
The first author of this paper has been discharged from Erasmus University because of allegations of scientific misconduct. The Investigative Committee of Academic Integrity of Erasmus University looked into possible breaches of academic integrity.

They published their assessment of the DECREASE trial on July 25, 2014 (http://www.erasmusmc.nl/1172194/2014/4771610) and concluded: “With regard to the conduct of the DECREASE-1 study, the written documentation of the research process is largely lacking. . . . There were wide differences in the memories of those involved regarding the way in which outcomes had been determined . . . Similar to the first author . . . (Dr Poldermans), the last author claimed that these determinations were made in accordance with the stipulations defined in the protocol . . . The members of the adverse event committee cannot confirm this. “Regarding the decision to prematurely terminate the DECREASE-1 . . . the Committee finds that this decision was not taken by the safety committee, as suggested in the publication . . . but by the 3 members of the executive board of the steering committee . . . .” “On the basis of these findings, the Committee is unable to confirm or dispel doubts about neither the care with which the DECREASE-1 study was conducted – and thus about the study’s integrity – nor about the reliability of its results.”

The editors of the European Heart Journal therefore decided to place an expression of concern related to this paper to inform their readers appropriately.

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Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery

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Aim To assess the long-term cardioprotective effect of bisoprolol in a randomized high-risk population after successful major vascular surgery. High-risk patients were defined by the presence of one or more cardiac risk factor(s) and a dobutamine echocardiography test positive for ischaemia.

Methods 1351 patients were screened prior to surgery, 846 patients had one or more risk factor(s), and 173 of these patients also had ischaemia during dobutamine echocardiography. One hundred and twelve patients could be randomized for additional bisoprolol therapy or standard care. Eleven patients died in the peri-operative period (up to 1 month after surgery). Randomized patients continued bisoprolol or standard care after surgery. During follow-up of 101 survivors (median 22 months, range 11–30) cardiac death or myocardial infarction was noted. No patient was lost during follow-up.

Results The incidence of cardiac events during follow-up in the bisoprolol group was 12% vs 32% in the standard care group (P=0.025). Cardiac death occurred in 15 patients, nine patients in the standard care and in six in the bisoprolol group; myocardial infarction occurred in six patients, five in the standard care and one in the bisoprolol group. The odds ratio for cardiac death or myocardial infarction after surgery in high-risk patients with additional bisoprolol therapy was 0.30 (0.11–0.83).


Key Words: Major vascular surgery, long-term follow-up, high-risk patients, beta-blockers.

See page 1253 for the Editorial comment on this article

Introduction

Cardiac events are the leading cause of late morbidity and mortality after successful major vascular surgery. For example, after peripheral bypass surgery the 3-year mortality is approximately 30–40%, and is mostly of cardiac origin[1]. The frequency of late postoperative cardiac morbidity reflects the high incidence of underlying coronary artery disease in this population[2]. Physicians who assess patients before surgery should focus not only on reducing peri-operative morbidity and mortality, but also on ensuring long-term survival. However, the optimal approach to the diagnosis and treatment of underlying coronary artery disease, often stable or asymptomatic in these patients, is unclear.

Dobutamine echocardiography is useful for the assessment of both peri-operative and late cardiac risk in candidates for vascular surgery. With respect to late
cardiac events, the most important prognostic features of dobutamine echocardiography are left ventricular function at rest and the extent of stress-induced ischaemia[3]. Pre-operative identification of high-risk patients by dobutamine echocardiography might permit intervention to reduce the incidence of late cardiac events in patients who have successfully undergone vascular surgery. Potential strategies for the reduction of late cardiac risk include myocardial revascularization, peri-operative beta-adrenergic blockade, and long-term administration of beta-blockers. So far, only peri-operative beta-blockade has been prospectively demonstrated to reduce the risk of late cardiac events[4]. However, the result of this study was the subject of considerable debate, as beta-blockers were stopped after discharge from hospital, but continued to be cardio-protective for a 2-year period.

We have previously shown that beta-blockade with bisoprolol reduces the incidence of peri-operative cardiac morbidity and mortality in high-risk patients undergoing major vascular surgery[3]. The principal purpose of this study was to assess the effect of long-term bisoprolol administration on the incidence of late cardiac events, in the same high-risk subjects.

Methods

Study protocol

Between 1996 and 1999 we prospectively screened all patients undergoing elective abdominal aortic or infrainguinal arterial reconstruction at seven participating centres. The Ethics Committee at each centre approved the study protocol, and all patients gave written informed consent. A total of 1351 consecutive patients were screened for the following cardiac risk factors: age over 70 years, angina, previous myocardial infarction, compensated or prior congestive heart failure, current treatment for diabetes mellitus, current treatment for cardiac arrhythmias, or limited exercise capacity (i.e. the inability to perform most normal activities). Any patient with one or more risk factors underwent dobutamine echocardiography. High-risk patients were defined by the presence of new or worsening wall motion abnormalities during dobutamine echocardiography. One hundred and twelve high-risk patients who were not currently taking beta-blockers were randomized to receive either oral bisoprolol 5–10 mg daily (n=59) or standard care (n=53). Eleven patients died in the peri-operative period, within 30 days of surgery. The 101 survivors (bisoprolol, n=57, and standard care, n=44) form the subject of this report.

Clinical care

The 101 survivors continued bisoprolol therapy or standard care and were followed at the Outpatient Clinic of the participating centres. The initial follow-up was performed 1 month after discharge from hospital. Subsequent visits and ECG recordings were scheduled at 3-monthly intervals. The study physicians adjusted the dose of bisoprolol using prescribed guidelines. If heart rate at rest was more than 60 beats . min⁻¹, the bisoprolol dose was increased to as much as 15 mg daily. If the resting heart rate was less than 50 beats . min⁻¹, the bisoprolol dose was reduced to as little as 2.5 mg daily.

Dobutamine echocardiography

The dobutamine echocardiography was performed as previously described[3]. A 16-segment, five-point model was used. Ischaemic myocardium was considered to be present in segments exhibiting worsening wall motion during stress, with the exception of akinesia becoming dyskinesia, which was considered to be a mechanical phenomenon. For each patient, the number of abnormal segments at rest was scored. A wall motion score index (total score divided by the number of assessable segments) was calculated at rest and during peak stress based on the standard 16-segment model. Extensive stress-induced ischaemia was defined as the presence of new wall motion abnormalities in at least four segments.

Follow-up

Patients were followed for 11 to 30 months after surgery, with a median duration of 22 months. Physicians who were blinded to the results of dobutamine echocardiography noted the occurrence of late cardiac events. In addition, each patient’s general physician was contacted, and hospital records were reviewed. The date of the last interview or review was used to calculate the follow-up time. Study end-points included cardiac death and myocardial infarction. Cardiac death was defined by clinical evidence of acute myocardial infarction, lethal cardiac arrhythmia, or refractory congestive heart failure, together with electrocardiograms and, when available, autopsy results. Non-fatal myocardial infarction was diagnosed by cardiac isoenzyme determinations and the development of new ECG changes.

Statistical analysis

Cardiac events are presented as a percentage. Differences in long-term event rates between patients randomized to bisoprolol or standard therapy were evaluated by Fisher’s exact test. Additionally, the method of Kaplan and Meier was applied to evaluate the occurrence of late cardiac events. The protective effect of bisoprolol was expressed by an odds ratio (OR) with corresponding 95% confidence interval (CI). A P-value of 0.05 was considered significant for all tests.
Results

Demographics

There were no major differences between the two groups with respect to either their clinical characteristics (Table 1) or the results of dobutamine echocardiography (Table 2). Importantly, there were no differences in resting left ventricular function, or the extent of stress-induced ischaemia.

Beta-blockade

In 11 patients the dose of bisoprolol was increased from 5 to 10 mg daily during follow-up. There was no reduction of bisoprolol dose in patients receiving 10 mg daily. The maintenance bisoprolol dose was 5 mg in 32 patients and 10 mg in 25 patients.

Follow-up results

Follow-up was complete in all patients. Cardiac events occurred in 21 patients, and consisted of cardiac death in 15 and non-fatal myocardial infarction in six. Cardiac death occurred in six (11%) patients from the bisoprolol group and in nine (20%) patients given standard care (P=0.259). Four of these latter patients (44%) had experienced a peri-operative non-fatal myocardial infarction. Non-fatal myocardial infarction occurred in one (2%) patient from the bisoprolol group, and in five (11%) patients given standard care (P=0.083). The composite end-point of either cardiac death or non-fatal myocardial infarction occurred in seven (12%) patients.

Table 1 Characteristics of randomized patients

<table>
<thead>
<tr>
<th></th>
<th>Bisoprolol (n=57)</th>
<th>Standard care (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70years</td>
<td>26 (46%)</td>
<td>15 (34%)</td>
</tr>
<tr>
<td>Male gender</td>
<td>50 (88%)</td>
<td>35 (80%)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>33 (59%)</td>
<td>25 (57%)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>21 (37%)</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (14%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6 (11%)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (11%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Myocardial revascularization</td>
<td>10 (19%)</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>Reduced exercise capacity</td>
<td>33 (58%)</td>
<td>30 (68%)</td>
</tr>
<tr>
<td>Peri-operative infarction</td>
<td>0 (0%)</td>
<td>9 (20%)*</td>
</tr>
</tbody>
</table>

Table 2 Dobutamine stress test results of the randomized patients

<table>
<thead>
<tr>
<th></th>
<th>Bisoprolol</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest wall motion score</td>
<td>1.31 (1-1.8)</td>
<td>1.42 (1-1.8)</td>
</tr>
<tr>
<td>Number of ischaemic segments</td>
<td>39 (68%)</td>
<td>18 (32%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>18 (11%)</td>
<td>26 (59%)</td>
</tr>
<tr>
<td>Angina during test</td>
<td>14 (25%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>ST changes during test</td>
<td>25 (43%)</td>
<td>17 (39%)</td>
</tr>
<tr>
<td>Double product peak</td>
<td>18 714</td>
<td>19 897</td>
</tr>
</tbody>
</table>

Double product peak=peak heart rate (beats min \(^{-1}\)) \times peak systolic blood pressure (mmHg).

Figure 1 Kaplan–Meier curves for cardiac death or myocardial infarction during follow-up, by results of bisoprolol therapy among 101 patients who survived vascular surgery. Each plot represents the cumulative percentage of patients remaining event free. There is a significant difference in event-free survival in patients with bisoprolol compared to patients with standard care (P=0.004).
in the bisoprolol group, and 14 (32%) patients given standard care ($P=0.025$) (Fig. 1). The odds ratio for cardiac death or myocardial infarction after surgery in high-risk patients with additional bisoprolol therapy was $0.3 (0.11–0.83)$, (Table 3).

**Dobutamine echocardiography**

Extensive myocardial ischaemia was present in 44 patients, while 57 patients experienced less extensive ischaemia. The protective effect of beta-blockers on cardiac events during follow-up was similar in both groups. The observed event rates were 11% in beta-blockers vs 31% in standard care, and 13% vs 33% in patients with and without extensive ischaemia, respectively.

**Limb ischaemia**

During follow-up, seven patients were readmitted for surgery because of recurrent limb ischaemia. There was no significant difference between the two groups, two patients were on bisoprolol therapy and five received standard care, $P=0.47$.

**Other medication**

During follow-up, there was no significant difference between the two groups in the use of any cardiovascular therapy (Table 4).

**Discussion**

This is the first randomized study showing a reduction in the incidence of late cardiac events among high-risk survivors of major vascular surgery who underwent peri-operative and prolonged postoperative beta-adrenergic blockade with bisoprolol. During the 2-year follow-up, 21 cardiac events occurred, seven (12%) in the bisoprolol group and 14 (32%) in the standard care group. The cardioprotective effect of bisoprolol was similar in patients with limited ischaemia, 1–3 ischaemic
segments during dobutamine echocardiography, compared to those with extensive stress-induced ischaemia. This reduction in cardiac events could not be explained by differences in demographics or change of medical therapy.

Patients undergoing major vascular surgery who demonstrate myocardial ischaemia during ambulatory ST-segment monitoring, or myocardial perfusion imaging are at increased risk of adverse late cardiac events, compared to those without myocardial ischaemia. Patients who survived a peri-operative cardiac event such as myocardial infarction or unstable angina are also at risk of late cardiac events. Patients with a peri-operative myocardial infarction experienced a 3.7-fold increase of cardiac death during follow-up, \( P = 0.02 \). Beta-blockers are well established in the treatment of ischaemic heart disease and heart failure and have been shown to improve outcome in non-surgical patients. We also showed that peri-operative beta-blockade with bisoprolol markedly reduces the risk of peri-operative myocardial infarction and cardiac death in high-risk vascular surgery candidates. Thus, it is not unexpected that prolonged postoperative beta-blockade with bisoprolol was also associated with a reduction in the risk of late cardiac death and myocardial infarction. The mechanism by which beta-blockers exert their protective effect are multifactorial. Proposed beneficial properties of beta-blockers include antiischaemic, antiarrhythmic and anti-renin–angiotensin effects. In addition, there is an augmentation of atrial and brain natriuretic peptide. There was no increase in the incidence of limb ischaemia in patients given bisoprolol. This is further evidence that beta-blockade is not contraindicated in the presence of ischaemic peripheral vascular disease.

Mangano et al. performed the only previous randomized study evaluating the long-term cardioprotective effect of beta-blockade in patients undergoing non-cardiac surgery. They studied 200 patients with clinical predictors of cardiac risk who underwent various non-cardiac surgical procedures. Patients were randomized to treatment with atenolol or placebo during hospitalization. Treatment was stopped after discharge. During a 2-year follow-up, patients previously treated with atenolol had a significantly lower overall death rate than those given placebo. Freedom from any cardiac event was also greater in patients given atenolol (82% vs 68%). No clear explanation for the sustained cardioprotective effect of atenolol was apparent. Our study differed substantially from that of Mangano et al. Our patients had a much greater risk of peri-operative cardiac events, and patients in the treatment group continued to receive bisoprolol throughout the follow-up period. Thus, the cardioprotective effect of bisoprolol in our study might have been related to its peri-operative administration, its long-term administration, or both.

The optimal antiischaemic strategy for high-risk patients after successful vascular surgery is controversial. Although our study suggests a role for long-term beta-blockade, others recommend myocardial revascularization. However, there are no randomized trials evaluating the role of either coronary angioplasty or coronary artery surgery for reduction of either peri-operative or late cardiac risk in patients undergoing non-cardiac surgery. Thus, we reserve coronary angiography and myocardial revascularization for patients with conventional indications for these procedures, such as those with unstable coronary syndromes, stable Class III or IV angina, or non-invasive test results that strongly suggest the presence of three-vessel, or left-main coronary artery disease. Administration of the cardioselective beta-blocker, bisoprolol, to remaining high-risk patients will substantially reduce the risk of both peri-operative and late cardiac events in these patients.

**Study limitations**

Patients were randomized based on their predicted risk of peri-operative complications, not on the risk of late complications. Importantly, patients and physicians were not blinded to the treatment, as the protocol dictated that bisoprolol therapy should be adjusted to the resting heart rate at the time of outpatient visits. This may have led to a reporting bias in the incidence of postoperative myocardial infarction. In addition, the standard treatment group included nine survivors of peri-operative myocardial infarction. These patients may have been at increased risk of late cardiac events during follow-up. Alternatively, the higher peri-operative death rate in the standard treatment group may have eliminated the highest risk patients and reduced the late risk in that group. Thus, we cannot be certain that the pre-trial late risk was comparable in the two study groups. Thus, although the observed cardio-protective effect of bisoprolol is evident this requires confirmation by other studies.

**Conclusion**

Peri-operative and long-term post-operative bisoprolol administration produced a significant, three-fold reduction in late cardiac death and myocardial infarction rates among high-risk patients after successful major noncardiac vascular surgery.

**References**


Appendix

The members of the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group and the participating centres were as follows:

Steering Committee: D. Poldermans, I. R. Thomson, H. van Urk, J. J. Bax, A. J. Man in’t Veld, L. L. M. van de Ven, and J. R. T. C. Roelandt; Statistical analysis: E. Boersma; Data-base management: V. C. Poldermans; Adverse events committee: P. van de Meer and P. Klootwijk; Safety committee: M. L. Simoons and G. A. van Es; Participating centres: the Netherlands: Erasmus Medical Center, Rotterdam (D. Poldermans, H. van Urk); Sint Clara Ziekenhuis Rotterdam (M. G. Schefler, T-I. Yo); Twee Steden Ziekenhuis, Tilburg (H. F. Baars, S. E. Kranendonk); Academisch Ziekenhuis, Utrecht (J. D. Blankensteijn, J. D. Banga) and Alkmaar Medisch Centrum, Alkmaar (J. H. Cornel, H. A. van Dijk). Italy: San Gerardo Hospital, Monza (G. Emanuelli, G. Trocino, A. Vituani, E. Zerbato); and Instituto di Ricovero e Cura a Carattere Scientifico Hospital, San Giovanni Rotondo (C. Vigna, G. Colacchio).