Abstract
Randomized trials of combined carotid endarterectomy (CEA) and coronary bypass surgery (CABG) versus staged CABG then CEA have shown a benefit for the combined approach (CEA-CABG). In patients undergoing unilateral CEA-CABG, those with bilateral carotid stenoses have worse outcomes than those with a unilateral stenosis. If treating the second carotid stenosis at the time of CEA-CABG improves outcomes is currently not known. Indeed there have been very few reported series of outcomes of bilateral CEA-CABG. Patients who underwent combined bilateral CEA-CABG were identified from hospital databases. The procedures were performed over a period of 28 years and represented 16% of CEA-CABG procedures executed by the surgeons involved. All but 4 patients underwent bilateral CEA-CABG alone. Five patients (10%) died in the perioperative period and there were 5 strokes (10%) for a combined stroke/death rate of 19%. There were no deaths in the second half of the series but the stroke rate remained high. The Kaplan-Meier estimates of 5 and 10 year overall survival were 78% (95%CI: 66-90) and 55% (95%CI: 40-70) respectively.

Keywords — Internal Carotid Artery Diseases, Carotid Endarterectomy, Coronary Artery Bypass Surgery.

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II. METHODS
Patients (n = 48) who underwent combined bilateral CEA-CABG were identified from cardiac surgical databases at Royal Prince Alfred Hospital (RPAH) and Westmead. Case notes and operative reports were retrieved to confirm the accuracy of data and for additional data acquisition. Follow up for survival analysis was performed by cross matching the names against the New South Wales Register of Births, Deaths and Marriages which is linked to the death registers in other Australian states. All patients underwent carotid angiography. Carotid stenoses of ≥70% on both sides were considered to be the indication for bilateral CEA regardless of symptoms. Six cardiothoracic surgeons performed 48 bilateral CEA-CABG operations in 5 hospitals over a period of 28 years (1980 – 2008). Perioperative stroke was defined as any localized neurological deficit of presumed central origin, documented on 2 separate clinical examinations regardless of the time between examinations, or any evidence of postoperative stroke on a CT scan.

Operative.
The carotid arteries were mobilized and the coronary bypass graft conduit harvested. Cardiopulmonary bypass with right atrial and aortic cannulation and core cooling was then established in all patients. The carotid endarterectomies were performed at 25°C and ventricular fibrillation (RPAH data) or 30°C and empty beating heart (Westmead Hospital data). In 47...
patients the carotid surgery was performed before the cardiac procedure. All the carotid endarterectomies were performed via standard longitudinal arteriotomies. The arteriotomies were closed primarily in 91 vessels, with a vein patch in 4 arteries, and an aorto-internal carotid artery bypass was performed in one patient. Cardiopulmonary arrest was used in all patients for the cardiac procedure. Proximal vein graft anastomoses to the ascending aorta were performed with a partial occlusion clamp in 40 patients, following removal of the aortic cross clamp. The project was approved by the Human Research Ethics Committees of RPA and Westmead Hospitals.

Statistical analysis.

The statistical package SPSS version 21 was used to analyse the data. The mean and standard deviation (SD) or median and interquartile range (IQR) in the case of skewed data were used to summarize continuous variables. Percentages were used to summarize categorical variables. The Kaplan-Meier survival curve was used to illustrate the overall survival distribution.

III. RESULTS

All patients underwent coronary artery surgery. Four patients underwent concomitant cardiac procedures (mitral valve 2, left ventricular reconstruction 1, and left ventricular thrombectomy 1). The main patient demographics and perioperative outcomes are shown in Table 1. Seventy percent of patients were entirely asymptomatic with respect to their carotid disease with a further 13% being asymptomatic during the 6 months prior to surgery.

<table>
<thead>
<tr>
<th>Demographics:</th>
<th>Postoperative</th>
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<tr>
<td><strong>Preoperative</strong></td>
<td><strong>Postoperative</strong></td>
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<tr>
<td>Carotid &lt;6 months</td>
<td>Death 17</td>
</tr>
<tr>
<td>symptoms &gt;6 months</td>
<td>Stroke 13</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Myocardial infarct 42</td>
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<tr>
<td>Urgent</td>
<td>IABP 57</td>
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<tr>
<td>Left main stenosis</td>
<td>DSWI 14</td>
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<tr>
<td>Triple vessel disease</td>
<td>Length of stay 88</td>
</tr>
<tr>
<td>Left ventricle &lt;30%</td>
<td>Mean (SD=14.7) 10</td>
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<tr>
<td>Ejection fraction:30-50%</td>
<td>Median (IQR 7-14) 8</td>
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<tr>
<td>Diabetes</td>
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<td>Renal failure</td>
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<td>Pulmonary disease</td>
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IABP = intra-aortic balloon pump
DSWI = deep sternal wound infection

The incidence of perioperative stroke and/or death was 19%. In this relatively small cohort of patients, no risk factors proved to be independently significant as a predictor for this outcome. There was one death due to stroke where a CT scan showed multiple cerebral infarcts consistent with multiple emboli. There was one permanent upper limb monoparesis and 3 strokes causing minor disability that largely resolved by 6 weeks postoperatively. There were 2 deaths due to myocardial infarction. There were no other episodes of myocardial infarction. During the second half of the series (24 patients over 12 years) there were 3 strokes (monoparesis and 2 minor disabilities) and no perioperative deaths. The total number of number of combined carotid and cardiac surgical operations performed by the surgeons undertaking bilateral CEA-CABG at various times over the 28 years was 293 such that bilateral CEA-CABG accounted for 16% of these procedures. In six patients, both internal mammary arteries were used as bypass conduits. Three of these patients (all female) developed sternal wound infection, one superficial and 2 deep mediastinal. Vagal nerve injuries occurred in 3 patients. The Kaplan-Meier estimates of 5 and 10 year overall survival were 78% (95%CI: 66-90) and 55% (95%CI: 40-70) respectively (Figure 1).

IV. DISCUSSION

Cardiovascular disease is the leading cause of death world wide and the importance of concurrent carotid and coronary disease has been recognized since the introduction of aorto-coronary bypass surgery, with the first series of combined CEA-CABG published in 1972.

Randomized trials.

A long awaited single centre randomized trial of combined CEA-CABG versus reversed staged CABG then CEA for patients with asymptomatic unilateral carotid disease, published by Hertz et al from the Cleveland Clinic in 1989, showed a reduced incidence of stroke in the combined CEA-CABG cohort. The difference was driven by an unusually high stroke rate in the staged cohort following CEA when
performed within 2 weeks of the CABG. In the second randomized trial published in 2011, the patients were extensively investigated and only those with unilateral disease and no evidence of ascending aortic or aortic arch atheromatous disease were included. This was in an attempt to ensure that the impact of the carotid disease was not clouded by stroke from other causes. The CEA stage in the staged cohort was performed 1 to 3 months after the CABG and in this trial the difference in the incidence of stroke was due to a high stroke rate between the CEA and the CABG in the staged group. Both trials used a threshold of ≥70% internal carotid stenosis at angiography and only included patients undergoing isolated CABG with the CEA.

The question of whether the carotid stenosis can be left untreated around the time of CABG has been raised and should be answered by the German multi-centre randomized trial (CABACS) comparing combined CEA-CABG versus CABG without carotid intervention, which commenced in 2010 with completion expected in 2018.

Single center series.
In the years between the publications of the 2 randomized trials, many reports of management of combined carotid and coronary disease were published. The lack of consistent definitions of “severe” carotid disease and of outcomes, and the failure to report outcomes for various subgroups separately, has made meaningful meta-analyses of the published data difficult. Retrospective analyses of staged management have often only included patients who have completed both stages thus eliminating from analysis those patients who sustained severe adverse events that precluded or substantially delayed progress to the second stage.

Several natural history studies of patients with carotid disease undergoing cardiac surgery without carotid intervention were published in the 1990s. These were used to formulate the American Heart Association guidelines for management of concurrent carotid and coronary disease, in which it was reported that “a carotid stenosis of 75% in an asymptomatic patient is an independent predictor of stroke immediately after CABG (OR of 9.87, P less than 0.005)”. However, the guidelines did not recommend CEA in asymptomatic patients with a stenosis of <80%. More recently, there have been a number of relatively small series of patients with carotid disease who have undergone cardiac surgery without carotid intervention and without neurological complications. It is likely that these series represent selective publication on the basis that the outcomes substantially varied from previous literature evidence. It is therefore debatable whether these represent an evolution in outcomes or statistical aberrations. The CABACS trial should resolve the question of evolution or aberration.

Registry data and guidelines.
The Nationwide Inpatient Sampling database (1998 – 2007) recorded 16,639 CEA-CABG procedures and 6,153 patients who had both procedures during the same admission but on different days. A further 20,737 patients underwent both procedures but without adequate date records and were not analysed. The mortality and neurological complications were similar between groups but the staged patients experienced more complications and higher costs. However, a report from the Society of Thoracic Surgeons (STS) database (2003 – 2007) showed that of 745,769 isolated CABG operations, 0.7% had CEA-CABG, 2.1% had prior CEA before CABG suggesting staged surgery in many, and a further 3.2% had a carotid stenosis >75% without intervention at the time of CABG. Multivariate analysis demonstrated poorer outcomes in the CEA-CABG group relative to the other 2 groups. This represents the best natural history registry data for such patients but does not appear to be consistent with the National Inpatient Sampling data and should not invalidate the 2 randomized trials.

Implications.
The majority of postoperative strokes that occur in patients with untreated carotid disease are not directly related to the carotid disease. Accordingly, it has been suggested that the carotid stenosis is simply a marker for wide spread vascular disease and that the treatment of the carotid stenosis will not reduce the stroke rate. Any benefit of CEA associated with CABG will not be apparent unless the study is sufficiently powered to detect a difference due to this less common cause of stroke. Likewise, a surgeon who routinely performs combined CEA-CABG may do so on 3% of patients and might optimally achieve a 5% stroke reduction in those patients. This would result in an overall stroke reduction in the total cardiac surgical cohort of just 0.15% which is unlikely to reach significance over most surgeons’ entire lifetime practice. However, a 5% reduction in stroke risk for any single patient is normally considered to be significant by the patient.

There remains a wide variation of opinion regarding the management of concurrent carotid and coronary disease. However, in Australia, there has been a tendency to avoid combined CEA-CABG over recent years. The Australian and New Zealand Society of Cardiothoracic Surgeons Cardiac Surgery Database recorded the number of combined procedures performed in New South Wales from 2007 to 2011 inclusive at 0.6% of the total cardiac surgical workload which is consistent with the rate of 0.7% recorded in the STS data described above. This was almost 10 times the incidence in Victoria where it was recorded at just 0.07%. In 2007, Kougias et al. from the Baylor Medical College, reported a series of 277 combined CEA-CABG representing 3.3% of the elective coronary surgical workload, after routine carotid ultrasound screening of 8277 pre-CABG patients.

Bilateral CEA-CABG.
Almost certainly, the published outcomes of the small series of bilateral CEA-CABG are at least in part subject to publication bias if they are not statistical aberrations. There is inadequate evidence to judge the true expected outcomes of bilateral CEA-CABG. Currently, the only available comparator is the published data for patients with bilateral carotid disease undergoing unilateral CEA-CABG but only short term results are available as there are too few reports of late follow up to assess the hazard of the un-operated carotid artery. These
results represent the natural history data as few centres are prepared to perform isolated CABG on these patients. For patients with bilateral carotid stenoses undergoing unilateral CEA-CABG, the carotid procedure is normally performed on the side with more severe disease. Often, the diagnosis of carotid stenosis is made with duplex ultrasound. The standard duplex criteria will only determine whether a stenosis is >80% but will not readily distinguish if one lesion is more stenosed than another or which carotid plaque is more unstable. Plaque instability is a predictor of carotid related stroke, however there is no reliable diagnostic test to determine this factor. The degree of carotid bifurcation stenosis in this setting is probably best determined by CT or catheter angiography. These imaging modalities will also be able to identify inflow and outflow lesions in the common carotid artery and carotid siphon. These tandem lesions may influence which side to treat. The use of acetazolomide stress cerebral SPECT may also be helpful in determining cerebral hemispheric hypoperfusion.

Study limitations. Our study included patients over a 28 year period during which time there was substantial evolution in cardiac surgery. This was likely reflected in the reduced mortality in the later half of the series although the stroke incidence was not reduced. Further improvements in operative techniques should provide better results. The study was a retrospective review with data acquired from databases and case notes. It is likely that definitions changed over time. It is not known exactly how the carotid stenoses were measured at angiography, although the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method is normally used in Australia. It is likely that most strokes following CABG are due to aortic disease. An aortic cross clamp was used in all patients and epi-aortic scanning was not used in any. An aortic partial occlusion clamp was also used in most patients and although it was not associated with all strokes, atheromatous embolization from the aorta was the likely cause of the single stroke death. There is an association between peripheral vascular disease and sternal wound infection and the occurrence of 2 deep sternal wound infections and 1 superficial wound infection out of six patients in whom bilateral internal mammary arteries were used raises concerns about the use of these conduits in this group of patients. Three other cases of combined bilateral CEA-CABG have been reported from Sydney hospitals with outcomes for 2 being published. All three patients survived but the incidence of stroke was not specifically stated.

Off-pump CABG and/or carotid stenting. A reduction in stroke rate has been reported where off pump coronary surgery has been performed without any aortic manipulation. Excellent results have also been reported for combined CEA-CABG when the CABG has been performed off pump. However, patients with concurrent carotid and coronary artery disease frequently have greater acuity with unstable angina, more severe coronary artery disease including left main coronary artery stenosis, and poorer left ventricular function, as noted in this study such that most of the combined operations are performed on cardiopulmonary bypass. Whether the surgery is performed on or off pump, the importance of careful and minimal aortic manipulation should be recognized at all times.

Lastly, there is the question of carotid artery stenting in patients with bilateral carotid and coronary disease, which cannot be answered on current data. Unless the carotid stenting and CABG are performed on the same day, the standard perioperative treatment of patients undergoing carotid stenting procedures mandates that the patient have dual antiplatelet agents of aspirin and clopidogrel for a minimum of six months. Performing CABG with dual antiplatelet treatment has a significant rate of perioperative haemorrhage. Reducing the antiplatelet dosage within the first six months of carotid stenting increases the chance of early carotid stent thrombosis. Carotid stenting prior to CABG has often entailed a delay of the CABG procedure by 4 weeks, during which there is a mortality rate even in stable patients and is unlikely to be acceptable in high acuity patients.

A retrospective analysis of outcomes of combined CEA-CABG, staged carotid stenting and CABG, and staged CEA-CABG noted the outcomes of the first 2 groups to be similar out to 1 year of follow up and both were better than staged CEA-CABG which recorded a high adverse event rate (including death) after the first stage. Beyond 1 year, the carotid stenting outcomes were significantly better than the other groups.

V. CONCLUSION

For patients with bilateral carotid and coronary artery disease, combined unilateral CEA-CABG has been the accepted standard of care. Despite the good outcomes in previously published series of combined bilateral CEA-CABG and the improved results in the latter part of this series, the question of management of the second carotid stenosis remains unanswered. The addition of carotid stenting and off pump surgery adds to the complexity of options for achieving optimal outcomes.

REFERENCES


