REVIEW

An Appraisal of Different Cardiac Risk Reduction Strategies in Vascular Surgery Patients

J. D. Kakisis1,2, F. Abir1, C. D. Liapis2 and B. E. Sumpio*1

1Department of Vascular Surgery, Yale University School of Medicine, New Haven, CT, U.S.A.
2Department of Propedeutic Surgery, Athens University Medical School, Laiko Hospital, Athens, Greece

Objectives: to summarize existing evidence regarding the benefits and the risks of all available interventional and medical means aimed at cardiac risk reduction in patients undergoing vascular surgery.

Design: review of the literature.

Materials and Methods: a critical review of all studies examining the impact of various prophylactic cardiac maneuvers on perioperative outcome following vascular surgery was performed. Overall mortality, cardiac mortality and myocardial infarction rate were used as the outcome measures.

Results: coronary artery bypass grafting is associated with a 60% decrease in perioperative mortality in patients undergoing vascular surgery, but in most of the cases this decrease does not outweigh the combined risk of the cardiac and the subsequent noncardiac vascular procedure. Data supporting the cardioprotective effect of percutaneous transluminal angioplasty in the perioperative setting are insufficient.

b-blockade has been shown to decrease perioperative mortality and cardiac morbidity in both high-risk (strong evidence) and low-risk (weak evidence) patients.

Conclusions: coronary revascularization is rarely indicated to simply get the patient through vascular surgery and should be reserved for patients who would need it irrespective of the scheduled vascular procedure. Among all available pharmacological agents, including b-blockers, a-agonists, calcium channel blockers and nitrates, only b-blockers have been proven to reduce the cardiac risk of vascular surgery.

Key Words: Vascular surgical procedures; Perioperative care; Postoperative complications; Myocardial revascularization; Drug therapy.

Cardiac complications are the leading cause of morbidity and mortality in patients undergoing peripheral vascular surgery.1,2 A review of the literature reveals that coronary artery disease (CAD) is found in 16–92% of patients with vascular disease, resulting in a perioperative myocardial infarction (MI) rate of 0–8% and accounting for 40–60% of perioperative deaths.2 To minimize cardiac risk of vascular surgery we must first identify the patient at risk for cardiac complications and then apply some prophylactic measure aimed at reducing that risk. Such a measure can be either interventional, in the form of coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), or medical, in the form of b-blockers, a-agonists, calcium channel blockers, nitrates or anticoagulants. These two strategies have not received equal attention. Extensive research into cardiac risk stratification has documented the sensitivity and specificity of various tests, including clinical examination, exercise ECG, Holter monitoring, dipyridamole thallium-201 imaging, radionuclide ventriculography, dobutamine stress echocardiography and coronary angiography.1,2 However, the efficacy of the various prophylactic measures that might improve the outcome of patients undergoing vascular surgery has not yet been determined.

The purpose of this review is to summarize existing evidence regarding the benefits and the risks of all available interventional and medical means aimed at cardiac risk reduction in patients undergoing vascular surgery. A Medline search of the English-language literature since 1975 was performed, using the key words: vascular surgery, complications, myocardial infarction, mortality, coronary revascularization, drug therapy, b-blockers, a-agonists, calcium channel blockers, nitrates and anticoagulants. Reference lists

* Please address all correspondence to: B. E. Sumpio, Chief, Vascular Surgery, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510, U.S.A.
from all relevant articles were reviewed to identify additional studies. Our search was limited to articles using mortality or myocardial ischaemia as the outcome measures.

Coronary Artery Bypass Grafting

Several studies in the late 70s demonstrated that patients who underwent successful myocardial revascularization carried a low risk of cardiac morbidity and mortality following a subsequent vascular surgical procedure (Table 1). Despite the fact that all of the patients included in these series had severe CAD treated by CABG, both perioperative mortality and MI rate during the subsequent noncardiac procedure were as low as 0–2.7%. It should be emphasized, however, that all of these initial reports were retrospective and none of them had a control group.

Nine case controlled studies have been performed since 1979, reporting on the perioperative outcome of vascular patients with prior CABG. Summation analysis of these studies reveals that vascular surgery in patients who have undergone previous CABG is associated with a mortality rate of 1.9% (18/958 patients), while mortality of patients without prior CABG is 4.5% (379/8347 patients). These data correspond to a 60% decrease in perioperative mortality, achieved by CABG (relative risk (RR): 0.4, 95% confidence interval (CI): 0.25–0.65, p < 0.001, χ² test). Similarly, the incidence of perioperative MI is significantly lower in patients with prior CABG (4/500 = 0.8%) compared to those without prior CABG (61/2491 = 2.4%), (RR: 0.32, 95% CI: 0.12–0.89, p = 0.02, Fisher’s exact test). Cardiac mortality also proved to be significantly lower in the prior CABG group (0/351 vs 39/2548 = 1.5%, p = 0.01, Fisher’s exact test).

Further analysis, according to the presence or not of CAD in the control group, reveals that CABG patients undergoing peripheral vascular surgery carry the same risk of perioperative death (3/319 = 0.94% vs 16/1663 = 0.96%), cardiac death (0/144 vs 4/1630 = 0.25%) and MI (3/319 = 0.94% vs 14/1663 = 0.84%) as patients without CAD. This risk is about 90% lower than the perioperative risk of patients with CAD who do not have previous coronary revascularization: perioperative mortality in CABG patients is 0.94% (3/319) versus 6.4% (30/466) in patients with medically treated CAD (RR: 0.14, 95% CI: 0.04–0.46, p < 0.001, Fisher’s exact test), cardiac mortality 0% (0/144) versus 5.8% (21/360) (p = 0.001, Fisher’s exact test) and MI rate 0.94% (3/319) versus 9.2% (43/466) (RR: 0.09, 95% CI: 0.03–0.3, p < 0.001, Fisher’s exact test).

Based on the aforementioned studies and their summation analysis, it seems that there is unanimity regarding the protective effect that successful CABG exerts during a subsequent vascular surgical procedure. However, the key word is “successful”. If CABG is to be performed solely for prophylactic purposes, then the risk of CABG should be added to the risk of the subsequent vascular operation. Otherwise, one could suggest that the coronary operation was simply a survival test, potentially eliminating patients who would have had cardiac complications following the noncardiac procedure. Hertzer’s report from the Cleveland Clinic provides a characteristic example of this additive risk. Perioperative mortality in this analysis was 3.4% for the whole group of patients undergoing aneurysm resection versus 1.6% for those who had preliminary myocardial revascularization. The respective values for lower extremity procedures were 1.8% versus 0% and for extracranial reconstructions 0.3% versus 0%. However, the perioperative mortality of the prophylactic CABG was 5.2%. Whether the benefits of prophylactic CABG outweigh this risk is debatable, since we do not know how these patients would have fared vascular surgery without preliminary myocardial revascularization.

Cutler and Leppo have also questioned the benefit of prophylactic CABG. In their series, five patients underwent sequential coronary revascularization and abdominal aortic aneurysm resection with no cardiac complications. However, a sixth patient died of haemorrhagic pancreatitis after CABG and a seventh died of a ruptured aortic aneurysm after catheterization but before coronary surgery. An eighth patient with severe aortic disease suffered a cerebrovascular accident after transaxillary coronary angiography. These results clearly illustrate the wide range of complications associated with preliminary CABG. Apart from the obvious surgical risk of the CABG itself, these complications also include untoward events during angiography as well as the risk of delaying vascular reconstruction. All of these factors should be taken into account and treatment plans designed to reduce the incidence of cardiac events in patients with peripheral vascular disease should be thoughtfully individualized.

Two decision analysis methodologies have been published and several important conclusions can be drawn from these models. First, the approach should be locally validated, based on the institutional mortality associated with coronary revascularization and the institutional mortality associated with the surgical procedure performed without preoperative intervention. In the case of AAA repair, prophylactic CABG is unequivocally justified only when the mortality from
Table 1. Perioperative outcome of patients with prior CABG.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of procedures</th>
<th>Purpose of CABG a</th>
<th>Type of procedures</th>
<th>Mortality (%)</th>
<th>Cardiac mortality (%)</th>
<th>MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior CABG</td>
<td>No CABG</td>
<td>Prior CABG</td>
<td>No CABG</td>
<td>Prior CABG</td>
<td>No CABG</td>
</tr>
<tr>
<td>McCollum, 3</td>
<td>1977</td>
<td>77</td>
<td>C</td>
<td>75% vascular</td>
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<td>0</td>
</tr>
<tr>
<td>Edwards, 4</td>
<td>1978</td>
<td>74</td>
<td>C</td>
<td>Vascular</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>Crawford, 5</td>
<td>1978</td>
<td>358</td>
<td>80% C</td>
<td>vascular</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Ennix, 6</td>
<td>1979</td>
<td>104</td>
<td>C</td>
<td>CEA</td>
<td>1</td>
<td>1.1–16.5</td>
</tr>
<tr>
<td>Hertzer, 7</td>
<td>1984</td>
<td>130</td>
<td>A</td>
<td>Vascular</td>
<td>0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Hertzer, 8</td>
<td>1984</td>
<td>61</td>
<td>A</td>
<td>AAA</td>
<td>1.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Hertzer, 9</td>
<td>1984</td>
<td>45</td>
<td>A</td>
<td>Lower extremity</td>
<td>1</td>
<td>2.1</td>
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<tr>
<td>Hertzer, 10</td>
<td>1984</td>
<td>24</td>
<td>A</td>
<td>Extracranial</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Hertzer, 11</td>
<td>1984</td>
<td>24</td>
<td>C</td>
<td>Abdominal aortic</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Golden, 12</td>
<td>1984</td>
<td>61</td>
<td>A</td>
<td>AAA</td>
<td>0</td>
<td>0–4.3</td>
</tr>
<tr>
<td>Nielsen, 13</td>
<td>1992</td>
<td>181</td>
<td>C</td>
<td>53% vascular</td>
<td>1.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Eagle, 14</td>
<td>1997</td>
<td>175</td>
<td>C</td>
<td>Vascular</td>
<td>1.1</td>
<td>0–2.8</td>
</tr>
<tr>
<td>Fleisher, 15</td>
<td>1999</td>
<td>116</td>
<td>A</td>
<td>AAA</td>
<td>2.6</td>
<td>4.1–9</td>
</tr>
<tr>
<td>Back, 16</td>
<td>2002</td>
<td>100</td>
<td>C</td>
<td>Vascular</td>
<td>2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

All of the studies included in the table are retrospective (the study by Eagle et al. 12 was a retrospective analysis of prospectively collected data for the CASS registry).

a Purpose of CABG in relation to the non-cardiac surgery: A = CABG performed in anticipation of the subsequent operation, C = patients had previous CABG coincidentally.

b No CAD – CAD.

c Patients operated on during the same time period without prior CABG.

† Patients submitted to stress testing alone (without coronary revascularization) – no preoperative testing.
AAA surgery in patients with severe CAD is higher than 9.5%. The decision analysis by Mason et al. reached similar conclusions, indicating that vascular surgery without preoperative coronary angiography and selective CABG generally leads to better outcomes. Preoperative CABG reduces overall mortality only when the estimated operative mortality of the noncardiac vascular surgery is substantially higher than 5% and the estimated operative mortality of coronary revascularization is relatively low (in the 2–3% range).

All of the above mentioned comparisons, however, can be criticized as being unfair against prophylactic CABG. The point of criticism is that they compare perioperative risks of the two strategies ignoring the fact that the risks of CABG are limited to the perioperative period, while its benefits may be evident for several years. Indeed, Hertzer’s reports from the Cleveland Clinic showed that the 5-year mortality, including perioperative deaths, of patients with peripheral vascular disease who had had coronary revascularization was half as the mortality of patients with severe CAD for whom CABG was warranted but never performed (28% vs 57%, \( p = 0.001 \)). The protection from cardiac-related death offered by myocardial revascularization was most apparent among men, hypertensives and nondiabetics. Using prospectively collected data from the CASS registry, Rihal et al. verified the long-term benefits of CABG in patients with vascular disease. In a cohort of 1834 patients with both coronary artery and peripheral vascular disease, the estimated probabilities of survival at 4, 8, 12 and 16 years were 88, 72, 55 and 41%, respectively, for the CABG group versus 73, 57, 44 and 34%, respectively, for the medical group \(( p < 0.0001 \)). Multivariate analysis showed that the type of therapy given was an independent predictor of survival, while subgroup analysis demonstrated that the benefits of surgical treatment on survival were limited to patients with three-vessel CAD and were inversely related to the ejection fraction. The results of the European Coronary Surgery Study, which is the only randomized, controlled study on the subject available to date, confirm these findings. The presence of peripheral vascular disease was associated with greatly decreased 8-year survival in both medically treated (81 vs 57.1%) and surgically treated (90 vs 84.8%) patients with CAD. However, the surgical strategy lowered the mortality rates by 65% in patients with peripheral vascular disease (from 42.9 to 15.2%), whereas in patients without peripheral vascular disease the respective value was 47% (from 19 to 9%). In other words, CABG proved to be more beneficial in patients with peripheral vascular disease than in those without.

Based on all the available data, the ACC/AHA Task Force Committee has published guidelines for the preoperative use of coronary revascularization. According to these guidelines, indications for CABG before noncardiac surgery are identical to those for CABG in general. CABG is rarely indicated to simply “get the patient through” noncardiac surgery and should be reserved for patients scheduled for elective noncardiac surgical procedures of high or intermediate risk who are found to have prognostic high-risk coronary anatomy and in whom long-term outcome would likely be improved by CABG. The much awaited results of the first randomized trial on the use of prophylactic coronary artery revascularization for elective vascular surgery will help refine these recommendations and support them with currently lacking level one evidence. This Veterans Administration study will also address important secondary issues such as the cost-effectiveness of various treatment strategies and the quality of life offered by each of them (coronary revascularization vs medical therapy).

Another question that needs to be answered relates to the optimal timing of prophylactic coronary revascularization. Several studies have shown that CABG and AAA repair, or CABG and carotid endarterectomy can be safely performed simultaneously in appropriately selected patients. On the contrary, some other authors stand by the staged approach, showing that simultaneous operations carry an increased perioperative risk. With a lack of a definite answer regarding the appropriate timing of CABG and peripheral vascular surgery, the current recommendation is that the therapeutic approach should be individualized, based on the patient’s coronary status and the urgency of the upcoming vascular operation.

**Percutaneous Transluminal Coronary Angioplasty**

There are few studies examining the impact of PTCA on the risk of subsequent noncardiac surgery (Table 2). Of these, only four have focused on vascular surgery and, as with CABG, none of them is randomized.

Two early reports have shown that the rate of major complications after noncardiac surgery is low in patients submitted to prior PTCA. Specifically, mortality rate was between 1.9 and 2.7%, while the incidence of MI was 0.7–5.6%. However, without a comparison group, it is debatable whether a MI rate of 5.6% can be considered low.

The first case controlled study on the subject was performed by Elmore et al. in 1993. This study
compared perioperative as well as long-term results of AAA repair between patients submitted to prophylactic PTCA or CABG. Both strategies achieved similar good results with regards to perioperative MI (0 vs 5.8% respectively), perioperative mortality (0% in both groups) and 3-year survival (92.3 vs 82.8% respectively). However, patients chosen for PTCA had significantly more late cardiac events including recurrent angina, MI and congestive heart failure, than those who underwent CABG (56.5 vs 27.3% respectively at 3 years). This finding is of particular importance if we take into account that patients selected for PTCA had significantly less 3-vessel disease on angiography than those scheduled for CABG. The less favorable long-term outcome in the PTCA group was attributed to the substantial rate of restenosis which is known to accompany PTCA.

An interesting analysis, stratified according to the type of vascular surgery, was performed by Fleisher et al.13 In this study, coronary revascularization, either in the form of PTCA or CABG, resulted in significantly lower perioperative mortality in patients undergoing aortic surgery when compared to the outcome of patients not submitted to any preoperative testing or those submitted to stress testing alone (without coronary revascularization). The less favorable long-term outcome in the PTCA group was attributed to the substantial rate of restenosis which is known to accompany PTCA.

An interesting analysis, stratified according to the type of vascular surgery, was performed by Fleisher et al.13 In this study, coronary revascularization, either in the form of PTCA or CABG, resulted in significantly lower perioperative mortality in patients undergoing aortic surgery when compared to the outcome of patients not submitted to any preoperative testing or those submitted to stress testing alone (without coronary revascularization). On the contrary, PTCA or CABG were not associated with reduced perioperative mortality after infrainguinal surgery. Of course, as in any other retrospective study, interpretation of these results is limited since the comparison groups probably had different comorbidities. In this context, the above-mentioned results might also suggest that PTCA or CABG reduce perioperative mortality of infrainguinal revascularization to levels comparable to those of patients in whom preoperative coronary revascularization is not warranted. This theory, however, is not supported by the findings of Back et al.14 In their series, perioperative mortality of patients with previous coronary revascularization was not significantly different from that of patients without revascularization (3.1 vs 1.1%, \( p = 0.2 \)) and, in fact, it was almost the same as the mortality of the high-risk subgroup of patients without previous CABG or PTCA (3.1 vs 3.3%, \( p = 1.0 \)). On the other hand, there was a trend towards lower perioperative mortality in patients with CABG within 5 years or PTCA within 2 years than in patients with remote revascularization (1.3 vs 6.3%).

In view of the contradictory results of retrospective series and in the absence of any prospective, randomized study, the ACC/AHA Task Force Committee has suggested that, until further data are available, indications for percutaneous coronary interventions in the perioperative setting should be similar to the indications under nonoperative situations.23 As for the optimal timing of the two procedures, it is recommended that surgery should be delayed for at least one week after balloon angioplasty to allow healing of the disrupted endothelium. This delay will also allow the prothrombotic effects of the noncardiac surgery not to be added to those of the cardiac intervention. On the other hand, the time interval between the coronary and the peripheral vascular procedure should not exceed one month, since restenosis after PTCA usually occurs within 2–5 months.

In order to improve immediate angioplasty results and reduce the rate of subsequent restenosis, coronary stents are being used with increased frequency nowadays. Despite their wide use, there is only one study examining the periprocedural course of patients who have previously undergone coronary stent placement.34 This study revealed a mortality of 20%, MI

### Table 2. Perioperative outcome of patients with prior PTCA.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of procedures</th>
<th>Purpose of PTCA</th>
<th>Type of procedures</th>
<th>Mortality (%)</th>
<th>Cardiac mortality (%)</th>
<th>MI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen,30 1991</td>
<td>193</td>
<td>C 33% vascular</td>
<td>2.1</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Huber,31 1992</td>
<td>54</td>
<td>A 52% vascular</td>
<td>1.9</td>
<td>1.9</td>
<td>5.6</td>
<td></td>
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<tr>
<td>Elmore,32 1993</td>
<td>14</td>
<td>A AAA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5.8</td>
</tr>
<tr>
<td>Gottlieb,33 1998</td>
<td>213</td>
<td>C Vascular</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Fleisher,13 1999</td>
<td>60</td>
<td>AAA</td>
<td>3.3</td>
<td>4.1–9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back,14 2002</td>
<td>28</td>
<td>A Infrainguinal</td>
<td>9.3</td>
<td>3.6–6.6</td>
<td></td>
<td></td>
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<tr>
<td>Kaluzka,34 2000</td>
<td>40</td>
<td>C Vascular</td>
<td>7.1</td>
<td>1.1</td>
<td></td>
<td></td>
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</table>

All of the studies included in the table are retrospective. 

* Purpose of PTCA in relation to the non-cardiac surgery: A = PTCA performed in anticipation of the subsequent operation, C = patients had previous PTCA coincidentally.

† Patients with prior CABG.

‡ Patients submitted to stress testing alone (without coronary revascularization) – no preoperative testing.

§ Patients operated on during the same time period without prior PTCA.

‖ Patients submitted to coronary stenting.
rate of 17.5% and an incidence of bleeding episodes of 27.5% among 40 patients who underwent noncardiac surgery less than 6 weeks after coronary stent placement. Interestingly, all deaths and MIs as well as 73% of the bleeding episodes occurred in patients subjected to surgery less than 14 days from stenting. Further investigation by electrocardiography, angiography and enzymatic tests showed that most of the fatal events were due to stent thrombosis, which, in turn, was attributed to interruption of one or both antiplatelet drugs before surgery. On the other hand, bleeding complications occurred more frequently in patients who had no discontinuation of either medication before surgery. Thus, as Kaluzza et al.34 remark, stent implantation before surgery appears to be a double-edge sword. Withholding the antiplatelet drugs increases the risk of stent thrombosis, while their continuation increases the risk of bleeding. In order to overcome these problems, noncardiac surgery should be postponed for at least 2 weeks and ideally 4–6 weeks after coronary stenting to allow complete endothelization of the stent before antiplatelet therapy is interrupted. If the noncardiac operation cannot be delayed, stent placement should be avoided if possible.

Medical Treatment

Several pharmacological agents including β-blockers, α-agonists, calcium channel blockers and nitrates have been utilized to reduce the cardiac risk of vascular surgery (Table 3). Among these, only β-blockers have been shown to effectively achieve this goal.

β-blockers

Two case controlled studies by Pasternack et al.35,49 published in the late 80’s, showed that perioperative metoprolol in patients undergoing peripheral vascular surgery resulted in significantly lower perioperative MI rate (3.1 vs 17.6% in the control group)36 and less intraoperative ischaemia with respect to duration and frequency of episodes.49 Yeager et al.50 confirmed the cardioprotective effects of β-blockers using a reverse study design. Instead of comparing perioperative outcome between patients receiving β-blockers and those receiving standard medical care only, they compared the use of perioperative β-blockers in a group of patients with perioperative MI and a matched group of randomly selected controls. The study

Table 3. Perioperative outcome of patients receiving cardioprotective medical therapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of procedures</th>
<th>Type of procedures</th>
<th>Mortality (%)</th>
<th>Cardiac mortality (%)</th>
<th>MI (%)</th>
<th>Ischaemia (%)</th>
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<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Control</td>
<td>Drug Control</td>
<td>Drug Control</td>
<td>Drug Control</td>
<td>Drug Control</td>
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<tr>
<td>β-blockers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pasternack,35 1987</td>
<td>32</td>
<td>51</td>
<td>AAA</td>
<td>3.1</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>Wallace,36 1998</td>
<td>99</td>
<td>101</td>
<td>40% vascular</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Poldermans,37 1999</td>
<td>59</td>
<td>53</td>
<td>Vascular</td>
<td>3.4</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Raby,38 1999</td>
<td>15</td>
<td>11</td>
<td>Vascular</td>
<td>0</td>
<td>9.1</td>
<td>33</td>
</tr>
<tr>
<td>α-agonists</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellis,39 1994</td>
<td>30</td>
<td>31</td>
<td>AAA</td>
<td>3.6</td>
<td>2-1.4</td>
<td>20.8</td>
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<tr>
<td>Talke,40 1995</td>
<td>18</td>
<td>6</td>
<td>Vascular</td>
<td>0</td>
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</tr>
<tr>
<td>Stuhmeier41 1996</td>
<td>145</td>
<td>152</td>
<td>Vascular</td>
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<td>0.7</td>
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<td>Mangano,42 1997</td>
<td>98–99</td>
<td>103</td>
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<td>1–0</td>
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<td>1</td>
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<tr>
<td>Oliver,43 1999</td>
<td>454</td>
<td>450</td>
<td>Vascular</td>
<td>1.8</td>
<td>4.4</td>
<td>1.3</td>
</tr>
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<td>CCBs</td>
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<td></td>
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<td>Godet,44 1987</td>
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<td>Vascular</td>
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<td>Nitrates</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Coriat,45 1984</td>
<td>23a</td>
<td>22b</td>
<td>84% vascular</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Dodds,46 1993</td>
<td>22</td>
<td>23</td>
<td>82% vascular</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Thompson,47 1996</td>
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<td>7.9</td>
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</tr>
<tr>
<td>Samson,48 2002</td>
<td>103</td>
<td>146</td>
<td>AAA</td>
<td>3.9</td>
<td>1.4</td>
<td>2.9</td>
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All of the studies included in the table are randomized, except for the study by Pasternack et al.35 in which matched controls were used and the study by Samson et al.48 in which heparin was used selectively based on criteria described by the authors.

* Nonfatal MIs only.
† Intraoperatively.
‡ Postoperatively.
§ Patients receiving iv mivazerol at a dose of 1.5 µg/kg/h – patients receiving iv mivazerol at a dose of 0.75 µg/kg/h.
¶ Patients receiving iv nitroglycerin at a dose of 1.0 µg/kg/min.
∥ Patients receiving iv nitroglycerin at a dose of 0.5 µg/kg/min.
Appraisal of Cardiac Risk Reduction Strategies

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demonstrated that β-blockers had been used less frequently in patients with perioperative MI than in control patients without perioperative MI (30 vs 50%, p = 0.01). Overall, β-blockade was associated with a 50% reduction in perioperative MI (p = 0.03).

The most convincing data available to date regarding the benefits of perioperative β-blockade come from two recent randomized trials. The first was a double-blind, placebo-controlled trial by Mangano et al. The β₁ selective antagonist atenolol was administered intravenously before and immediately after surgery (40% major vascular procedures) and orally thereafter until the patient was discharged from the hospital (up to a maximum of 7 days). Overall mortality after discharge was significantly lower among the atenolol-treated patients than among the placebo group at 6 months (0 vs 8%, p < 0.001), 1 year (3 vs 14%, p < 0.005) and 2 years (10 vs 21%, p = 0.01). Perioperative β-blockade appeared to be safe, well tolerated and cost-effective with an overall cost per life-year saved of $2500 based on the most conservative assumption.

The rationale of the prolonged cardiac protection offered by perioperative β-blockade is that long-term adverse outcomes after noncardiac surgery are significantly more frequent in patients who have suffered one or more episodes of perioperative myocardial ischaemia. Indeed, a subsequent report by the same group showed that an episode of myocardial ischaemia during postoperative days 0–2 increased the RR of death during the next 2 years by a factor of 2 (26 vs 13%; RR: 2.06, 95% CI: 1.04–4.06). This study also showed that atenolol reduced the incidence of myocardial ischaemia during the postoperative days 0–2 (17.2 vs 33.7%, p = 0.008) and 0–7 (24.2 vs 38.6%, p = 0.029). However, there were no differences between the two treatment groups in the incidence of in-hospital cardiac death, noncardiac death and MI. The failure to detect any such differences was due to the low incidence of these adverse outcomes (<3%). More than 1500 patients per group would be required to have an 80% chance of detecting a 50% reduction in an event with an incidence of 3%, while, in this study, only 99 patients were randomized in the atenolol group and 101 in the placebo group.

The second randomized trial on the perioperative and long-term results of β-blockade during vascular surgery was performed by Poldermans et al. and was published in two parts in 1999 and 2001. In this study, bisoprolol reduced the perioperative incidence of both death from cardiac causes (3.4% in the bisoprolol group vs 17% in the standard-care group, p = 0.02) and nonfatal MI (0 vs 17% respectively, p < 0.001). Thus, the number of patients needed to be treated with bisoprolol in order to prevent one death or nonfatal MI was only 3. This result prompted the safety committee to interrupt the study after the planned interim analysis.

A subsequent report by the same group showed that, during the 2-year follow-up, the composite endpoint of either cardiac death or nonfatal MI occurred in 12% of the patients receiving bisoprolol versus 32% of those receiving standard care only (odds ratio: 0.3, 95% CI: 0.11–0.83). The cardioprotective effect of bisoprolol was similar between patients with limited, moderate or extensive stress-induced ischaemia.

Based on these data, the ACC/AHA Task Force Committee has recommended the perioperative administration of β-blockers in all patients undergoing vascular surgery who have signs of ischaemia on preoperative testing. β-Blockers should also be administered in patients who have used them in the recent past for the treatment of angina as well as in patients with symptomatic arrhythmias or hypertension. The mere presence of major risk factors for CAD is also considered a relative indication for the perioperative administration of β-Blockers. This indication gains particular importance in vascular surgery since the majority of vascular patients will fall within this category. As for the treatment plan, administration of β-blockers should ideally start at least one week before elective surgery with the dose individualized to achieve a resting heart rate of 50–60 beats/min.

The efficacy of β-blockade in low risk patients is less well established since the randomized trials cited above were performed in selected, high risk patients. Recently, a cohort multicenter study by Boersma et al. including 1351 patients scheduled for elective major vascular surgery showed that the utility of β-blockade extended in the low risk subgroup of patients as well. Among this subgroup, the composite end-point of perioperative death or MI occurred in 0.8% (2/263) of patients receiving β-blockers, compared to 2.3% (20/855) of patients who did not receive β-blockers. The respective values in the high risk subgroup were 6.2% (6/97) versus 12.5% (17/136). Although the retrospective nature of this study limits the interpretation of its data, it seems that all patients undergoing vascular surgery may benefit from perioperative β-blockade irrespective to risk category.

A drawback of β-blockers is their potential side-effects including hypotension, bradycardia, congestive heart failure and bronchospasm. In this context, a cardioselective β-blocker with short half-life, such as esmolol, might be advantageous. Only two studies have assessed the role of esmolol in the perioperative setting. The first study, by Cucchiara et al. showed that esmolol was effective in blunting the increases in...
heart rate and arterial blood pressure during and following endotracheal intubation in patients undergoing carotid endarterectomy without an increase in adverse effects. The second study, by Raby et al. demonstrated that patients receiving esmolol during vascular surgery had fewer episodes and a shorter duration of perioperative ischaemia as compared with patients receiving placebo. Multivariate analysis showed that it was only heart rate control that independently predicted postoperative ischaemia and not esmolol administration.

$\alpha$-agonists

Five randomized, double-blind, placebo controlled trials have examined the role of $\alpha_2$-agonists in patients having noncardiac surgery. In the first of these studies, Ellis et al. tested the hypothesis that the addition of clonidine to a standardized general anesthetic could decrease the incidence of perioperative myocardial ischaemia in patients with known CAD or at least two atherosclerotic risk factors. The study showed that clonidine safely reduced the incidence of intraoperative myocardial ischaemia from 21.8 to 3.6%, while it failed to decrease the incidence of postoperative myocardial ischaemia (placebo: 19.2%, clonidine: 21.4%), possibly due to inadequate dosing. All of the patients in this series underwent major noncardiac surgery, the exact type of which is not reported.

A second study, by Talke et al. showed that the $\alpha_2$-agonist dexmedetomidine improved perioperative haemodynamic management of patients undergoing vascular surgery. However, the study was too small to detect differences in clinical outcome.

A much larger study was performed by Stuhmeier et al. in 1996 and showed that the administration of clonidine 90 min before scheduled induction of anaesthesia reduced the incidence of perioperative myocardial ischaemic episodes from 39 to 24% in patients undergoing vascular surgery (29% supracaortic, 36% aortic and 35% infraaortic reconstructions). Nevertheless, the rate of fatal cardiac events and nonfatal MIs was not different between the clonidine and the placebo group.

Similar results were reported in another study by the McSPI (Multicenter Study of Perioperative Ischaemia) group which included 317 patients from 23 medical centers in 7 European countries. Perioperative administration of the $\alpha_2$-adrenergic receptor agonist mivazerol proved to be safe and efficacious in improving haemodynamic stability in patients undergoing vascular surgery (excluding aortic procedures). In addition, the higher of the two doses of mivazerol that were evaluated (1.5 vs 0.75 $\mu$g/kg/h) achieved a significant reduction in the incidence of intraoperative myocardial ischaemia, from 34.3 to 19.5%. However, the high dose, low dose and placebo groups did not differ in the rate of MI (2, 1 and 5.8%, respectively) or in the incidence of cardiac death (1, 0 and 1% respectively). As the authors comment, the relatively small sample size limits the ability to interpret these results and they suggest the need for larger-scale trials that would define the effect of mivazerol on cardiovascular outcome.

Such a study was published two years later and included 2854 patients from 61 European centers. In this trial (the European Mivazerol Trial – EMIT), mivazerol failed to reduce the rate of MI, overall mortality or the composite endpoint of MI or death in patients with established CAD undergoing noncardiac surgery. However, a subgroup analysis, focused on 904 patients undergoing vascular surgery, showed that there were fewer composite endpoints (MI or death) in those receiving mivazerol (RR: 0.67), fewer cardiac deaths (RR: 0.33) and less overall mortality (RR: 0.41), although the incidence of perioperative MI was not significantly altered. It seems that $\alpha_2$-agonists, such as mivazerol, may be protective for patients with CAD undergoing vascular surgery, though further trials, specifically designed to test this hypothesis, are needed before final recommendations can be issued.

Calcium channel blockers

To date, there has been only one prospective study examining the role of calcium channel blockers in patients undergoing vascular surgery. This was a randomized, double-blind, placebo controlled trial but very small, with only 15 patients allocated to each group. Despite the small size of the study groups, intravenous administration of diltiazem was found to be effective in reducing the incidence of intraoperative myocardial ischaemia (from 73 to 40%) during carotid endarterectomy or aortobifemoral bypass grafting. On the other hand, there were no perioperative MIs in either group, most probably due to their small size. Larger trials are needed before definite conclusions can be drawn.

The retrospective review by Yeager et al. also failed to show any benefit associated with the administration of calcium channel blockers in terms of perioperative MI reduction. In this study, 49% of the patients with perioperative MI had received calcium channel blockers during vascular surgery, while the respective value in matched patients without perioperative MI was 42% ($p = NS$). In conclusion, existing data do not currently support the

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perioperative use of calcium channel blockers as a prophylactic treatment against cardiac events.

Nitrates

Two randomized trials have sought to determine the role of iv nitroglycerin in the prevention of intraoperative or perioperative myocardial ischaemia in patients undergoing noncardiac surgery (mostly vascular). The first study, randomly assigned patients to two different dosing schemes of intraoperative nitroglycerin (0.5 and 1.0 μg/kg/min). The higher dose resulted in a significantly lower incidence of myocardial ischaemia (63.6 vs 17.4%), whereas no intraoperative MIs occurred in any of these groups. The small size of the trial (45 patients) does not allow definite conclusions to be drawn.

The second randomized trial was equally small (45 patients) but differed from the first study in that it compared the outcome of patients receiving 0.9 μg/kg/min of iv nitroglycerin with the outcome of patients not receiving prophylactic nitroglycerin at all. Despite this study design, no difference in the incidence of myocardial ischaemia was found between the two groups (nitroglycerin group: 31.8%, control group: 30.4%), or in the incidence of MI (0 vs 4.3%, respectively).

Based on these data, the prophylactic use of nitroglycerin cannot be recommended. Until larger trials, sufficiently powered to detect differences in the hard endpoints of MI or death, are available, intraoperative administration of nitroglycerin should be limited to patients with ongoing myocardial ischaemia without hypotension.

Heparin

A multicenter randomized trial, published in 1996, showed that the use of intraoperative heparin during elective AAA repair reduced the incidence of perioperative MI from 8.6 to 2.1% (p = 0.02). The authors speculate that dilatation of the left ventricle after aortic cross-clamping leads to coronary artery plaque fissuring, with heparin preventing subsequent thrombosis. Their findings, however, were not reproduced by a recent retrospective study by Samson et al., in which selective use of heparin during AAA repair was not associated with a decrease in perioperative MI rate.

Approach to the Patient

The suggested decision model (Fig. 1) starts with an evaluation of the urgency of the vascular operation. In case of a real emergency which necessitates immediate intervention, the patient should proceed directly to the operating room, since there will be neither enough time for a formal cardiac assessment nor any other therapeutic alternative. In case of an urgent or an elective operation, a routine cardiac evaluation should be performed, including clinical examination and resting ECG. If the ECG is negative and the patient is at low cardiac risk, in terms of concomitant atherosclerotic risk factors, he/she should be cleared to go to the operating room. Perioperative β-blockade may be helpful in such cases (weak evidence). High-risk patients scheduled for vascular surgery as well as patients with positive or equivocal results of routine preoperative testing should be submitted to further noninvasive tests, including exercise or pharmacological stress test and dipyridamole thallium imaging. If the results of these tests are negative, the patient should proceed to the operating room under β-blocker prophylaxis (strong evidence). If noninvasive testing is positive, then a coronary angiogram is warranted. Nondiabetic patients with 1 or more significant lesions in 1 or 2 coronary arteries suitable for angioplasty should undergo PTCA, provided the vessels to be dilated subtend a large area of viable myocardium. Patients with three-vessel disease, those with two-vessel disease and significant proximal left anterior descending coronary artery stenosis as well as those with significant left main coronary artery stenosis or left main equivalent should undergo CABG.

In cases of severe, inoperable lesions, modification of the operative approach should be considered. Endovascular instead of open repair of AAA and extra-anatomic instead of aortobifemoral bypass for aortic occlusive disease might be reasonable alternatives. If modification of surgery is not feasible, then the surgical risk and the risk posed by the peripheral vascular disease should be balanced. If the estimated risk of the operation is higher than the risk posed by the peripheral vascular disease, then the operation should be cancelled. If the risk of the peripheral vascular disease is higher, the patient should proceed to the operating room under β-blockade. In any case, close cooperation between the vascular surgeon, the cardiologist and the anaesthesiologist is a "sine qua non", with the vascular surgeon assessing the risk posed by the vascular disease and potentially modifying the surgical approach, the cardiologist deciding on the appropriate diagnostic work-up and setting the indication for coronary revascularization and the anaesthesiologist involved in both risk assessment and perioperative risk reduction.

Undoubtedly, contemporary advances in noninvasive testing, perioperative management and surgical
or interventional techniques have made the treatment of patients with concomitant cardiac and peripheral vascular disease reasonably safe in most of the cases. However, several areas are in need of further research. Apart from the classic disruption of the myocardial oxygen supply-demand balance, the pathophysiology of perioperative MI possibly involves the vascular endothelium, the mechanism of coagulation, the systemic inflammatory response as well as the effect of haemodynamic forces, such as shear stress, on unstable coronary plaques. Clarification of these pathologic processes will allow better risk stratification and further reduction of cardiac complications of vascular surgery in the future.

References
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19 Hertzner NR, Young JR, Beven EG, O'Hara PJ, Graor RA, Ruscavage WF, Majolovec LC. Late results of coronary bypass in patients with peripheral vascular disease: I. Five-year survival according to age and clinical cardiac status. Cleve Clin Q 1986; 53: 133-143.


