Systematic Preoperative Coronary Angiography and Stenting Improves Postoperative Results of Carotid Endarterectomy in Patients with Asymptomatic Coronary Artery Disease: A Randomised Controlled Trial

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Abstract

Objective: To evaluate the usefulness of systematic coronary angiography followed, if needed, by coronary artery angioplasty (percutaneous coronary intervention (PCI)) on the incidence of cardiac ischaemic events after carotid endarterectomy (CEA) in patients without evidence of coronary artery disease (CAD).

Materials and methods: From January 2005 to December 2008, 426 patients, candidates for CEA, with no history of CAD and with normal cardiac ultrasound and electrocardiography (ECG), were randomised into two groups. In group A (n = 216) all the patients had coronary angiography performed before CEA. In group B, all the patients had CEA without previous coronary angiography. In group A, 66 patients presenting significant coronary artery lesions at angiography received PCI before CEA. They subsequently underwent surgery under aspirin (100 mg day⁻¹) and clopidogrel (75 mg day⁻¹). CEA was performed within a median delay of 4 days after PCI (range: 1–8 days).

Risk factors, indications for CEA and surgical techniques were comparable in both groups (p > 0.05). The primary combined endpoint of the study was the incidence of postoperative myocardial ischaemic events combined with the incidence of complications of coronary
Patients with coronary artery disease (CAD) are at high risk of postoperative myocardial complications.\textsuperscript{1,2} Given the systemic nature of atherosclerosis, candidates for peripheral arterial reconstruction for obstructive disease have a higher probability of having associated CAD than candidates for nonvascular surgical intervention.\textsuperscript{3} Systematic preoperative coronary angiography in peripheral vascular surgical candidates has already shown the high prevalence of CAD in this population. Studies have also shown the high sensitivity of coronary angiography compared with other cardiac investigations, and the benefit of coronary artery bypass grafting (CABG) before peripheral revascularisation.\textsuperscript{3,4} The results of these studies, together with the improvement of coronary artery catheterisation technique, and the contemporary availability of coronary stenting over CABG could theoretically support the performance of coronary angiography, and possibly stenting, as part of the standard preoperative protocol for patients scheduled to undergo peripheral arterial revascularisation. Nonetheless, disparate opinions exist concerning the indication for coronary angiography and coronary revascularisation before elective peripheral vascular surgery.\textsuperscript{5}

In addition, even if some studies have shown the safety and efficacy of coronary angiography and revascularisation in preventing postoperative cardiac events in non-cardiac surgery,\textsuperscript{6–9} other reports have failed to demonstrate the benefit of such an aggressive preoperative protocol, with the risk of operative bleeding due to the aspirin and clopidogrel regimen, which is required when performing coronary stenting.\textsuperscript{1,10–13}

One possible explanation of these contradictory results may be the inclusion of non-comparable groups of patients, with differing preoperative cardiac status and risk factors. To avoid this problem, in this study, we randomised all patients scheduled to undergo an elective carotid endarterectomy (CEA) without any clinical history or electrical signs of ischaemic heart disease. In group A, all patients had coronary angiography, followed, if needed, by coronary angioplasty with stenting. Patients randomised to group B received a standard cardiac evaluation before endarterectomy. Our hypothesis was that, in patients with a significant carotid stenosis even without any history of CAD, systematic preoperative coronary angiography followed, if needed, by coronary stenting could significantly improve the postoperative cardiac outcome after CEA, as compared with patients receiving a standard preoperative cardiac evaluation.

**Methods**

**Study design**

This randomised trial was conducted at two academic surgical centres and in one affiliated surgical service. The trial was supported by a grant from the University of Rome. The institutional review board of the University approved the trial protocol and all patients provided written informed consent. Random assignment of patients to the two treatment groups was done independently of participating centres in a one-to-one ratio. The randomisation sequence was generated by a computer program and supplied to centres using sealed opaque envelopes generated in blocks of six.

**Selection of patients**

Patients referred for CEA were eligible for enrollment if they had no apparent evidence of CAD, defined as the absence of any clinical sign or history of ischaemic cardiac disease, associated with the absence of electrical signs of cardiac ischaemia at rest and with a left ventricular ejection fraction >50\% at trans-thoracic echocardiogram. Patients suspected of having coronary disease or dyspnoea; patients with previous events of myocardial ischaemia or previously treated either with percutaneous coronary intervention (PCI) or with coronary artery bypass grafting (CABG); or patients with other cardiac dysfunctions, including arrhythmias, were excluded from the study.

After determination of eligibility for the trial, including a standard preoperative cardiac evaluation, patients were randomly assigned either to undergo CEA (group B) or to complete this evaluation with coronary angiography followed, if needed, by PCI prior to CEA (group A).

In group A, coronary arteries, as seen on angiography, were considered abnormal if they had one or more coronary
stenosis >75%, and were treated by either PCI or CABG. This decision was made following a multidisciplinary discussion between the interventional cardiologist, the cardiac surgeon and the vascular surgeon in charge of the patient.

PCI always involved angioplasty and stenting.

During the stenting procedure, all patients received an intravenous bolus of tirofiban followed by a dual oral anti-platelet drug regimen, consisting of 100 mg of aspirin and 75 mg of clopidogrel daily. This treatment was continued until the morning of scheduled CEA, and resumed the evening of the operation. CEA was performed with a mean delay of 4 days after PCI (extremes 1–8 days). After PCI, and after CEA, all patients had a continuous ECG performed for 24 h, and their serum troponin concentration was assessed at 4, 8, 12 and 24 h after the procedure. Patients requiring CABG underwent combined CEA and CABG during the same hospitalisation.

Before CEA, patients in both groups received atorvastatin. In addition, 141 patients (65%) in group A, and 152 (72%) in group B received beta-blocking drugs. In group B, all patients received 100 mg of aspirin, starting at least 1 week before CEA.

The indications for CEA included carotid artery stenosis >60% according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, either asymptomatic or symptomatic. Carotid endarterectomy was performed under general anaesthesia, with transcervical cerebral oxymetry monitoring (INVOS 5100C, Somanetics, Troy, MI, USA). The surgical technique consisted of either an eversion endarterectomy or an endarterectomy with a polyester patch closure. Indications for shunting were a recent stroke, occlusion of the contralateral internal carotid artery or a significant decrease of ipsilateral cerebral hemisphere oxygenation after clamping of the carotid bifurcation. Cervical drainage was routinely left in place and removed the day after surgery.

Before clamping, all patients received 50 IU kg⁻¹ of heparin, which was not reversed by protamine at the end of the procedure. After carotid revascularisation, all patients were admitted to the recovery room for 4–5 h. In the absence of complications, they returned to the ward within 24 h, and were discharged 3 days after surgery.

Primary endpoint

The primary combined endpoint of the study was the occurrence of any postoperative myocardial ischaemic event, combined with any complication related to coronary angiography and stenting.

The occurrence of an ischaemic myocardial event was defined as any electrical abnormality on the ECG suggestive of ischaemia associated with an elevation of serum troponin level, associated or not with clinical symptoms.

Electrical signs consistent with myocardial ischaemia included S-T segment depression or elevation and T-wave inversion. Postoperative deaths either associated with any modification of the above-mentioned cardiac parameters, or with the detection of recent areas of ischaemia at myocardial post-mortem examination, were considered to be due to myocardial infarction.

Results of PCI were analysed in intention to treat. Failures to perform the planned PCI, or residual stenosis of more than 20% after coronary PCI were considered as a failure of the procedure. The site of arterial puncture was assessed for haematoma, thrombosis or other complications. These events were considered as complications of PCI if they required surgical treatment.

Secondary endpoint

Secondary endpoint included death and stroke rates, cranial nerve palsy and cervical haematoma. Cervical haematomas were recorded only if they required surgical evacuation.

Statistical analysis

The study was designed with a power of 80% to detect differences in primary outcome in 200 patients per group, with a two-sided alpha of 0.05, on the basis of a 5% difference in the incidence of postoperative coronary events after CEA in patients with coronary angiography compared with patients without coronary angiography. Proportions were compared using the chi-square and Fisher’s exact tests.

Binary logistic regression analysis with SPSS® was used to measure the effects of binary risk factors on postoperative cardiac ischaemic events whilst adjusting for inter-relationships between them. The output is presented with the coefficient and statistics of the variables that have been included in the model and the constant, with calculation of the B value that represents the change in the outcome resulting from a unit change in the predictor variable. The Wald statistic, which has a chi-square distribution, reflects whether the B coefficient for that predictor was significantly different from zero. The Hosmer and Lemeshow test was also computed for this model as a chi-square to ensure that the data fit the model well.

Results

From January 2005 to December 2008, 426 patients were enrolled in the study. Among these, 216 were randomised to undergo preoperative coronary angiography (group A) prior to CEA, and 210 underwent CEA without prior coronary angiography (group B). No significant differences between the two study groups were observed concerning demography or risk factors (Table 1).

In group A, 68 patients (31%) had a significant stenosis of the coronary arteries. Sixty-six patients underwent treatment with PCI and two with CAGB. The pattern of the coronary lesions and details of treatment are summarised in Table 2. PCI was performed with a median delay of 4 days (range: 1–8 days) before CEA and always consisted of angioplasty and stenting. In general, 94 coronary artery stents were deployed, with 82 drug-eluting stents and 12 bare stents. Forty-three patients (65%) received one stent and 23 patients (35%) more than one. Indications for carotid surgery and details of surgical technique were comparable in both groups (Table 3).

Primary endpoint

No postoperative myocardial ischaemic event occurred in group A, whereas nine ischaemic events were observed in
group B (4.2%) \( p = 0.01 \). These events consisted of one fatal myocardial infarction extending to the septum, and eight cases of non-fatal coronary ischaemia with electrical and enzymatic alterations that could be managed by an appropriate medical treatment. These eight patients had a coronary angiography within 2–6 weeks after carotid surgery followed by a successful PCI in five patients with, respectively, one single-vessel, one double-vessel, one left main and two triple-vessel coronary lesions. CABG was performed in one patient with left main coronary artery disease. The remaining two patients had coronary lesions with extensive triple-vessel disease including occlusion of tributaries not amenable to coronary revascularisation.

Using univariate analysis, smokers and patients in group B not having preoperative coronary angiography had a higher risk of a postoperative coronary ischaemic event (Table 4). Binary logistic regression analysis was used to confirm the relationship between predictor variables and postoperative cardiac ischaemia. As shown in Table 5, preoperative coronary angiography was the only independent variable that was significantly correlated with the occurrence of postoperative coronary ischaemia after CEA. The odds ratio for the patients in group A indicates that, when keeping all other variables constant, patients having coronary angiography before carotid surgery were 4 times less likely to have a cardiac ischaemic event after carotid surgery. In this series, no patients having preoperative coronary angiography followed, when positive, by PCI or CABG, had a postoperative cardiac ischaemic event. In addition, no complication related to coronary angiography or to PCI occurred in this series.

### Secondary endpoint

Concerning survival, two patients died during the postoperative period, one from myocardial infarction and the other from stroke. Both deaths occurred in group B (0.9%). There was no mortality in group A \( p = 0.24 \).

The 30-day postoperative death and stroke rate (Table 6) was 0.5% in group A and 1.8% in group B (two strokes, including one fatal stroke and one death following myocardial infarction) \( p = 0.36 \). No cervical haematoma requiring re-operation was observed in either group.

### Discussion

The goal of this study was to assess the value of systematic preoperative coronary angiography prior to CEA to prevent postoperative myocardial ischaemic events in patients with a normal ECG and normal cardiac echography and without any history of coronary ischaemia. Our findings support the hypothesis that performing preoperative coronary angiography followed, if needed, by PCI prior to CEA, significantly reduces the incidence of postoperative cardiac ischaemic events without any added morbidity. The optimal cardiac evaluation before peripheral vascular surgery and major non-cardiac surgery remains a matter of debate. Numerous studies have yielded contradictory results, and, overall, they failed to demonstrate the real benefit of systematic coronary angiography in the preoperative cardiac work-up of these patients.\(^1\)\(^{10-12}\) Several reasons may have contributed to these inconclusive results: in particular, differences in patient selection, whereby patients with different stages of CAD were included; type of peripheral bypass considered; and the evolution of medical devices for PCI, including catheters and stents.

As the incidence of significant asymptomatic CAD in patients with peripheral arterial disease is well known,\(^{15-17}\) we thought that it would be interesting to discover if treating significant, although asymptomatic, CAD ahead of a peripheral arterial revascularisation was a valuable option.

To obtain a homogeneous clinical trial, this randomised study was deliberately restricted to patients undergoing CEA with no history or evidence of CAD. These patients were enrolled at three centres performing CEA with comparable surgical and anaesthesiological protocols. This decision was taken to avoid major differences in PCI and CEA technique and competence that may have biased the results. Nevertheless, subjecting asymptomatic coronary patients even with significant coronary stenosis to PCI may be considered more risk than profit for the patient, especially when dealing with single- and double-vessel disease, without left main equivalent disease. However, in the present study, two out of eight patients in group B

### Table 1

<table>
<thead>
<tr>
<th>Demography and risk factors.</th>
<th>Group A</th>
<th>Group B</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs) ( \pm ) SD</td>
<td>77 ( \pm ) 7</td>
<td>74 ( \pm ) 7</td>
<td>0.79</td>
</tr>
<tr>
<td>Men (%)</td>
<td>65</td>
<td>68</td>
<td>0.60</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76</td>
<td>80</td>
<td>0.90</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>40</td>
<td>43</td>
<td>0.62</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>29</td>
<td>26</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24</td>
<td>22</td>
<td>0.73</td>
</tr>
<tr>
<td>Lower limb occlusive disease (%)</td>
<td>10</td>
<td>8</td>
<td>0.40</td>
</tr>
<tr>
<td>Chronic renal insufficiency (%)</td>
<td>4</td>
<td>5</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**Table 1 Demography and risk factors.**

The 30-day postoperative death and stroke rate was 0.5% in group A and 1.8% in group B (two strokes, including one fatal stroke and one death following myocardial infarction) \( p = 0.36 \). No cervical haematoma requiring re-operation was observed in either group.

**Table 2** Coronary lesions in patients (Group A).

<table>
<thead>
<tr>
<th>Coronary lesions</th>
<th>Patients N (%)</th>
<th>PCI N (%)</th>
<th>CABG N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-vessel disease</td>
<td>43 (64)</td>
<td>43 (64)</td>
<td>–</td>
</tr>
<tr>
<td>Double-vessel disease</td>
<td>19 (28)</td>
<td>19 (28)</td>
<td>–</td>
</tr>
<tr>
<td>Triple-vessel disease</td>
<td>3 (4)</td>
<td>2 (2.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Left main disease</td>
<td>3 (4)</td>
<td>2 (2.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Total</td>
<td>68 (100)</td>
<td>66 (97)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

**Table 2 Coronary lesions in patients (Group A).**

Pattern of asymptomatic coronary lesions seen at coronary angiography in 68 patients (Group A). These lesions were treated before carotid surgery by coronary angioplasty and stenting (PCI) in 66 patients and by coronary bypass (CABG) in 2 patients.
experiencing non-fatal postoperative myocardial ischaemia actually had single-vessel disease (one patient) and double-vessel disease (one patient), which were successfully treated by PCI. Surgery probably triggered the symptoms and led to treatment in these two patients who would otherwise have experienced symptoms and coronary complications later in life. It can be speculated that, in this group of patients, preoperative PCI can prevent postoperative ischaemia and eventually protect patients from later coronary ischaemic events.

Patients with PCI received dual anti-platelet treatment with aspirin and clopidogrel that cannot be discontinued for at least 6 months after PCI. In this setting, patients undergoing CEA may be considered at risk of postoperative bleeding. This gives rise to the problem of either delaying CEA, with the consequent risk of stroke, or operating early on patients receiving dual anti-platelet treatment. We have shown in this study, as others,18–22 that CEA can be performed safely within a week of PCI in patients receiving dual anti-platelet treatment. No major bleeding or cervical haematomas, and no coronary stent thromboses were observed in this series. In addition, obtaining a perfect haemostasis of the surgical field at the end of CEA was not more demanding and did not significantly lengthen the duration of CEA, when compared with CEA performed in patients receiving only aspirin (Table 3).

Previous studies have shown the beneficial effect of postoperative beta-blocker therapy and of statins in reducing the risk of myocardial ischaemic events in major non-cardiac surgery and in vascular surgery.23–25 This study did not address the issue of whether optimal postoperative medical treatment could equal coronary revascularisation in reducing the risk of postoperative ischaemic myocardial events. However, given that this study was randomised and that all the patients received statins, anti-platelet agents and a consistent number of them in both groups were receiving beta-blockers, it is clear that coronary angiography followed, if needed, by PCI seems to allow better protection from myocardial ischaemic events than statins, anti-platelet agents and beta-blockers alone. Patients having PCI received clopidogrel in addition to aspirin, and, compared with other patients, this might be considered a potential bias. We recognised this potential limitation from the beginning of the trial; nonetheless, we thought that it would have been unethical to expose all the patients of both groups to the potential bleeding risks of dual anti-platelet treatment, assuming that dual treatment and statins would have little difference in impact on coronary

Table 3  Carotid endarterectomy. Indications and technique.

<table>
<thead>
<tr>
<th>Indications for carotid surgery</th>
<th>Group A</th>
<th>Group B</th>
<th>Odds ratio (95%CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>157 (72)</td>
<td>151 (71)</td>
<td>1.04 (0.68–1.59)</td>
<td>0.91</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>46 (22 )</td>
<td>50 (24 )</td>
<td>0.87 (0.55–1.36)</td>
<td>0.56</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (6)</td>
<td>9 (4)</td>
<td>1.43 (0.59–3.42)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Operative technique

| CEA with patch closure                                            | 177 (82 )| 176 (84 )| 0.87 (0.53–1.45)  | 0.69    |
| CEA (eversion)                                                    | 39 (18 ) | 34 (16 )|                  |         |
| Carotid shunt                                                     | 26 (12 ) | 19 (9)   | 1.45 (0.77–2.70)  | 0.27    |
| Duration of operation (minutes ± SD)                             | 123 ± 21 | 127 ± 12| 0.82              |         |
| Preoperative bleeding (mL ± SD)                                   | 126 ± 42 | 112 ± 36| 0.78              |         |

Indications for carotid surgery and operative surgical techniques were comparable in both groups. CEA: carotid endarterectomy, SD: standard deviation.

Table 4  Effects of risk factors and of preoperative coronary angiography on the occurrence of postoperative cardiac ischaemic event. Univariate analysis.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male vs female</td>
<td>0.75</td>
<td>0.26–2.15</td>
<td>0.59</td>
</tr>
<tr>
<td>Hyperlipidemia vs none</td>
<td>0.86</td>
<td>0.30–3.07</td>
<td>0.94</td>
</tr>
<tr>
<td>Diabetes vs none</td>
<td>2.28</td>
<td>0.80–1.95</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension vs none</td>
<td>1.14</td>
<td>0.31–3.10</td>
<td>0.84</td>
</tr>
<tr>
<td>Lower limb occlusive disease vs none</td>
<td>2.68</td>
<td>0.72–9.97</td>
<td>0.18</td>
</tr>
<tr>
<td>Smoker vs non-smoker</td>
<td>2.98</td>
<td>1.01–8.88</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary angiography vs none</td>
<td>0.23</td>
<td>0.06–0.83</td>
<td>0.01</td>
</tr>
</tbody>
</table>

With Univariate Analysis (Pearson’s Chi-Square and Fisher’s Exact Test), two variables were significantly correlated with the onset of postoperative cardiac ischaemia. Smokers had a three-fold increase of postoperative cardiac ischaemia and patients randomised to coronary angiography (group A) followed possibly by coronary revascularization were 4 times less likely to sustain postoperative myocardial ischaemia.
artery disease stabilisation compared with single anti-platelet treatment and statins. A further randomised trial comparing patients with PCI and dual anti-platelet regimen versus patients with dual anti-platelet regimen alone for treating asymptomatic coronary artery lesions could specifically address this important issue. This study did not address the issue of the efficacy of systematic coronary angiography and eventual PCI or CABG on late survival in patients undergoing CEA. Although the COURAGE trial has shown that optimal medical treatment is equivalent to PCI for the treatment of stable coronary disease, the limited use of drug-eluting stents and patient-selection bias in the COURAGE trial do not allow for the exclusion of the potential benefit of optimal coronary revascularisation together with best medical treatment in patients having asymptomatic but significant coronary artery disease discovered at the time of CEA. Considering other studies that failed to demonstrate a substantial benefit of coronary artery revascularisation over the best medical treatment in patients undergoing aortic surgery, the same comments may apply since they exclude patients with common trunk coronary lesions, use mainly bare stents and discontinue anti-platelet drugs before surgery.

In conclusion, our study demonstrates the potential benefit of systematic coronary angiography, followed, if needed, by PCI, in patients with significant but asymptomatic coronary artery disease before CEA. We recognise, however, that our results, coming from a relatively small randomised study, should be confirmed by larger trials that should include a long-term follow-up to analyse the potential impact of this aggressive approach on survival and freedom from long-term coronary events.

Conflict of Interest

The authors have declared no conflict of interest.

Funding

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References