ORIGINAL INVESTIGATION

Optimizing Long-term Cardiac Management After Major Vascular Surgery

Role of β-Blocker Therapy, Clinical Characteristics, and Dobutamine Stress Echocardiography to Optimize Long-term Cardiac Management After Major Vascular Surgery

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Background: Survivors of major vascular surgery are at increased risk of late cardiac complications.

Objective: To examine the cardioprotective effect of β-blockers.

Methods: A follow-up study was conducted in 1286 patients who survived surgery for at least 30 days. Patients were screened for cardiac risk factors and dobutamine stress echocardiography (DSE) results; 1034 patients (80%) underwent preoperative DSE, and 370 (29%) received β-blockers. The main outcome measure was late cardiac death or myocardial infarction.

Results: Seventy-four patients (5.8%) had late cardiac events. Cardiac event rates in patients with 0, 1 to 2, and 3 or more risk factors were 1.6%, 4.7%, and 19.2%, respectively. In patients without risk factors, β-blockers were associated with improved event-free survival (2.8% vs 0%), and DSE had no additional prognostic value. In patients with 1 to 2 risk factors, the presence of ischemia during DSE increased cardiac events from 3.9% to 9.8%. However, if patients with ischemia were treated with β-blockers, the risk decreased to 7.2%. In patients with 3 or more risk factors, DSE and β-blockers stratified patients into intermediate- and high-risk groups. In patients without ischemia, β-blockers reduced the cardiac event rate from 15.1% to 9.5%, whereas the cardioprotective effect was limited in patients with 3 or more risk factors and positive DSE findings.

Conclusions: Long-term β-blocker use is associated with a reduction in the cardiac event rate, except for patients with 3 or more risk factors and positive findings on DSE.

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AFTER MAJOR vascular surgery, patients are at increased risk of cardiac complications during short- and long-term follow-up. Although the incidence of perioperative cardiac death and myocardial infarction (MI) after elective surgery has decreased gradually during the past decades, 30-day operative mortality (5%-6%) and 5-year mortality (45%), both of which arise principally from cardiac causes,[1] remain high. The frequency of late postoperative cardiac morbidity reflects the high prevalence of underlying coronary artery disease (CAD) in this population. To date, the optimal approach to the diagnosis and long-term management of CAD, which is often stable or asymptomatic in these patients, is unclear.

Dobutamine stress echocardiography (DSE) is a useful tool for the diagnosis of CAD, and it is valuable in the assessment of perioperative and late cardiac risk in patients scheduled for major vascular surgery.[2,3] Of the long-term prognostic features of DSE, the most important are poor left ventricular function at rest and the extent of stress-induced ischemia.[4] Preoperative identification of high-risk patients using DSE may initiate strategies to reduce the incidence of late cardiac events in patients who have successfully undergone major vascular surgery. Interventions such as perioperative and long-term use of a β-blocker medication and myocardial revascularization may be applied.

In the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) study, we[2] showed that perioperative β-blocker use was associated with a reduced incidence of perioperative cardiac complications in a large cohort of vascular surgery patients. The present study builds on these results by examining the relation of clinical characteristics, DSE results, β-blocker use, and the incidence of long-term cardiac events in the survivors of the same cohort.

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*A complete listing of the DECREASE Study Group members was published previously (*N Engl J Med. *1999;341:1789-1794).*
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METHODS

STUDY PROTOCOL

Between January 1, 1996, and December 31, 1999, we prospectively screened all patients undergoing elective abdominal aortic or infrainguinal arterial reconstruction at 8 participating medical centers. The hospital ethics committee at each center approved the study protocol, and all of the patients gave written informed consent. A total of 1351 consecutive patients were screened for the following cardiac risk factors: age older than 70 years, current or previous angina pectoris, previous MI, compensated or previous congestive heart failure (CHF), current treatment for diabetes mellitus, previous cerebrovascular events, and renal failure (serum creatinine level >2.0 mg/dL [>180 µmol/L]). Any patient with 1 or more risk factors or a reduced exercise capacity underwent DSE. Overall, DSE prior to surgery was performed in 1097 patients (81%). Stress-induced ischemia was present in 199 patients (18%). Initially, β-blockers were administered to 360 patients (27%). Two hundred forty-eight patients (18%) underwent abdominal aortic aneurysm repair, 640 (47%) underwent aortofemoral reconstruction, and 463 (34%) underwent infrainguinal procedures. A total of 1299 patients (96%) survived after surgery for at least 30 days; 1286 successfully completed follow-up.

LONG-TERM ADMINISTRATION OF β-BLOCKERS

Of the 360 patients who were taking a β-blocker medication at the time of surgery, 301 were treated with long-term β-blockers and 59 were randomized to receive β-blockers within the framework of the DECREASE study.[5] Follow-up data were successfully obtained for 346 patients (8 patients died during the postoperative period and 6 were loss to follow-up). During long-term follow-up, β-blockers were administered to an additional 24 patients as a result of CAD-related symptoms. Thus, the total number of patients using β-blockers during long-term follow-up was 370. Continuous administration of β-blockers required that the resting heart rate was 50 to 70/min and that systolic blood pressure was 100 mm Hg or greater. Patients were reassessed at each visit, and the β-blocker dose was adjusted according to heart rate and systolic blood pressure. All of the patients visited the outpatient clinic every 3 months, and at each visit a questionnaire was filled with reference to the use, type, and dose of β-blockers.

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Dobutamine stress echocardiography was performed as previously described.[6] The left ventricle was divided into 16 segments, and wall motion was scored on a 5-point ordinal scale (1 indicates normal wall motion; 2, mild hypokinesis; 3, severe hypokinesis; 4, akinesis; and 5, dyskinesis). For each patient, a wall-motion score index was calculated at rest and during peak stress based on the standard 16-segment model. The results of DSE were considered positive if new wall-motion abnormalities occurred (ie, if wall motion in any segments worsened by ≥1 grades during the test, except for akinesia becoming dyskinesia).

FOLLOW-UP STUDY

In December 1999, a follow-up study was performed of all patients who survived after surgery for at least 30 days. Study end points were defined as a composite of cardiac death and MI. Hospital records and death certificates were used to ascertain the cause of death, which was considered cardiac if death was directly attributable to MI, CHF, or ventricular arrhythmia in the absence of any other precipitating factor or if death was sudden and unexpected. Myocardial infarction was defined by a serum creatine kinase level greater than 110 U/L, with a myoglobin isoenzyme fraction greater than 10%, and a finding of new Q waves lasting more than 30 milliseconds on the 12-lead electrocardiogram. The occurrence of death (any cause), stroke, and new or progressive angina pectoris was also noted.

STATISTICAL ANALYSIS

Descriptive statistics such as the frequency and percentage of categorical variables are provided, as are the mean and SD of continuous variables. The Kaplan-Meier method was applied to evaluate the prognostic importance of the extent of stress-induced ischemia and β-blocker use with respect to cardiac event–free survival. Differences among survival curves were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were applied to evaluate the relations among a few baseline clinical characteristics, DSE results, β-blocker therapy, and the composite end points. All of the variables were entered into the multivariable stage, irrespective of the significance level in univariable analysis. Multivariable models were constructed by backward deletion of the least significant characteristics. In the final model, variables that reached $P<.15$ were retained. The additional and additive prognostic values of DSE results and β-blocker therapy were analyzed using further regression analyses. We specifically evaluated the interaction between β-blocker therapy and DSE results. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported. All analyses were performed using statistical software (SPSS; SPSS Inc, Chicago, Ill).

RESULTS

PATIENT CHARACTERISTICS

Characteristics of the 1286 patients who survived for at least 30 days after surgery and completed follow-up are described in **Table 1**. Patients receiving β-blockers during long-term follow-up had a clinical risk profile that was worse than that of patients not taking such medications: patients taking β-blockers had higher rates of angina pectoris (34% vs 10%), previous MI (58% vs 26%), and CHF (7% vs 4%). There was no relationship between the type of surgery and the use of β-blocker medication.

FOLLOW-UP

Follow-up data were successfully obtained in 1286 patients (95%) at a median of 23 months (25th-75th percentile, 14-33 months). Seventy-four patients (5.8%) experienced cardiac death (n=58) or nonfatal MI (n=16) during follow-up. Among 14 patients who experienced a nonfatal perioperative MI, 3 late cardiac deaths occurred during follow-up. Twenty-seven patients had a stroke, and there were 39 noncardiac deaths (3.0%). The cause of noncardiac death was cancer in 16 patients, respiratory insufficiency in 10, sepsis secondary to infected prosthetic grafts in 7, and other causes in 9. In addition, 12 patients (0.9%) had late coronary revascularization because of progression of angina pectoris. Of these 12 patients, 3 (25%) underwent the revascularization within 30 days of major vascular surgery. The distribution of all revascularization in patients with 0, 1 to 2, and 3 or more risk factors was 0.3%, 1.1%, and 1.7%, respectively.

UNIVARIABLE ANALYSES

In univariable analyses, a history of CHF was most important determinant of adverse cardiac outcome among selected clinical variables (**Table 2**). Patients with a CHF history (4.7% of total study population) had an almost 5-fold increased risk of late cardiac death or MI compared with those without such a history. Other important univariable determinants of late cardiac complications were a history of MI, current or previous angina pectoris, advanced age, and renal failure. There was no relationship between the type of surgery and long-term cardiac complications.

In univariable analysis, patients using β-blockers were at slightly higher risk of late cardiac complications, but this association was not significant (HR, 1.1; 95% CI, 0.7-1.8; $P=.56$). Among the 252 patients who did not undergo DSE, no late cardiac complications occurred in the 24 patients using β-blockers, whereas there were 3 events (1.3%) in the remaining patients. In the 840 patients without stress-induced ischemia during DSE, 197 were using β-blockers. Nine late cardiac complications (4.6%) occurred in this group vs 32 (5.0%) in those not using β-blockers. Finally, in the 194 patients with stress-induced ischemia, 148 used β-blockers; 15 using β-blockers (10.1%) had late cardiac events vs 15 (32.6%) not using β-blockers.

A positive test result during DSE was a significant predictor of late cardiac complications (**Table 3**). Patients without stress-induced ischemia had a significantly lower rate of late cardiac death or MI than patients with stress-induced ischemia during DSE (4.9% vs 15.5%; $P<.001$). In addition, the extent of stress-induced ischemia also provided important prognostic information, as the event rate ranged from 11.5% in those with stress-induced ischemia in 1 to 2 segments to 18.7% in patients with stress-induced ischemia in 3 or more segments. Event-free survival curves for patients without testing, for those with negative stress test results, and for those with mild (1-2 segments) or extensive (≥3 segments) ischemia during stress are presented in **Figure 1**.

Table 1. Characteristics of the 1286 Patients Who Survived for at Least 30 Days After Major Vascular Surgery

Characteristic	Patients, No. (%) β-Blockers (n = 370)	Patients, No. (%) No β-Blockers (n = 916)	*P* Value*
Age >70 y	153 (41)	390 (43)	.68
Male sex	283 (77)	714 (78)	.57
Current or stable angina pectoris	127 (34)	89 (10)	<.001
Previous myocardial infarction	216 (58)	234 (26)	<.001
Congestive heart failure	27 (7)	33 (4)	<.01
Diabetes mellitus	58 (16)	118 (13)	.23
Previous cerebrovascular accident	40 (11)	66 (7)	.04
Renal failure	19 (5)	29 (3)	.11
Type of surgery			
Infrainguinal reconstruction	126 (34)	314 (34)	.82
Abdominal aortic aneurysm repair	65 (18)	148 (16)	
Aortofemoral reconstruction	179 (48)	454 (50)	

*Fisher exact test, 2-sided.

Table 2. Univariable Relation Between Clinical Baseline Characteristics and Long-term Cardiac Death or Myocardial Infarction

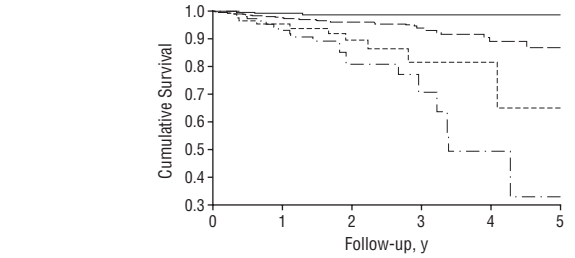
Variable	Patients, No. (n = 1286)*	Events, No. (%) (n = 74)†	Hazard Ratio (95% Confidence Interval)	χ^2 Test	*P* Value
Age >70 y					
Yes	543	47 (8.7)	2.4 (1.5-3.8)	13.0	<.001
No	743	27 (3.6)	1.0		
Current or stable angina pectoris					
Yes	216	29 (13.4)	2.6 (1.7-4.2)	16.3	<.001
No	1050	45 (4.3)	1.0		
Previous myocardial infarction					
Yes	450	48 (11.0)	3.3 (2.1-5.4)	23.7	<.001
No	822	25 (3.0)	1.0		
Congestive heart failure					
Yes	60	13 (22.0)	4.7 (2.6-8.6)	26.0	<.001
No	1201	61 (5.1)	1.0		
Diabetes mellitus					
Yes	176	15 (8.5)	1.7 (0.9-3.0)	3.0	.08
No	1093	59 (5.4)	1.0		
Previous cerebrovascular accident					
Yes	106	9 (8.5)	1.5 (0.8-3.1)	1.4	.23
No	1155	65 (5.6)	1.0		
Renal failure					
Yes	48	8 (16.7)	3.6 (1.7-7.4)	11.6	.001
No	1222	66 (5.4)	1.0		
Type of surgery					
Infrainguinal reconstruction	440	31 (7.0)	1.4 (0.9-2.4)	2.3	.13
Abdominal aortic aneurysm repair	213	13 (6.1)	1.4 (0.7-2.6)	1.0	.31
Aortofemoral reconstruction	633	30 (4.7)	1.0		

*Numbers may not sum to 1286 owing to missing data.
†A composite of cardiac death and myocardial infarction. Numbers may not sum to 74 owing to missing data.

Table 3. Univariable Relation Between Dobutamine Stress Echocardiography Results and Long-term Cardiac Death or Myocardial Infarction

Variable	Patients, No. (n = 1034)	Events, No. (%), (n = 71)*	Hazard Ratio (95% Confidence Interval)	χ^2 Test	*P* Value
Dobutamine stress echocardiography					
No new wall-motion abnormalities	840	41 (4.9)	1.0		
New wall-motion abnormalities	194	30 (15.5)	3.8 (2.4-6.2)	31.1	<.001
Segments with new wall-motion abnormalities, No.					
0	840	41 (4.9)	1.0		
1-2	87	10 (11.5)	2.7 (1.3-5.3)	7.7	.005
≥3	107	20 (18.7)	5.0 (2.8-8.5)	33.8	<.001

*A composite of cardiac death and myocardial infarction.



No. at Risk						
No DSE	252	250	249	249	249	249
No Ischemia During DSE	840	822	811	806	800	799
Mild Ischemia During DSE	87	83	80	79	78	77
Extensive Ischemia During DSE	107	100	93	91	88	87

Figure 1. Kaplan-Meier survival curves for the prediction of late cardiac complications for patients without dobutamine stress echocardiography (DSE), for those with a negative test result, and for those with mild or extensive stress-induced ischemia.

MULTIVARIABLE ANALYSES

In multivariable analysis, advanced age, a history of MI, a history of CHF, and angina pectoris remained significant predictors of late cardiac complications (**Table 4**). After correcting for differences in clinical characteristics, patients who used β-blockers were at lower risk of cardiac death or MI than patients who did not use β-blockers, but this association was not significant (adjusted HR, 0.7; 95% CI, 0.4-1.2; *P*=.18).

When clinical data were combined with DSE results, advanced age, previous MI, and CHF retained their predictive power with respect to late cardiac death and MI, but angina pectoris lost most of its predictive value (Table 4). The presence or absence of stress-induced ischemia during DSE was the most important determinant of late cardiac outcome. In association with clinical data and DSE results, β-blocker use was associated with a significantly reduced risk of late cardiac complications (adjusted HR, 0.3; 95% CI, 0.2-0.6; *P*<.001). We also repeated the same analysis with respect to a composite end point of all-cause mortality and MI. In this analysis, the association among clinical data, DSE results, and β-blocker use showed that β-blockers still retained their significant protective effect (adjusted HR, 0.5; 95% CI, 0.3-0.8; *P*=.009).

Table 4. Multivariable Model to Predict Perioperative Cardiac Death or Myocardial Infarction

Variable	Hazard Ratio (95% CI)	χ^2 Test	*P* Value
Clinical Characteristics Only			
Age >70 y			
Yes	2.2 (1.4-3.5)	10.3	.001
No	1.0		
Current or stable angina pectoris			
Yes	1.8 (1.1-2.9)	5.0	.03
No	1.0		
Previous myocardial infarction			
Yes	2.4 (1.4-4.0)	11.1	.001
No	1.0		
Congestive heart failure			
Yes	2.8 (1.5-5.3)	10.0	.002
No	1.0		
Combination of Clinical Characteristics and Results of DSE			
Age >70 y			
Yes	2.6 (1.5-4.3)	13.2	<.001
No	1.0		
Previous myocardial infarction			
Yes	2.2 (1.3-3.8)	8.9	.001
No	1.0		
Congestive heart failure			
Yes	3.1 (1.6-5.8)	12.4	<.001
No	1.0		
New wall-motion abnormalities			
Yes	3.3 (2.0-5.5)	22.4	<.001
No	1.0		

Abbreviations: CI, confidence interval; DSE, dobutamine stress echocardiography.

RISK CLASSIFICATION MODEL

Based on the number of cardiac risk factors, DSE results, and β-blocker use, a previously developed simple scheme was applied to estimate the risk of late cardiac complications (**Figure 2**). A clinical risk score was determined based on patient age and clinical history. In patients without risk factors, β-blocker use was associated with improved event-free survival, 2.8% (4/145) vs 0% (0/34), and DSE had no additional prognostic value. In patients with 1 to 2 risk factors, the presence of ischemia during DSE increased cardiac events from 3.9% (22/565) to 9.8% (12/122). However, if patients with ischemia were treated with β-blockers, the risk decreased to 7.2% (7/97). In patients with 3 or more risk factors, DSE results and β-blocker use stratified pa-

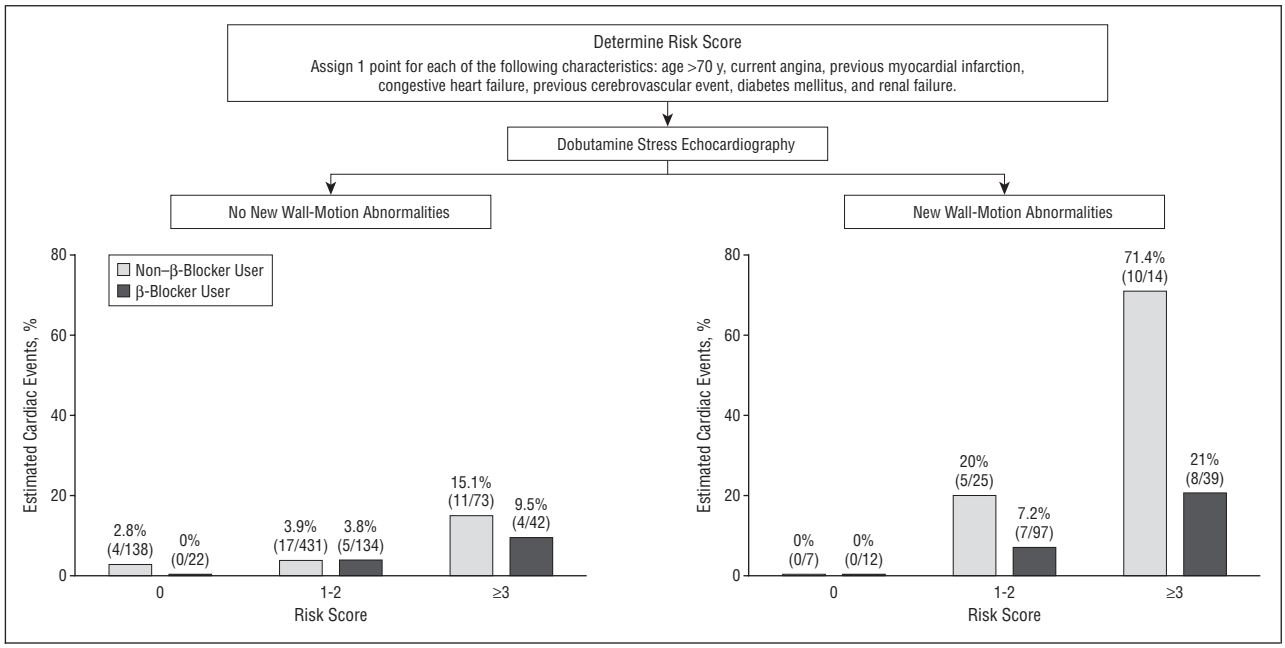


Figure 2. Risk of cardiac death and myocardial infarction during long-term follow-up as observed in subpopulations.

tients into intermediate- and high-risk groups. In patients without ischemia, β-blocker therapy reduced the cardiac event rate from 15.1% (11/73) to 9.5% (4/42). However, patients with 3 or more risk factors and ischemia were at considerable risk despite β-blocker use (20.5% [8/39]).

COMMENT

The present analysis of 1286 patients who underwent major vascular surgery demonstrates that advanced age, current or stable angina pectoris, previous MI, and CHF were the most important clinical determinants of late cardiac death and nonfatal MI. In addition to clinical data, DSE results were predictive of long-term adverse cardiac outcomes. In univariable analyses, there was no significant association between β-blocker use and late cardiac complications. In multivariable analyses, after correcting for clinical and test characteristics, patients with stress-induced ischemia receiving β-blockers had significantly lower risk compared with those not receiving β-blockers. The cardioprotective effect of β-blocker therapy depended on the presence of cardiac risk factors and the extent of stress-induced myocardial ischemia during DSE.

Univariable analyses showed that patients with advanced age, angina pectoris, CHF, and renal failure were more likely to have late cardiac complications than were those without such a history. In contrast, diabetes mellitus and previous cerebrovascular accident were not independent predictors of long-term cardiac complications. In multivariable analyses, advanced age, angina pectoris, and CHF remained significant predictors of cardiac death and nonfatal MI, but renal failure, diabetes mellitus, and previous cerebrovascular accident did not. These findings may reflect a changing patient population or improved long-term management, although it may also be a matter of a relatively low number of events. Despite these observations, these factors may be predictive of long-term complications. Therefore, diabetes mellitus, renal failure, and previous cerebrovascular accident were still used for the clinical risk index.

Consistent with the results of other studies,[4,7] the present DSE results were powerful predictors of long-term cardiac complications. Patients who had stress-induced myocardial ischemia were at substantial risk of late cardiac complications compared with patients who had a negative test result. In addition, the extent of stress-induced ischemia was also an independent predictor of late cardiac events. In univariable analyses, patients using β-blockers were not at significantly lower risk than those not receiving β-blockers, but after adjustment for cardiac risk factors and test characteristics, patients who took β-blockers had a 70% lower risk than nonusers. These observations may reflect the fact that patients who were at higher risk of CAD, confirmed by the presence and extent of stress-induced myocardial ischemia, benefited the most from long-term β-blocker use.

The ability of β-blockers to reduce the perioperative incidence of cardiac complications has been widely studied and confirmed by several investigators.[8-14] However, there are only 2 randomized trials evaluating the long-term cardioprotective effect of β-blockers in this group of patients. Mangano et al[8] studied 200 patients with clinical predictors of cardiac risk who underwent noncardiac surgical procedures. Patients were randomized to receive atenolol or placebo during the perioperative period. Atenolol was administered intravenously or orally beginning 2 days before and continuing for 7 days after surgery. Patients were monitored perioperatively for cardiac events and then were followed for 2 years after surgery. There was no difference in the incidence of perioperative MI or death from cardiac causes. During 2-year follow-up, patients previously treated with atenolol had significantly lower rates of all-cause mortality (9% vs 21%) and cardiac death (4% vs 12%) than those given placebo. The failure of atenolol therapy to significantly alter the perioperative outcome may be related to the low incidence of serious perioperative cardiac events in the study

population (3%). The study included patients with known CAD and those with only coronary risk factors, and patients underwent various surgical procedures. Recently, a study by Poldermans et al[15] demonstrated the cardioprotective effect of long-term administration of bisoprolol in a small-scale randomized trial: long-term bisoprolol use produced a significant, 3-fold reduction in late cardiac death and MI compared with placebo. The present study extends these findings by including a large cohort of patients who underwent successful vascular surgery and patients who continued to receive β-blockers throughout follow-up.

CLINICAL IMPLICATIONS

The optimal treatment strategy to prevent cardiac complications in high-risk patients after successful vascular surgery is controversial. In patients without cardiac risk factors or with negative DSE findings, who were at low risk of cardiac complications, β-blocker therapy had only a marginal additional protective effect. However, considering the unpredictable progression of CAD in these patients, long-term β-blocker therapy might be considered. Patients with multiple cardiac risk factors with or without mild stress-induced myocardial ischemia should receive continuous β-blocker medication to be at lower risk of long-term cardiac complications. In contrast, β-blocker therapy had a limited long-term protective effect in patients with extensive stress-induced myocardial ischemia. Coronary angiography and subsequent coronary revascularization should be considered in these patients.

Only 50% of those patients who underwent late coronary revascularization had stress-induced myocardial ischemia compared with patients without positive test results. The late revascularization was not predicted in the remaining group of patients, which can be considered as a result of the progression of CAD. Accordingly, we suggest that after successful vascular surgery, patients should undergo repetitive late cardiac testing with DSE to reevaluate the risk of late cardiac complications. Patients with multiple cardiac risk factors or a positive test result should be followed carefully, and symptoms of myocardial ischemia should be aggressively treated.

STUDY LIMITATIONS

This study has certain limitations that should be considered when interpreting the results. The risk stratification and modification scheme using a clinical risk score, DSE results, and β-blocker therapy was developed after events had occurred. In addition, only patients participating in the DECREASE study were randomized to receive perioperative and long-term β-blockers or standard care. Patients and physicians were not masked to the treatment, as continuous β-blocker use should be adjusted to the resting heart rate at outpatient visits. Therefore, the results of this study could be affected by the fact that patients treated with β-blockers received more medical attention during follow-up than did those without β-blocker use.

In conclusion, this study revealed the utility of cardiac risk factors and additional DSE testing in the long-term management of patients who underwent successful major vascular surgery. The results of the present study demonstrate that stress-induced ischemia during DSE has additional prognostic value, irrespective of the clinical risk profile. Patients receiving β-blockers had significantly lower risk than patients not receiving them. However, the cardioprotective effect of β-blockers was more likely to depend on the presence or absence of cardiac risk factors and stress-induced myocardial ischemia during DSE testing.

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