterectomy at the time of CABG

Symptomatic coronary stenosis and ACS

Evaluation of the English literature published on ACS, CABG and CEA failed to identify a randomized controlled trial of any size to generate a sound clinical recommendation concerning the potential use of CEA to reduce the risk of stroke after CABG. We identified 58 studies published with

data on both both symptomatic and asymptomatic carotid artery stenosis that met the minimum defined criteria.^{5,7,18-21,23-74} By pooling patients from these 58 papers, we identified 925 patients with symptomatic or asymptomatic carotid artery stenosis of 50% or greater who were subjected to CABG without simultaneous CEA. In addition, CABG and CEA (under the same general anesthesia) was performed on 3693 patients with symptomatic or asymptomatic carotid artery stenosis of 50% or greater. The combined stroke and death rate was not significantly different for the 2 groups (relative risk = 1.0, *p* = 0.9). Although not statistically significant, the trend was toward a higher stroke rate for the 3693 patients who underwent the combined procedure than for patients with carotid artery stenosis who underwent CABG alone (Table IV).

ACS

We then evaluated studies that provided stroke and mortality data for ACS alone, with and without CEA at the time of CABG. From the 58 papers reviewed, we identified 555 patients with ACS of 50% or greater who were subjected to CABG without simultaneous CEA and 554 patients with ACS of 50% or greater who underwent combined CABG and CEA. The combined stroke and death rate was not significantly different for the 2 groups (relative risk = 0.9, *p* = 0.5). Once again, although not statistically significant, the trend was toward a higher stroke rate in patients who underwent combined CABG and CEA when compared with those with ACS who underwent CABG alone (Table V).

More significant ACS might be associated with a greater risk of stroke.

Table II

Relative Risk of Ipsilateral Hemispheric Stroke (HS) From Asymptomatic Carotid Artery Stenosis (ACS) After Coronary Artery Bypass Grafting (CABG) for 5 Prospective Natural History Studies

Study	No. of patients	ACS		HS		Relative risk
		No.	(%)	No.	(%)	
Turnipseed et al, 1980 ²¹	170	14	(8.2)	2	(0.5)	0
Breslau et al, 1981 ¹⁹	78	5	(6.4)	1	(1.3)	0
Barnes et al, 1981 ¹⁸	324	40	(12.4)	3	(0.9)	3.6*
Gerraty et al, 1992 ²²	213	?	?	2	(0.9)	0
Schwartz et al, 1995 ²⁰	582	130	(22)	7	(1.2)	8.7†

**p* = 0.3.
†*p* = 0.002.

Table III

Methodologic Criteria for the Critical Assessment of an Article on Prognosis Demonstrated by 5 Natural History Studies for ACS and Stroke After CABG

Study	Inception cohort	Referral pattern	Complete follow-up	Objective outcome criteria	Blind outcome assessment	Multivariate statistical adjustment
Turnipseed et al, 1980 ²¹	Yes	Yes	Yes	No	No	No
Breslau et al, 1981 ¹⁹	Yes	Yes	Yes	No	No	No
Barnes et al, 1981 ¹⁸	Yes	Yes	Yes	No	No	No
Gerraty et al, 1992 ²²	Yes	Yes	Yes	Yes	Yes	No
Schwartz et al, 1995 ²⁰	Yes	Yes	Yes	No	No	No

From the collected data, an analysis of patients with ACS of 70% or greater was performed. The risk of stroke or death was 5.3% for CABG and 5.5% for CABG with CEA (relative risk = 1.0, $p = 0.99$). It was difficult to determine separate outcome for symptomatic and asymptomatic stenosis in many of the studies; consequently, confidence in the result of this additional analysis suffers from the limitation of a small sample size ($n = 19$ for ACS and CABG, $n = 200$ for ACS and CABG with CEA).

DISCUSSION

Our survey of Canadian cardiac surgeons appears to have reached its target, with respondents performing approximately 77% of all CABG procedures done in Canada in the year preceding the study. These surgeons represented all regions and provinces of Canada where CABG is performed (Table I). The management of ACS that is present before CABG was not uniform among the responding surgeons. Approximately 1 in 5 cardiac

surgeons would treat significant ACS with CEA at the time of CABG with the intention of reducing the incidence of stroke. These surgeons were responsible for approximately 2095 CABG procedures in the year preceding the survey (17.3% of procedures performed by respondents). If this proportion of surgeons and cases were generalized to the total population, 2736 of Canadian patients requiring CABG would be managed by surgeons who would perform CEA at the same time if carotid screening revealed significant stenosis. Current screening studies suggest that approximately 18% of patients who undergo CABG harbour carotid artery stenosis of 50% or greater in at least one artery and approximately 8% harbour carotid artery stenosis of 80% or greater in at least one artery.^{28,34,37,41,75} Given this prevalence, 219 (with greater than 80% carotid artery stenosis) to 493 (with greater than 50% carotid artery stenosis) CABG patients might be subjected to a combined operation by the 20% of Canadian cardiac surgeons who recommend CEA for CABG pa-

tients with ACS. This would potentially leave 1046 (with greater than 80% carotid artery stenosis) to 2354 (with greater than 50% carotid artery stenosis) CABG patients with carotid artery stenosis who would be managed by the 80% of Canadian cardiac surgeons who do not recommend CEA for CABG patients with ACS. It is not certain from our critical appraisal of the current literature which management strategy would best minimize the risk of stroke for these CABG patients with ACS; however, there appears to be little sound data to support a combined operation.

Radiologic and pathological studies suggest that most strokes after CABG do result from embolic phenomena.^{76,77} Cardiac surgeons are aware of the potential for embolization from atherosclerotic disease of the aortic arch during CABG. In our survey, the majority of surgeons (73%) believed that such embolization was most responsible for hemispheric stroke after cardiac surgery. Transesophageal and epiaortic ultrasonography is being used increasingly to identify and potentially avoid sequelae from such serious atherosclerotic disease of the arch.^{3,7,78-80} There may also be a significant relationship between disease of the aortic arch and carotid artery stenosis.^{78,79} Consequently, it would seem necessary to control each variable for the other when considering reports of stroke risk after CABG. Such studies are not currently available.

Carotid endarterectomy is an invasive surgical procedure that carries its own potential for significant morbidity and mortality. It would seem that at least a significant risk from untreated ACS should be demonstrated with scientifically sound data before a routine program of CABG/CEA for ACS is considered. The benefit of such a program would require confirmation, preferably with a randomized controlled trial. It is interesting to note that 72 (94%) of the 77 respond-

Table IV

Outcome of All Patients With Carotid Artery Stenosis of 50% or Greater After CABG or CABG and Carotid Endarterectomy (CEA)

Procedure	Stroke	Death	Stroke or death
	No. (%)	No. (%)	No. (%)
CABG ($n = 925$)	40 (4.3)	46 (5.0)	83 (9.0)
CABG and CEA ($n = 3693$)	201 (5.4)	169 (4.6)	341 (9.2)
Relative risk	0.8 ($p = 0.2$)	1.1 ($p = 0.6$)	1.0 ($p = 0.9$)

Table V

Outcome of Patients With Only ACS of 50% or Greater After CABG or CABG and CEA

Procedure	Stroke	Death	Stroke or death
	No. (%)	No. (%)	No. (%)
CABG ($n = 555$)	21 (3.8)	27 (4.9)	47 (8.5)
CABG and CEA ($n = 554$)	28 (5.1)	26 (4.7)	53 (9.6)
Relative risk	0.8 ($p = 0.3$)	1.0 ($p = 1.0$)	0.9 ($p = 0.5$)

ing surgeons believed that the clinical literature is inadequate to support the use of CEA for this purpose. Despite this, 20% of surgeons supported the use of simultaneous CABG and CEA for ACS. There were 5 surgeons (6.5% of total) who believed that adequate clinical literature existed to support this practice.

Despite the large number of publications since 1980 concerning carotid artery stenosis and cardiac surgery, we experienced difficulty finding methodologically sound studies to guide decision-making. We were able to identify only 5 prospective cohort (natural history) studies that attempted to document the risk of stroke from ACS at the time of CABG. Carotid artery stenosis is an attractive candidate as a risk factor for stroke after CABG. A significant proportion of the patient population is at risk for ACS before CABG, and ACS is known to increase the risk of stroke in other patients, on long-term follow-up. Four of the 5 studies that we identified did not demonstrate a significant relationship between ACS and hemispheric stroke at the time of cardiac surgery,^{18,19,21,22} but they had a relatively small sample size and might not have had adequate power to effectively rule-out ACS as a potential risk factor. This premise is supported in part by the result of the fifth study by Schwartz and colleagues.²⁰ This was the largest study group, and they did demonstrate a statistically significant relationship with univariate analysis between ACS and hemispheric stroke after cardiac surgery. In this study, the relative risk of ipsilateral hemispheric stroke was 8.7 for ACS of 50% or greater ($p = 0.002$) (Table II). The relative risk of stenosis without occlusion was 4.6 ($p < 0.05$). Although the study by Schwartz and colleagues is the largest prospective natural history study available to date, the results are not likely generalizable and raise concern when the study is evaluated against pub-

lished standards for natural history studies. The study was performed at an American veterans' affairs medical centre in men only and with a particularly heavy load of atherosclerotic disease of the carotid arteries. Another concern is the failure of the study to demonstrate a relationship between increasing severity of stenosis and risk of stroke, a gradient effect. The relative risk of ACS of 80% to 99% for ipsilateral hemispheric stroke dropped to 3.8 and was not statistically significant ($p = 0.1$). Although this is the largest reported prospective study, the sample size was inadequate to perform a reliable multivariate analysis to determine if the adjusted risk from ACS remained statistically and clinically significant. In addition, the study did not control for atherosclerotic disease of the aortic arch.

When we evaluated the 5 studies against published criteria for the critical analysis of natural history studies, all were found to be lacking. Although all assembled an inception cohort, the referral patterns were not well described and had to be inferred by the study location. Only 1 study reported objective outcome criteria that were assessed in a blinded fashion.²² This study was a negative one and was difficult to interpret because the authors did not report the actual number of patients with significant ACS who underwent cardiac surgery. They did report; however, that none of these patients had an associated stroke. None of the studies attempted, or were able, to adjust for extraneous prognostic or confounding variables with the statistical analysis (Table III). As a result of this analysis against published standards, it appears that the current natural history literature is inadequate to reliably determine whether or not ACS is associated with a significant independent risk of ipsilateral hemispheric stroke at the time of CABG.

This relationship might be inferred if studies of CABG with CEA for ACS

demonstrated a significant risk reduction for stroke after CABG. Unfortunately, there are no randomized controlled trials available to address this potential. There are suggested standards for evaluating the level of evidence from clinical studies that can be used to grade clinical recommendations for treatment.^{15,16} In the absence of a randomized controlled trial, a clinical recommendation would depend upon the best available literature from nonrandomized trials, large case series and historical controls. Unfortunately, there are many conflicting results and recommendations available from such studies. From the 58 studies included in our review, 41 (69%) promoted a combined operation; the remainder either remained neutral or advised against such an approach. We attempted to make some sense of the available literature by pooling the patient population from the studies that we selected using criteria outlined above (Tables IV and V). This information did not demonstrate any evidence of risk reduction from CEA for carotid artery stenosis at CABG. In fact, the absolute proportion of unfavourable outcomes was generally higher with CABG and CEA than with CABG alone despite the presence of ACS. This observation did not reach statistical or clinical significance. It was somewhat surprising since we expected an element of publication bias in favour of CEA associated with the publication of nonrandomized studies and clinical series. It is interesting that the initial analysis that included a pooled population of patients with symptomatic and asymptomatic stenosis did not demonstrate more favourable results for CABG and CEA, given the proven benefit of CEA for symptomatic stenosis in the general population and the recommendation of the ad hoc committee of the American Heart Association for symptomatic carotid artery stenosis that is present at the time of CABG.^{9,12}

The result of our pooled data, in addition to the lack of data from randomized controlled trials, does not provide any compelling evidence to support a clinical recommendation for CABG and CEA to reduce the risk of stroke after CABG.^{15,16} This conclusion reflects the opinion and practice of the majority of Canadian cardiac surgeons who responded to the survey. It is interesting that most Canadian cardiac surgeons who support the use of CABG and CEA for ACS believe that this practice is not actually supported by the current clinical literature. Our review would tend to support this belief.

The burden of proof concerning the ability of an intervention to reduce risk should be required of those who advocate that intervention. However, the lack of scientifically sound clinical data to support CEA to reduce the risk of stroke from ACS at the time of CABG is not synonymous with proof of a lack of risk from ACS for stroke at CABG. The risk of stroke and death for those with ACS who undergo CABG or CABG and CEA appears to be significantly higher than for those reported in large contemporary clinical series of CABG.^{1,2} The pooled data in Tables IV and V reveal a death rate of 4.9% after CABG for patients with ACS. This is higher than the overall death rate of 3.6% from CABG in Canada between 1992 and 1995.⁸¹ The stroke rate alone (3.8%) in those with ACS who undergo CABG without CEA is not, however, significantly different from reported stroke morbidity figures. The actual risk of stroke after CABG that can be attributed to ACS can only be quantified by an appropriately designed clinical study. Until such a study is completed, ACS should likely be considered at least a potential risk factor for stroke after CABG. In particular, higher degrees of ACS (80% or greater) may carry an increased risk that is not evident from the reviewed studies. In the most ex-

treme case, if all the strokes that occurred in the 555 patients recorded in Table V actually occurred in those with ACS of 80% or greater, then the rate of stroke in this patient group would be 8.5% and the rate of stroke and death would be 19%. The lack of sound data appears to have influenced most Canadian cardiac surgeons against the routine use of CABG and CEA for ACS to reduce the risk of stroke after CABG. Those who advocate such a practice have relied, in the majority, on information other than their interpretation of the clinical literature to support their practice pattern.

Although a short-term (30-day) risk reduction has not yet been demonstrated from CABG with CEA in the literature by any methodologically sound study or from our pooled data, one could speculate that such a benefit might become apparent with longer follow-up. The recent publication from the Asymptomatic Carotid Atherosclerosis Study¹⁰ demonstrated a statistically significant benefit from CEA for the treatment of duplex-defined ACS. An absolute risk reduction of 5.9% for the aggregate risk of ipsilateral stroke and any perioperative stroke or death was demonstrated over 5 years of follow-up. The clinical relevance of this absolute risk reduction continues to be hotly debated.^{11,82,83} Particularly relevant to the current topic was the observation that the Asymptomatic Carotid Atherosclerosis Study¹⁰ required a low 3% perioperative morbidity and mortality rate at the time of CEA to recognize the statistical significance of the study. The morbidity and mortality data from our pooled results suggest that a combined stroke and death rate as low as 3% is not being achieved. (Tables IV and V) In addition, it is not certain that results from the highly selected patient population in the Asymptomatic Carotid Atherosclerosis Study, who represented good-risk patients

for elective surgery, could be generalized to the CABG patient population. In summary, the long-term potential benefit of CABG with CEA for ACS to reduce the risk of stroke can only be speculated; however, our current data would tend to suggest that such a benefit is unlikely.

CONCLUSIONS

Canadian cardiac surgeons are not confident that the current clinical literature has adequately addressed the independent risk of stroke from ACS after CABG and the potential for CABG with CEA to reduce this risk. Our analysis of the quality of the literature would support these views. Despite the large volume of studies in print, methodologically sound natural history and intervention studies are absent. This may be responsible for the discrepant approach to patients with ACS at CABG reported by those responding to the survey. In addition, there is no compelling evidence from the our pooled data to support routine use of CABG with CEA to reduce the risk of stroke from ACS after CABG. The practice patterns of Canadian cardiac surgeons generally reflect these findings. It would seem appropriate to recommend a properly conducted prospective natural history study that also assesses the influence of aortic arch atherosclerosis, to document the independent risk resulting from ACS for hemispheric stroke after CABG before consideration of the time, cost and effort required for a multicentre randomized controlled trial of CEA for ACS at CABG.

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