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CAROTID MASTERCLASS

Will Carotid Angioplasty Become the Preferred Alternative to Staged Or Synchronous Carotid Endarterectomy in Patients Undergoing Cardiac Surgery?

J. Van der Heyden^{a,*}, H.W. Lans^a, J.W. van Werkum^a,
M. Schepens^b, R.G. Ackerstaff^c, M.J. Suttorp^{a,☆}

^a Department of Interventional Cardiology, St-Antonius Hospital, Nieuwegein, The Netherlands

^b Department of Cardiothoracic and Cardiovascular Surgery, St-Antonius Hospital, Nieuwegein, The Netherlands

^c Department of Clinical Neurophysiology, St-Antonius Hospital, Nieuwegein, The Netherlands

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Abstract In the absence of randomized trials, the optimal management of patients who present with concomitant carotid and coronary artery disease remains an enduring controversy, with much of the debate revolving around whether staged or synchronous carotid endarterectomy (CEA) will reduce peri-operative morbidity and mortality after cardiac surgery. Although encouraging results have been reported using either strategy, there remains no consensus as to which is preferable. More recently, however, carotid artery angioplasty with stenting (CAS) has emerged as a potential alternative to CEA. In 'high-risk for CEA' patients, CAS has shown comparable short and long-term outcome rates to CEA. Accordingly, CAS followed by cardiac surgery could offer a less invasive (and safer) therapeutic option in cardiac patients. This paper reviews the evidence to date supporting the use of CAS + CABG, while highlighting potential situations where such a strategy might be harmful. In particular, it will focus on how the need for dual antiplatelet therapy after CAS can be balanced with avoiding unnecessary bleeding complications after cardiac surgery.

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* Corresponding author. Jan Van der Heyden, MD, Department of Interventional Cardiology, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands. Tel.: +31 30 6099111; fax: +31 30 6092277.

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E-mail address: jvdheijden@antonius.net (J. Van der Heyden).

Introduction

The optimal management of patients with concomitant carotid and coronary artery disease who are scheduled to undergo coronary bypass (CABG) remains controversial. The

heterogeneity of this subset of patients who present with generalized atherosclerosis (and the lack of high-quality natural history data) is the key to understanding this controversy.

The fact that candidates for cardiac surgery present with varying degrees of cerebrovascular disease is not surprising and, we would contend, differentiation between neurologically symptomatic and asymptomatic patients is unnecessary. Silent brain infarcts are a common finding on magnetic resonance imaging (MRI) in neurologically asymptomatic elderly patients. Breteler *et al.* reported that white matter brain abnormalities on MRI were found in nearly one-third of patients with a history of hypertension, diabetes mellitus, peripheral vascular disease and myocardial infarction.¹ Consequently, it is our contention (though not that of all observers) that the treatment of carotid disease prior to CABG should involve all patients, irrespective of their neurological status. In practice, this implies equal treatment for symptomatic and asymptomatic patients, differing only in the stenosis threshold for intervening.

The aetiology of peri-operative neurological events during cardiac surgery is multifactorial. Although carotid artery disease is an important factor, it is probably only responsible for about 50% of post-CABG strokes,² while more than half of all territorial infarctions on computed tomography (CT) or at autopsy are not related to carotid disease alone.³ Atherosclerosis of the ascending aorta can also cause stroke due to macro-embolisation to the cerebral vessels and the role of ascending aorta atherosclerosis still needs to be evaluated. It has probably been seriously underestimated. Notwithstanding differences of opinion regarding the predominant cause of post-CABG stroke, hypoperfusion (due to a severely stenotic carotid artery) or micro-embolisation (from an ulcerated carotid plaque) are important aetiological mechanisms.^{4,5} Hypotension induced ischaemic neurological injury during cardiopulmonary bypass is hard to avoid in patients with severe carotid stenosis. During cardiopulmonary bypass cerebral autoregulation is severely impaired, making cerebral blood flow directly proportional to cerebral perfusion pressure.⁵

Established Proof or Accumulated Facts

Despite the limited available evidence regarding the benefit of prophylactic carotid revascularisation, many cardiac surgery patients with advanced carotid and coronary disease are currently treated with staged or synchronous carotid/coronary interventions. The rationale being that this strategy will reduce perioperative mortality and neurological morbidity. However, the overall effectiveness of this approach is ultimately dependent on the procedural risk. If it is too high, it is unlikely to confer benefit.

In a recent systematic review and meta-analysis, Naylor *et al.*⁶ observed a 10–12% cumulative risk of death, stroke or myocardial infarction (MI) following staged or synchronous operations and questioned whether these risks were too high to confer any clinical benefit (compared with isolated CABG) in patients who were predominantly neurologically asymptomatic. As a consequence, there has been considerable interest in establishing whether CAS might be a safer and better alternative. CAS is less-invasive, it does not require a neck incision, it does not cause cranial

nerve injury and it involves shorter hospital stays.^{7–9} In studies of patients considered 'high risk for CEA', CAS was considered at least 'as good as' CEA.⁷

The concept of performing CAS prior to cardiac surgery is not novel, but relatively few studies have reported their outcomes and several have shown conflicting results (Table 1). In favour of CAS + CABG were studies by Ziada, Kovacic and van der Heyden.^{10–12} Ziada reported significantly fewer adverse events in patients who underwent CAS prior to cardiac surgery, despite a higher baseline risk profile compared to those undergoing combined CEA and CABG.¹⁰ Kovacic reported a death, stroke, or MI rate of 10% among 20 patients undergoing staged CAS-CABG.¹¹ The largest series is by Van der Heyden where 356 patients were evaluated regarding safety, procedural risk and durability.¹² In this study, the death rate was 3.7%, while the stroke rate and MI rates were 3.1% and 2.0% respectively. Table 1 also details the rates of MI after CAS but before CABG. The overall periprocedural MI rate of 2.0% is in contrast with observational studies of CEA and CABG, which vary from 3.6% (synchronous) to 6.5% (staged).⁶ It should also be borne in mind that a considerable number of patients undergo CABG plus valve replacement or major aortic repair. McKhann *et al.* reported that these procedures incur a peri-operative stroke rate of 7.9% (CABG + valve) and 8.7% when aortic repair was included.¹³ This advocates a progressive preoperative risk stratification and a dedicated management by selecting the optimal treatment to pursue the lowest complication rate. In these 'high risk' patients, CAS prior to cardiac surgery could prove to be a valuable alternative to the surgical approach.^{14,15}

By contrast, unfavourable results following staged CAS + CABG procedures in 52 patients were reported by Randall.¹⁶ Interestingly, the relative paucity of periprocedural neurological events after CAS was offset by a much higher risk of death/stroke after CABG (19.2%). This was attributed to a prolonged delay to performing CABG.

Optimal Timing and Antiplatelet Therapy

Randall's series exposed an important paradox regarding how one had to balance the optimal (dual) antiplatelet therapy required for CAS against not leaving the patient too long before undergoing CABG (ie how long did the patient have to be left on clopidogrel to minimise the risks of stent thrombosis but avoid other haemorrhagic complications). Platelet accumulation immediately after CAS and embolization to distal sites is an important cause of procedural complications.

Antiplatelet therapy with clopidogrel is effective in reducing stent thrombosis in patients undergoing CAS and reduces the risk of vascular events in other arterial beds, thereby expanding the benefits of antiplatelet therapy and providing a rationale for long-term use.¹⁷ However, it is well known that antiplatelet drugs also increase bleeding complications during cardiac surgery and dual antiplatelet regimes could greatly increase the risk of bleeding in the perioperative period.¹⁸ Two trials comparing dual antiplatelet regime versus aspirin alone during CAS have clearly shown that dual antiplatelet therapy is necessary for optimal outcomes.^{19,20} In the majority of patients, stent

Table 1 Short-term Outcome of Staged CAS and Cardiac Surgery

Reference	year	n	after CAS and prior to Cardiac Surgery, n (%)			after Cardiac Surgery n (%)			Total n (%)					
			death	stroke	MI	death	stroke	MI	death	stroke	MI			
Ziada ¹⁰	2005	56	2 (3.6)	1 (1.8)	0	1 (1.8)	0	2 (3.6)	1 (1.8)	2 (3.6)	3 (5.4)	1 (1.8)	2 (3.6)	6 (10.7)
Kovacic ¹¹	2006	20	0	1 (5)	0	0	0	1 (5)	1 (5)	1 (5)	0	1 (5)	1 (5)	2 (10)
Randall ¹⁶	2006	52	3 (5.8)	0	1 (1.9) ^a	4 (7.7)	3 (5.8)	n.a.	n.a.	3 (5.8)	7 (13.5)	3 (5.8)	n.a.	n.a.
Van der Heyden ¹²	2007	356	1 (0.3)	5 (1.4)	2 (0.6) ^b	12 (3.4)	6 (1.7)	5 (1.4) ^b	11 (3.1)	7 (2.0)	13 (3.7)	11 (3.1)	7 (2.0)	31 (8.7)

n.a., not applicable.

^a patient died after MI.

^b nonfatal MI.

endothelialization occurs between 28 and 96 days after CAS.^{21,22} During this vulnerable time period, the exposed metallic stent acts as a prothrombotic surface for platelet activation.¹⁹ Not surprisingly, CAS advocates are very reluctant to stop clopidogrel prematurely. Accordingly, some sort of compromise is inevitable.

In practice, the delay between performing CAS and cardiac surgery will inevitably be determined by the urgency of the cardiac disease. Hemodynamic instability, dynamic ST-T changes on electrocardiography, refractory angina despite optimal medical therapy or severe left main disease warrant immediate action. In those patients requiring urgent cardiac surgery, there are three possible options. First, CAS is performed using dual antiplatelet therapy which is not then stopped prior to performing an urgent CABG procedure (unlikely to find universal favour with cardiac surgeons). Mendiz²⁴ has reported a series of 30 patients undergoing “fast track” or “synchronous” CAS-CABG, with no strokes or neurological deaths. Their practice was to perform CAS and then immediately transfer the patient to the operating room. Aspirin and unfractionated heparin were administered during CAS and clopidogrel was started after CABG.²⁴ Kramer *et al.* reported no deaths or neurological events among 37 patients treated with CAS who underwent CABG within 48 hours.²⁵ In their series, antithrombotic therapy during and after CAS consisted of unfractionated heparin and the glycoprotein IIb/IIIa receptor antagonist eptifibatid (continued ≤6 hours before CABG). The third option is to consider combined CEA and CABG.

If, however, the patient’s cardiac condition allowed three weeks to elapse before CABG was scheduled, it is our practice to perform CAS (with dual antiplatelet therapy) and then stop the clopidogrel 7 days pre-CABG (aspirin continued) before restarting the clopidogrel after recovery from surgery.²³ In our experience, no carotid-stent thrombosis or increased perioperative bleeding complications have been observed and this may evolve to be the best compromise in non-urgent patients. Ziada’s patients received oral aspirin and clopidogrel before CAS and in 50 patients adjunctive glycoprotein IIb/IIIa platelet inhibition was used. After discharge from CAS they were treated for 2 to 4 weeks with aspirin and clopidogrel. The latter was stopped 1 week before surgery which was performed after a median time of 40 days. In Kovacic’s population aspirin and clopidogrel were commenced prior to cardiac surgery. If possible, CABG was not scheduled within 4 weeks of carotid stenting. The mean interval between carotid stenting to CABG was 69.6 ± 39.6 days. Antiplatelet therapy was ceased >3 days prior to cardiac surgery in 10/20 patients and continued up to and including the day before surgery in the remainder. In Randall’s study the routine use of dual antiplatelet therapy before stent insertion was introduced during the study period, with 82.7% of patients pre-treated with combined aspirin and clopidogrel. The timing of cardiac surgery after stenting was at the discretion of the cardiac surgeon with no further detail mentioned. After the introduction of routine use of clopidogrel in carotid stenting, it was recommended that this was continued for ≥14 days. Future antithrombotic therapy might involve new generation thienopyridines, such as prasugrel and cangrelor, which have a faster onset of action, as well as more

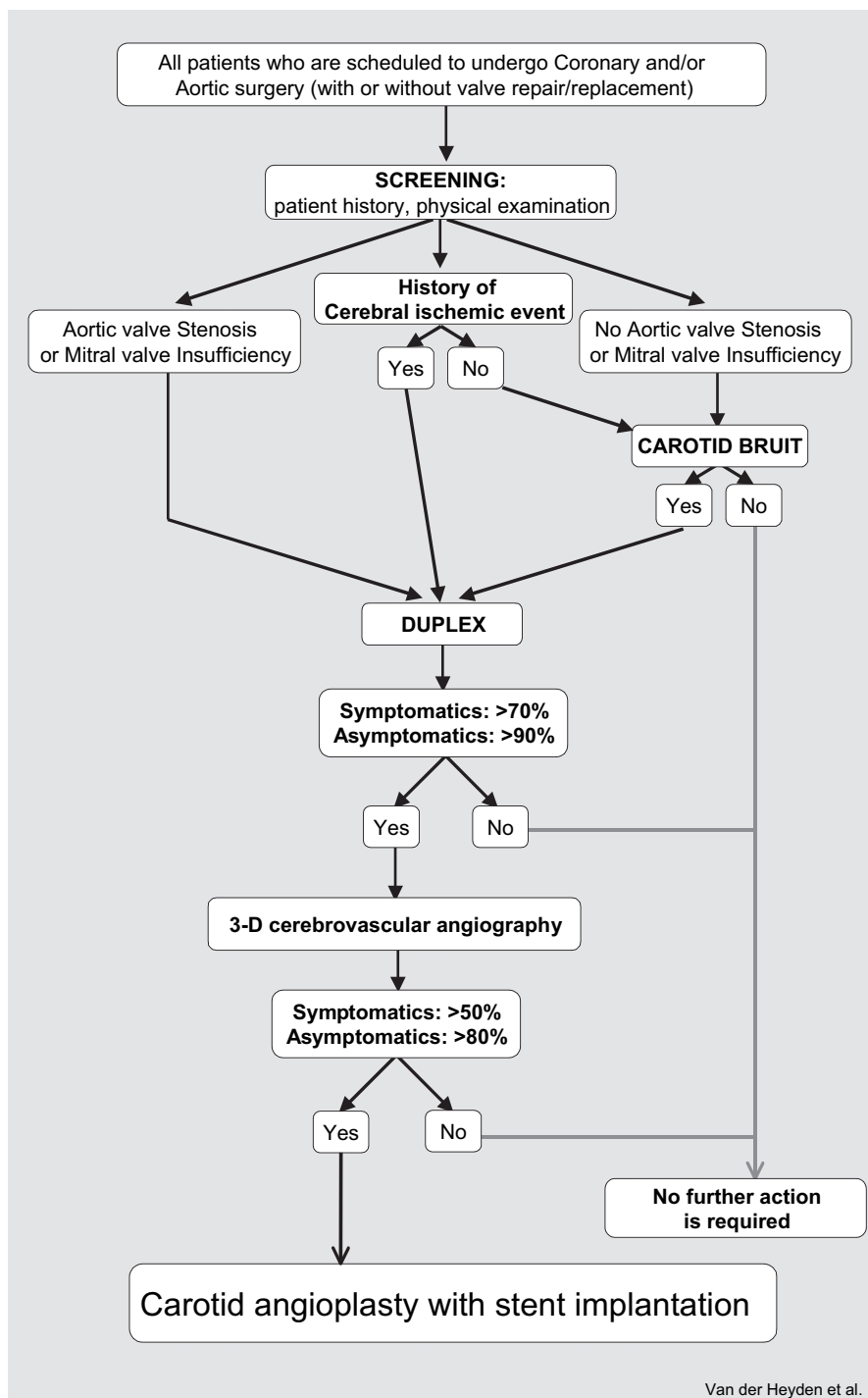


Figure 1 Institutional guidelines for the screening of patients scheduled for cardiac surgery.

potent, and less variable, inhibition of platelet function *ex vivo*.²⁶

Case Selection

In Nieuwegein, all patients scheduled for cardiac surgery are screened for carotid artery disease by means of history and physical examination and selective Duplex ultrasound according to institutional guidelines (see Fig. 1). A carotid

artery stenosis is considered “significant” when a diameter reduction of at least 70% is measured in symptomatic patients or more than 90% in asymptomatic patients. Patients fulfilling these stenosis thresholds then undergo diagnostic cervical-cerebral angiography which also includes intracranial views to determine the patency and completeness of the circle of Willis. Three-dimensional rotational angiography is performed in order to obtain detailed information about the target stenosis.²⁷

Significant carotid artery disease is defined as a target lesion in the common carotid artery, internal carotid artery, or at the bifurcation with a angiographic stenosis severity of more than 50% of the luminal diameter in symptomatic patients or >80% in those without symptoms according to NASCET criteria.^{28,29} Patients are accepted for CAS by a consensus decision involving a neurologist, cardiovascular surgeon and interventional cardiologist. When the aortic arch is markedly unfolded and peripheral vascular disease or severe tortuosity makes any endovascular procedure more hazardous, the patient is referred for combined CEA-CABG. Furthermore, patients with allergy and/or insensitivity to acetylsalicylic acid, heparin, or clopidogrel and severe renal insufficiency are also not suited for CAS.

Procedural Complications

Whether or not the 3 % rule for isolated CEA can be achieved in such a high risk population remains uncertain. However, undertaking a CAS procedure with a $\leq 3\%$ complication rate in asymptomatic patients and $< 6\%$ in symptomatic patient, should remain the goal of all interventionists.^{30,31} Patients with recent onset neurological symptoms may pose an additional problem. They face the highest risk of stroke in the first few weeks of the index event and CAS/CEA may have to be performed with the acceptance that the procedural risk will be higher.³² Delaying the intervention might reduce the procedural risk but it lessens the benefit of intervening because of the number of strokes that happen whilst waiting.

Future perspectives

Ideally, a randomised trial would establish the roles of medical therapy, CEA and CAS. Unfortunately, the target population is too small. In a nationwide US survey, among the population of patients undergoing CABG, those undergoing combined CEA-CABG accounted for only 1.1% in 1993 and 1.6% in 2002.³³ Even lower was the proportion of combined CEA-CABG procedures compared with CABG in a recent Canadian survey (0.5%).³⁴ Finally, high-volume centers report between 13 and 30 combined surgical procedures per year. Consequently, given the assumption of a 30-day death, stroke, or MI rate in the CEA-CABG group of 12% and a noninferiority boundary of 3%, such a study would require an enrollment of 4000 patients to be adequately powered.³⁵ In the absence of such a trial, a realistic way of improving the evidence would be to perform small, randomized studies focusing on surrogate end points, such as the occurrence of new lesions on MRI or measuring the amount of microemboli detected on transcranial Doppler during procedures.³⁶

Conclusion

In the absence of evidence, the optimal revascularization strategy for the heterogeneous group of patients with concomitant coronary and carotid disease will have to be decided on a case-by case basis by a multidisciplinary team that includes neurologists, surgeons, and interventionists.

This will take into account the comorbidities of the patient, the degree of urgency of cardiac surgery, and local expertise.

Conflict of Interest

None.

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