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Effect of Clonidine on Cardiovascular Morbidity and Mortality after Noncardiac Surgery

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Background: **Perioperative myocardial ischemia occurs in 20–40% of patients at risk for cardiac morbidity and is associated with a ninefold increase in risk of cardiac morbidity.**

Methods: **In a prospective, double-blinded, clinical trial, we studied 190 patients with or at risk for coronary artery disease in two study groups with a 2:1 ratio (clonidine, n = 125 *vs.* placebo, n = 65) to test the hypothesis that prophylactic clonidine reduces the incidence of perioperative myocardial ischemia and postoperative death in patients undergoing noncardiac surgery. Clonidine (0.2 mg orally as well as a patch) or placebo (tablet and patch) was administered the night before surgery, and clonidine (0.2 mg orally) or placebo (tablet) was administered on the morning of surgery. The patch or placebo remained on the patient for 4 days and was then removed.**

Results: **The incidence of perioperative myocardial ischemia was significantly reduced with clonidine (intraoperative and postoperative, 18 of 125, 14% *vs.* placebo, 20 of 65, 31%; *P* = 0.01). Prophylactic clonidine administration had minimal hemodynamic effects. Clonidine reduced the incidence of postoperative mortality for up to 2 yr (clonidine, 19 of 125 [15%] *vs.* placebo, 19 of 65 [29%]; relative risk = 0.43 [confidence interval, 0.21–0.89]; *P* = 0.035).**

Conclusions: **Perioperative administration of clonidine for 4 days to patients at risk for coronary artery disease significantly reduces the incidence of perioperative myocardial ischemia and postoperative death.**

SIXTY million Americans have cardiovascular disease, and 1 million/yr die. Approximately 100,000 of the 400,000 patients/yr in the United States who undergo cardiac surgery and 1.5 million of the 30 million who undergo noncardiac surgery have perioperative cardiovascular morbidity at a cost exceeding $20 billion annually.[1,2] Perioperative myocardial ischemia is a potentially avoidable risk factor associated with a ninefold increase in cardiac morbidity before hospital discharge and a twofold greater long-term (2-yr) risk.[1,3,4] Reduction in perioperative myocardial ischemia reduces mortality.[4]

Prophylactic β blockade administered perioperatively reduces the incidence of myocardial ischemia[4] and death in patients at risk who undergo noncardiac surgery.[5,6] Clonidine, an α_2 agonist, reduces the incidence of myocardial ischemia in patients who undergo vascular[7] and cardiac surgery[8] but has not been shown to reduce the incidence of a hard outcome such as death.

The current study tests the hypothesis that clonidine administered prophylactically reduces the incidence and severity of perioperative myocardial ischemia and has long-term survival benefits.

Materials and Methods

Consent

This study was approved by the Committee for Human Research, University of California, San Francisco, and was performed with written informed consent from all patients. Two hundred two patients at risk for coronary artery disease and scheduled to undergo noncardiac surgery at the San Francisco Veterans Affairs Medical Center consented to this randomized, double-blinded, placebo-controlled clinical trial. Procedures were followed in accordance with institutional guidelines.

Criteria for the Study

Inclusion criteria required that patients were (1) scheduled for elective noncardiac surgery; (2) able to sign informed consent before surgery; and (3) had either definite coronary artery disease (as indicated by previous myocardial infarction, typical angina, or atypical angina with electrocardiogram changes indicative of ischemia in response to exercise or scintigraphic evidence of a myocardial perfusion defect) or presence of the risk factor of previous or current vascular surgery, or presence of at least two of the following risk factors: age 60 yr or older, hypertension, smoking within a year, serum cholesterol 6.2 mM (240 mg/dl) or greater, or diabetes mellitus. Duration of the patient having the risk factor was not included as a criterion.

Exclusion criteria included (1) unstable angina in the

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month before surgery; (2) uninterpretable Holter electrocardiogram secondary to left bundle-branch block, cardiac pacemaker dependency, or marked resting ST-segment and T-wave abnormalities that precluded electrocardiogram ST-segment interpretation; (3) preoperative use of clonidine, α methyldopa, or tricyclic antidepressants; (4) symptomatic aortic stenosis; (5) systolic blood pressure less than 100 mmHg; and (6) refusal or inability to give informed consent. All patients scheduled, who qualified under the inclusion and exclusion criteria, were approached for consent. Surgery included major vascular, intraabdominal, orthopedic, neurosurgical, intrathoracic, head and neck, and plastic procedures.

Study Drug Administration

Randomization was performed by computer in a 2:1 ratio before the study was initiated, and the statistician and the pharmacist held the code. The 2:1 ratio was chosen by a previous statistician, and no one conducting the study was aware of this choice. No stratification or balancing techniques were used. All study drug was provided in a blinded fashion by the hospital pharmacist to the nurse caring for the patient who administered it. Patients in the clonidine group received a 0.2-mg oral tablet of clonidine (Catapres; Boehringer Ingelheim, Ridgefield, CT) and a 7.0-cm^2 transdermal patch of clonidine (Catapres-TTS-2; Boehringer Ingelheim) the night before surgery. This patch provided continuous systemic delivery of 0.2 mg/day. Because a therapeutic plasma concentration of clonidine is achieved 48 h after initial application of the transdermal patch, the patients also received an oral loading dose of clonidine, 0.2-mg tablet (Catapres), 1 h before surgery as premedication. Patients in the placebo group received an oral placebo tablet and an inert transdermal occlusive skin patch the night before surgery and an oral placebo tablet 1 h before surgery. The patch was removed on postoperative day 4. No control of postoperative medication was attempted after removal of the patch. No patients were given clonidine after the perioperative period because of this study.

Study Evaluations

After preoperative history and physical examination, standard laboratory testing, and 12-lead electrocardiography were completed, three-channel Holter electrocardiographic monitoring was begun 12 h before surgery and continued for 7 days after surgery.

Anesthetic Care

All patients were monitored with standard clinical monitors. Blood pressure, heart rate, and oxygen saturation were recorded with a computer. A standardized anesthetic was used for all cases including midazolam ($\leq$ 50 μg/kg intravenous), sodium thiopental ($\leq$ 5 mg/kg intravenous), fentanyl ($\leq$ 5 μg/kg intravenous), isoflurane, oxygen, and, if appropriate, nitrous oxide. Muscle relaxation was obtained with vecuronium or succinylcholine. Reversal of neuromuscular blockade was produced with glycopyrrolate and neostigmine.

Hemodynamics were managed by protocol. All limits were predefined, and the anesthetist was provided with a written list of the limits and protocol requirements. A research coordinator observed all anesthetic cases to ensure protocol adherence. Hypertension as defined by systolic blood pressure 30% of preinduction values or greater was treated with increases in isoflurane in 0.25% increments every 3 min up to a level of twice the minimum alveolar concentration (MAC). If this therapy was unsuccessful, a 50-μg intravenous fentanyl bolus was given and could be repeated. If persistent hypertension was observed despite increases in anesthetic concentration, 0.1–0.5 mg/kg esmolol followed by infusion for tachycardia and hypertension or nitroprusside could be started for increased peripheral resistance. Hypotension as defined by systolic blood pressure 30% of preinduction values or less was treated with decreases in isoflurane in 0.25% increments. Fluid boluses were used for low preload, and 0.1-mg phenylephrine boluses were used for low peripheral resistance. Hypotension with heart rate below 45 beats/min was treated with intravenous injection of 5 mg ephedrine. Tachycardia as defined by heart rate 30% of preinduction values or greater was treated with increases in isoflurane in 0.25% increments up to a level of twice the MAC, then 50 μg intravenous injection of fentanyl, and then intravenous injection of 0.1–0.5 mg/kg esmolol followed by an infusion. Bradycardia as defined by heart rate 30% of preinduction values or less was treated with decreases in 0.25% isoflurane and, if persistent, intravenous injection of atropine up to 1 mg.

Postoperative pain was controlled with patient-controlled analgesia with morphine, unless the patient was allergic, with a starting dose of 1 mg/injection, a lockout of 6 min, no basal rate, and no limit. Inadequate analgesia was treated by increasing dose and lockout. Patients who requested an epidural catheter were given one, and it was maintained with morphine infusion. Patients receiving epidural narcotics were not included in the total narcotic calculations.

Holter Electrocardiography

Patients were monitored using a three-channel AM Holter electrocardiogram recorder (series 8500; Marquette Electronics, Milwaukee, WI) preoperatively, intraoperatively, up to 7 days postoperatively, and at least 12 h after the study drug was discontinued. The technique and outcome definitions were identical to those of our previous studies.[1,4] Three bipolar leads (CC5, CM5, and ML electrocardiographic leads) were recorded using silver–silver chloride electrodes. Lead resistance was

tested daily, and faulty leads (resistance greater than 5 kΩ) were replaced. The effect of patient positional variation on electrocardiographic morphology was measured before the study in the supine, upright, and left and right lateral decubitus positions.

Holter electrocardiographic data were analyzed for ST-segment deviation (Marquette Laser Holter Analysis System SXP software version 5.8; GE Marquette Medical Systems, Milwaukee, WI) indicative of ischemia after all abnormal QRS complexes were excluded, such as ventricular ectopic beats and beats with conduction abnormalities. The ST segments were trended continuously in three leads for the duration of the tape. The baseline ST-segment level was defined as the average ST segment during a stable period (usually 15–60 min) preceding each ischemic episode. All possible ischemic episodes were reviewed independently by two investigators blinded to patient randomization and clinical course. Disagreements were resolved by consensus, and if consensus could not be reached, a third blinded investigator, unaware of the other two assessments, evaluated the data.

Electrocardiographic ischemic episodes were defined as reversible ST-segment changes lasting at least 1 min and involving either a shift from baseline (adjusted for positional changes) of 0.1 mV or greater of ST-segment depression (with slope ≤ 0) or a shift from baseline of 0.2 mV or greater of ST-segment elevation at the J point. ST-segment depression was measured 60 ms after the J point, unless that point fell within the T wave, in which case it was shortened to a minimum of J plus 40 ms. Holter analysis was corrected for positional variation by taking the maximum shift noted by positional changes. If positional changes during Holter setup caused 0.05 mV of baseline shift, the criterion for ischemia was increased by 0.05 mV. This technique decreases the sensitivity of Holter electrocardiographic detection of ischemia because more episodes fail to make baseline; however, it makes the results more specific. The following parameters were measured as indications of severity of each episode: (1) duration, (2) maximum ST-segment change, (3) total area under the curve (defined as the integral of ST-segment depression in mV *vs.* time), and (4) heart rate (at 5 and 10 min before onset of an episode, at onset, at maximum ST-segment change, at offset, and at maximum heart rate during an episode).

Ischemic episodes were divided into separate time periods by the duration of effect of the topical clonidine administration. The periods include before surgery, day of surgery until postoperative day 3 when the patch was removed, days 4 and 5 when withdrawal phenomena might be most evident, and day 6 or more when withdrawal phenomena would subside. These periods were chosen during study design.

Dysrhythmia Analysis

Holter electrocardiographic data were analyzed for the occurrence of dysrhythmias using validated Marquette Laser Holter Analysis System software version 5.8. Ventricular and supraventricular ectopic complexes were identified and counted as isolated, bigeminal cycles, couplets, and runs. The beats in each run, the beats in the longest run, the rate of the longest run, the beats in the fastest run, and the rate of the fastest run were calculated. Minimum, average, and maximum heart rate values were calculated. Totals of each variable were calculated for the preoperative day and each postoperative day.

Twelve-lead Electrocardiogram

Twelve-lead electrocardiograms were obtained preoperatively and daily for the first 7 days after surgery, on the 10th and 14th days, weekly thereafter, at discharge from the hospital, and whenever clinically indicated (by shortness of breath, chest pain, or syncope). All electrocardiographic data were analyzed by two investigators unaware of clinical data. New Q waves were identified by Minnesota codes I1 or I2. Persistent changes in ST segments and T waves were identified by Minnesota codes IV or V.[9]

Hemodynamics

From 1 h before surgery until 1 h after surgery, the systolic, diastolic, and mean arterial blood pressures and heart rate were recorded continuously. Episodes of hemodynamic abnormality were defined as 5 min of sequential recordings exceeding the following limits: systolic blood pressure less than 80 mmHg or greater than 180 mmHg; diastolic blood pressure less than 50 mmHg or greater than 100 mmHg; and heart rate less than 40 beats/min or greater than 100 beats/min.

Measurements of Creatine Phosphokinase and MB Isoenzyme

On postoperative days 1, 3, and 5, blood samples were analyzed for concentrations of creatine phosphokinase (CPK) and MB isoenzyme (CPK-MB), with additional samples analyzed if clinical condition or electrocardiographic changes suggested myocardial ischemia or infarction. CPK concentration was determined using the Kodak Ektachem (Rochester, NE) technique, and CPK-MB concentration was determined using an Abbott (North Chicago, IL) IMX immunoassay at the San Francisco Veterans Affairs Medical Center laboratory. A CPK-MB isoenzyme concentration of 0.83 mM (or 50 U/l) was chosen as the threshold for evidence of myocardial infarction.[1]

Serum Catecholamine Measurements

Blood specimens for serum dopamine, epinephrine, and norepinephrine were collected at screening, an hour before surgery, immediately after surgery, and at

postoperative day 1. Blood specimens were drawn and were immediately centrifuged (5,000 rpm for 15 min), and the serum was stored at −80°C. All catecholamine analysis was performed by Unilab Corporation (Tarzana, CA) using high-performance liquid chromatography.

Clonidine Concentrations

Blood specimens for clonidine concentrations were collected on postoperative day 2 and immediately centrifuged (5,000 rpm for 15 min), and the serum was stored at −80°C. Clonidine concentrations were measured by gas chromatography mass spectrometry (Quest Diagnostics, Teterboro, NJ).

Adverse Cardiac Events

All definitions of adverse cardiac events were defined by protocol and were similar to those definitions in our previous study.[4] The primary endpoints for the perioperative trial were defined as the incidence[4] and severity[4] of myocardial ischemia occurring while on the study drug (preoperative and postoperative days 0 to 3), detected using Holter electrocardiographic monitoring. Safety endpoints were validated by two investigators blinded to patient study group. Long-term follow-up consisted of review of the medical chart and a phone interview. Patients who could not be contacted by phone were sent a letter; if the letter returned unanswered, the social security death registry, medical charts at the San Francisco Veterans Affairs Medical Center, and the Internet were searched. Death certificates were obtained for all deaths. Patients were considered alive until the time of the last contact, and then if they were not dead at the time of the last contact, they were censored at the time of last contact. There was no assumption of being alive or dead; subjects were only treated as alive or dead at a time point if it could be verified.

Assessment of Analgesia

Adequacy of analgesia was assessed by visual analog scale. Patients marked on a 0–10 scale corresponding to their pain while at rest. Zero represented no pain, and 10 represented the worst pain imagined. Total use of morphine during each 24-h period was recorded. Patients not receiving adequate analgesia had their dose of morphine increased and the lockout interval increased. Patients who received epidural morphine infusions were excluded from the patient-controlled anesthesia morphine use calculations.

Statistical Analysis

Power analysis was performed before study initiation. The study was designed to have 80% power to detect a 50% reduction in the incidence of perioperative myocardial ischemia detected by Holter electrocardiogram during postoperative days 0–3. Previous work demonstrated that the incidence of myocardial ischemia using this definition of Holter electrocardiographic ST-segment analysis in patients with these risk factors is 40%.[1,4] All analysis was two-sided, with $P = 0.05$ as the level of significance.

Analysis was performed by intention to treat. No exclusion or censoring were permitted except in the secondary analysis regarding perioperative β blockade or epidural use. No interim analysis was permitted. All analysis was prespecified except for the analysis excluding patients who received β blockade or epidurals. We used the analysis plan from our previous study of atenolol with similar outcome variables.[4] Continuous variables were analyzed using parametric (Student *t* test) and nonparametric (Wilcoxon rank sum test) techniques. Two-way repeated-measures analysis of variance was used where appropriate. Continuous variables are presented as mean ± SD. Proportions were compared using the Fisher exact test (two tailed). Treatment group perioperative myocardial ischemia incidences were compared for both the entire studied population (n = 190) and the subset of patients free of perioperative β blockers (n = 178). Survival analysis was performed using the Kaplan-Meier method; log-rank and Wilcoxon tests were computed to assess homogeneity between the treatment strata. The interaction of the three variables of clonidine, ischemia, and 2-yr survival were tested using multivariable logistic regression. These variables were chosen from their significance in previous studies.[4] A general search for predictors of mortality was not performed. No other models were tested and no corrections were made for multiple comparisons because 2-yr mortality and perioperative myocardial ischemia were predetermined independent outcome variables. All analyses were performed using SAS (Statistical Analysis System) software (version 6.12; SAS Institute, Cary, NC).

Results

A total of 202 patients consented and were randomized, but 12 patients were withdrawn before surgery. Ten patients had the surgical procedure canceled for unrelated reasons, and the patients were withdrawn from the study. Three patients had systolic blood pressures between 80 and 90 mmHg on the morning of surgery. Two of these patients continued and one withdrew from the study after surgery was canceled. One patient developed chest pain preoperatively, surgery was canceled, and the patient was withdrawn from the study. Demographic information for the 190 patients who completed the study is listed in table 1. The emphasis in all tables is on comparison of percentages rather than the numbers of patients. There were no statistically significant differences in population characteristics between patients randomized to the treatment groups.

Table 1. Characteristics of the Patients

Characteristic	Clonidine (n = 125)	Placebo (n = 65)	*P* Value*
Cardiac history, % (No.)			
Definite coronary artery disease	41 (51)	35 (23)	0.53
Previous myocardial infarction	26 (33)	15 (10)	0.10
Previous coronary artery bypass grafting	17 (21)	15 (10)	1.00
Previous percutaneous transluminal coronary angioplasty	12 (15)	3 (2)	0.06
Typical angina	14 (17)	14 (9)	1.00
History of dysrhythmia	13 (16)	12 (8)	1.00
History of congestive heart failure	13 (16)	6 (4)	0.21
Cardiac risk factors, % (No.)			
Current smoking	43 (54)	43 (28)	1.00
Hypertension	73 (91)	71 (46)	0.86
Cholesterol ≥ 6.21 mM or 240 mg/dl	38 (21)	30 (9)	0.49
Diabetes mellitus	26 (32)	31 (20)	0.49
Age ≥ 65 yr	68 (85)	77 (50)	0.24
Preoperative medications, % (No.)			
Antiarrhythmic	0 (0)	0 (0)	1.0
β Blocker	9 (11)	2 (1)	0.06
Calcium channel blocker	25 (31)	23 (15)	0.86
Diuretic	16 (20)	12 (8)	0.67
Digoxin	5 (6)	8 (5)	0.52
Nitrates	10 (12)	6 (4)	0.58
Age, yr	68.0 ± 7.5	69.2 ± 8.7	
Type of surgery, % (No.)	—	—	0.21
Major vascular	25 (31)	29 (19)	NA
Intraabdominal	16 (20)	23 (15)	NA
Intrathoracic	4 (5)	8 (5)	NA
Other	55 (69)	40 (26)	NA
Postoperative epidural for analgesia	9 (11)	11 (7)	0.32

* Fisher exact test (two tailed).

NA = not applicable.

Intraoperative hemodynamics were similar in the two groups (table 2), with the exception that the placebo-treated patients (clonidine, 25% *vs.* placebo, 48%; $P = 0.01$) had more intraoperative hypertension (systolic blood pressure > 180 mmHg). The requirements for pharmacologic management of hemodynamics (table 3) were similar, with the exception that more patients in the placebo-treated group received intraoperative β blockade (clonidine, 7% *vs.* placebo, 19%; $P = 0.03$). Clonidine-treated patients had significantly lower minimal, maximal, and average heart rates (table 4) than placebo patients.

Clonidine blood concentrations on postoperative day 2 averaged 0.53 ± 0.29 ng/ml *versus* 0.005 ± 0.03 ng/ml for placebo ($P = 0.0001$). There was no statistical difference in pain scores on the visual analog scale (clonidine, 3.5 ± 2.8 *vs.* placebo, 3.5 ± 3.1; $P = 0.997$) or in morphine (MSO_4) use (clonidine, 66.5 ± 6.5 mg *vs.* placebo, 63.2 ± 8.9 mg; $P = 0.77$). Overall, there was a statistically significant increase in concentrations of serum epinephrine ($P = 0.05$) and norepinephrine ($P = 0.001$) with time (table 5). In addition, clonidine reduced concentrations of serum epinephrine ($P = 0.05$) and serum norepinephrine ($P = 0.002$) but not serum dopamine ($P = 0.64$) (table 5).

The incidence of perioperative myocardial ischemia, defined by 1 mm of ST-segment depression lasting at least 1 min on Holter electrocardiographic monitoring, was reduced in patients treated with clonidine compared with those receiving placebo preoperatively, on the day of surgery, and on postoperative days 0–3. The preoperative incidence of myocardial ischemia was 0 for

Table 2. Intraoperative Hemodynamics

Variable	Clonidine (n = 125)	Placebo (n = 65)	*P* Value*
	% (No.) of Patients		
Systolic blood pressure < 80 mmHg	19 (24)	17 (11)	0.84
Systolic blood pressure > 180 mmHg	25 (31)	48 (31)	0.01†
Diastolic blood pressure < 50 mmHg	56 (70)	48 (31)	0.29
Diastolic blood pressure > 100 mmHg	24 (30)	29 (19)	0.49
Heart rate < 40 beats/min	10 (12)	3 (2)	0.14
Heart rate > 100 beats/min	26 (32)	32 (21)	0.39

* Fisher exact test (two tailed). † Statistically significant at $P \leq 0.05$.

Table 3. Intraoperative Cardiovascular Medications

Medication	Clonidine (n = 125) % (No.) of Patients	Placebo (n = 65) % (No.) of Patients	*P* Value*
Dopamine	2 (2)	3 (2)	0.61
Epinephrine	0 (0)	2 (1)	0.34
Phenylephrine	5 (5)	8 (5)	0.52
Ephedrine	3 (4)	3 (2)	1.00
Atropine	0 (0)	0 (0)	1.00
β Blocker	7 (9)	19 (12)	0.03†
Calcium channel blocker	14 (17)	7 (4)	0.15
Diuretics	2 (3)	5 (3)	0.41
Nitrates	8 (10)	11 (7)	0.59

* Fisher exact test (two tailed). † Statistically significant at $P \leq 0.05$.
NA = not applicable.

clonidine patients *versus* 5% for placebo patients ($P = 0.04$; table 6). The incidence of myocardial ischemia on the day of surgery and postoperative days 0–3 was 14% among clonidine patients *versus* 31% for placebo patients ($P = 0.01$; table 6). In addition, even after removing all patients receiving preoperative β blockade (clonidine, 11; placebo, 1), the incidence of ischemia analysis results remained virtually unchanged (tables 6 and 7). No significant difference was noted in severity of ischemic episodes between clonidine- and placebo-treated patients (table 8).

There were no differences in the incidence of perioperative in-hospital clinical events (table 9) or CPK-MB release (table 10). Thirty-day mortality was reduced in patients assigned to the clonidine group (1 of 125 [0.8%] *vs.* 4 of 65 [6.2%]; $P = 0.048$; table 9). In long-term follow-up, the incidence of postoperative death was reduced in patients given clonidine (fig. 1) (relative risk [RR] = 0.43 [confidence interval (CI), 0.21–0.89]; $P = 0.035$ by Fisher exact test [table 9] or RR = 0.45 [CI, 0.24–0.84]; $P = 0.012$ by log-rank test). Nineteen of 125 (15%) of the patients died in the clonidine group and 19 of 65 (29%) in the placebo group died within 730 days after surgery ($P = 0.035$; table 9). A two-variable model with both myocardial ischemia and clonidine demonstrates significance ($P = 0.025$). Assignment to the clonidine group (RR = 0.70 [CI, 0.50–0.97]; $P = 0.03$) reduced the risk of mortality. However, the occurrence of a single episode of myocardial ischemia did not significantly affect mortality (RR = 1.28 [CI, 0.85–1.85]; $P = 0.22$). Intraoperative hypertension was not a significant risk factor for mortality. Eliminating all of the patients who were taking preoperative β blockers had no effect on the 30-day (clonidine, 1 [0.9%] *vs.* placebo, 4 [6.3%]; $P = 0.04$) and 2-yr (clonidine, 18 [16%] *vs.* placebo, 18 [28%]; $P = 0.03$) mortality results. Removing all of the patients who received preoperative or intraoperative β blockers resulted in a loss of significance for the 30-day (clonidine, 1 [0.9%] *vs.* placebo, 1 [1.9%]; $P = 0.60$) and 2-yr (clonidine, 18 [17%] *vs.* placebo, 14 [27%]; $P = 0.12$) mortality results. Eliminating all of the patients who received an epidural had no effect on the 30-day (clonidine, 1 [0.8%] *vs.* placebo, 4 [6.6%]; $P = 0.03$) or 2-yr (clonidine, 18 [15%] *vs.* placebo, 17 [28%]; $P = 0.02$) mortality. Differences in postoperative medical therapy with clonidine, β blockers, calcium channel blockers, nitrates, or angiotensin-converting enzyme inhibitors did not differ between the two groups (table 11).

Table 4. Holter-detected Arrhythmias for Postoperative Days 0–7

Characteristic	Clonidine (n = 125)	Placebo (n = 65)	*P* Value*
Duration, s	149,288 ± 80,327	162,176 ± 70,917	0.23
QRS complexes, No.	605,714 ± 268,846	662,755 ± 293,916	0.29
Ventricular ectopics, No.	6,892 ± 19,582	4,526 ± 12,035	0.77
Supraventricular ectopics, No.	13,339 ± 26,291	16,295 ± 27,834	0.34
Minimal heart rate, beats/min	40 ± 10	46 ± 12	0.00†
Average heart rate, beats/min	61 ± 10	67 ± 11	0.001†
Maximal heart rate, beats/min	138 ± 30	156 ± 41	0.001†

Plus–minus values are presented as mean ± SD.
* Analysis of variance. † Statistically significant at $P \leq 0.05$.

Table 5. Serum Catecholamine Concentrations

Catecholamine	Clonidine				Placebo				*P* Value*
	Screen	Preoperative	Postoperative	POD 1	Screen	Preoperative	Postoperative	POD 1	
Epinephrine (pg/ml)	38 ± 37	48 ± 79	223 ± 332	67 ± 74	33 ± 21	37 ± 35	412 ± 555	85 ± 104	0.05
Norepinephrine (pg/ml)	618 ± 401	357 ± 522	555 ± 468	591 ± 358	704 ± 444	473 ± 366	1054 ± 791	853 ± 555	0.002
Dopamine (pg/ml)	22 ± 25	35 ± 176	23 ± 43	24 ± 26	20 ± 18	16 ± 13	29 ± 26	29 ± 33	0.64

* Two-way analysis of variance with all pairwise multiple comparison procedures (Tukey test). Significant increases were noted over time in epinephrine and norepinephrine concentrations ($P = 0.05$ and 0.001).
POD = postoperative day.

Table 6. Incidence of Holter-detected 1-Millimeter ST Depression Lasting at Least 1 Minute in All Study Patients

Study Period	Clonidine (n = 125)	Placebo (n = 65)	*P* Value*
	% (No.) of Patients		
Preoperative†	0 (0)	5 (3)	0.04‡
Day of surgery and days 1–3 after surgery§	14 (18)	31 (20)	0.01‡
Days 4 and 5 after surgery‖	9 (8)	18 (8)	0.16
Days 6 or more after surgery#	2 (1)	21 (6)	0.01‡

Not all patients stayed in the hospital for 7 days postoperatively.

* Fisher exact test. † Holter results missing for 1 placebo patient and 2 clonidine patients. ‡ Statistically significant at $P \leq 0.05$. § Holter results for 124 clonidine patients and 65 placebo patients. ‖ Holter results for 87 clonidine patients and 44 placebo patients. # Holter results for 47 clonidine patients and 28 placebo patients.

Table 7. Incidence of Holter-detected 1-Millimeter ST Depression Lasting at Least 1 Minute in Study Patients, Excluding Patients Who Received β Blockers

Study Period	Clonidine (n = 114)	Placebo (n = 64)	*P* Value*
	% (No.) of Patients		
Preoperative†	0 (0)	5 (3)	0.05‡
Day of surgery and days 1–3 after surgery§	15 (17)	30 (19)	0.03‡
Days 4 and 5 after surgery‖	10 (8)	19 (8)	0.26
Days 6 or more after surgery#	2 (1)	21 (6)	0.01‡

Not all patients stayed in the hospital for 7 days postoperatively.

* Fisher exact test. † Holter results missing for 1 placebo patient and 2 clonidine patients. ‡ Statistically significant at $P \leq 0.05$. § Holter results for 113 clonidine patients and 64 placebo patients. ‖ Holter results for 80 clonidine patients and 43 placebo patients. # Holter results for 42 clonidine patients and 28 placebo patients.

Table 8. Severity of ST Depression Lasting at Least 1 Minute (Among Postoperative Ischemic Patients Only)

Study Period	Clonidine (n = 21)	Placebo (n = 23)	*P* Value*
Total ischemic episodes (n = 199 episodes), No.	67	132	
Episodes (per patient with an episode), No.	3.2 ± 2.6	5.7 ± 9.3	0.51
Absolute ST-segment change, mV	1.6 ± 0.5	1.7 ± 0.7	0.72
Duration of episodes, min	52.0 ± 76.2	47.1 ± 81.1	0.15
|Area under the curve|, mV/s	64.6 ± 79.8	89.0 ± 251.8	0.51
Extreme ischemic episodes per patient			
Duration of longest episode, min	96.2 ± 120.0	104.5 ± 132.5	0.73
Maximal |area under the curve|, mV/s	103.1 ± 111.0	197.5 ± 419.5	0.69
Maximal heart rate during episode, beats/min	118.5 ± 19.2	124.2 ± 19.2	0.24

* Analysis of variance.

Table 9. Hard Outcomes

Outcomes	Clonidine (n = 125)	Placebo (n = 65)	*P* Value*
	% (No.) of Patients		
30-day mortality	0.8 (1)	6.2 (4)	0.048†
2-yr mortality	15.2 (19)	29.2 (19)	0.035†
In-hospital events			
Myocardial infarction by electrocardiogram or CPK-MB‡	4.0 (5)	4.6 (3)	0.86
Myocardial infarction by electrocardiogram alone	2.4 (3)	3.1 (2)	1.0
Myocardial infarction by CPK-MB alone	3.2 (4)	4.6 (3)	0.69
Myocardial infarction by both electrocardiogram and CPK-MB	1.6 (2)	3.1 (2)	0.61
Congestive heart failure	0.0 (0)	3.1 (2)	0.22
Unstable angina	0.8 (1)	1.5 (1)	0.78
Ventricular tachycardia	0.8 (1)	1.5 (1)	0.78
Cerebrovascular accident	0.8 (1)	0.0 (0)	1.00

* Fisher exact test. † Statistically significant at $P \leq 0.05$. ‡ Myocardial infarction diagnosed by electrocardiogram and creatine phosphokinase MB isoenzyme (CPK-MB).

Table 10. Creatine Phosphokinase Concentration and Creatine Phosphokinase MB Isoenzyme Percentage

Test	POD	Clonidine Mean ± SD	Placebo Mean ± SD	Minimum–Maximum	Student *t* Test	Wilcoxon Rank Sum Test
CPK, U/l	1	767.6 ± 1202.9	867.6 ± 1245.6	33–5000	0.617	0.095
	3	658.0 ± 1045.2	578.7 ± 853.9	26–5000	0.657	0.660
	5	268.4 ± 391.6	309.2 ± 508.3	7–2481	0.640	0.397
CPK-MB, %	1	8.9 ± 17.5	17.0 ± 45.1	1–101	0.141	0.010
	3	3.5 ± 3.9	8.2 ± 20.6	1–16	0.083	0.141
	5	2.9 ± 5.5	4.7 ± 10.5	1–35	0.347	0.663

CPK = creatine phosphokinase; MB = isoenzyme; POD = postoperative day.

Discussion

The current trial demonstrated that prophylactic perioperative administration of the α_2 agonist clonidine significantly reduces the incidence of perioperative myocardial ischemia and postoperative mortality in patients who have or who are at risk for coronary artery disease and undergo noncardiac surgery. In previous trials, prophylactic β-blockade reduced the incidence of death after noncardiac surgery.[4–6] The current trial demonstrates similar efficacy for prevention of death with a drug in a different pharmacologic class. Clonidine provides an alternative therapy for prevention of cardiac morbidity in patients with or at risk for coronary artery disease who undergo noncardiac surgery.

The treatment effect we observed is similar in magnitude to the reduction in risk with atenolol prophylaxis.[4,5] It is less effective than the 90% reduction in risk observed with bisoprolol; however, those patients started β blockade at least 1 week before and continued 30 days after surgery.[6] In the atenolol study, β blockade was started in the preoperative area just before surgery and continued for 7 days.[4,5] In the current study, clonidine was started the night before surgery and continued for 4 days. Prophylactic anti-ischemic therapy before surgery prevents perioperative ischemic events and reduces risk of death.[4] Early initiation of anti-ischemia prophylaxis is probably superior to immediate preoperative administration because it prevents ischemia in the period before surgery.

The current study demonstrated improved 30-day and 2-yr survival in patients with or at risk for coronary artery disease who received prophylactic clonidine therapy. Two studies of prophylactic clonidine therapy have demonstrated a reduction in the incidence of perioperative myocardial ischemia in patients undergoing noncardiac surgery. In a randomized trial of 61 patients undergoing noncardiac surgery, Ellis *et al.*[10] found that clonidine reduced enflurane requirements, intraoperative tachycardia, and myocardial ischemia (1 of 28 clonidine patients *vs.* 5 of 24 placebo patients; $P = 0.05$), but those effects were short-lived. The incidence of postoperative myocardial ischemia (6 of 28 clonidine patients *vs.* 5 of 26 placebo patients) did not differ between the two groups. No effects on myocardial infarction or mortality were observed, and no long-term follow-up was performed. A randomized trial in 297 patients undergoing

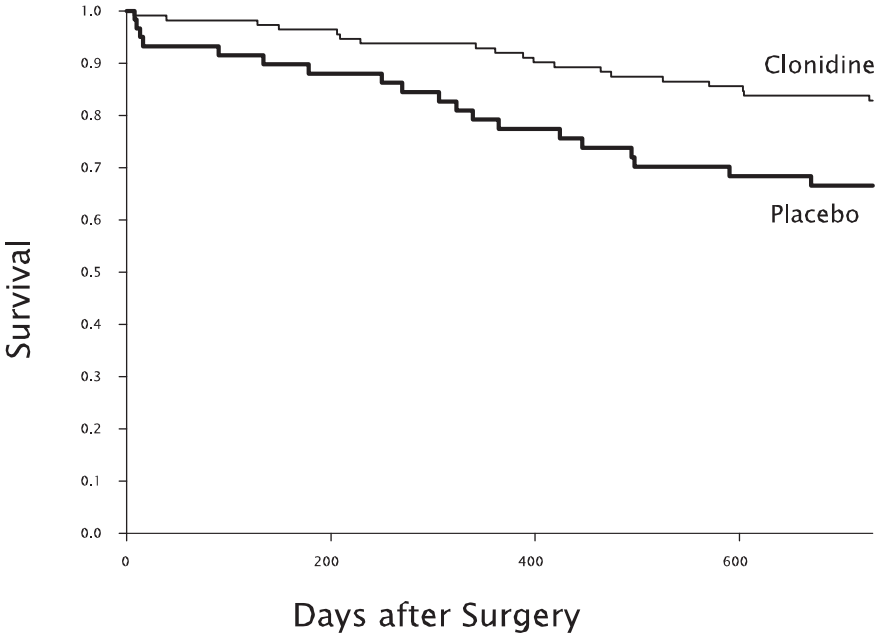

Fig. 1. Survival for clonidine-treated *versus* placebo-treated patients. Survival curves for 2 yr after surgery for patients treated with clonidine (n = 125) and placebo (n = 65). Clonidine reduced the incidence of death ($P = 0.01$ by log-rank test and $P = 0.01$ by Wilcoxon test).

Table 11. Use of Cardiovascular Medications before and after Surgery, According to Study Group

	Alive			Taking Clonidine			Taking β Blockers		
	Clonidine, % (No.)	Placebo, % (No.)	*P* Value	Clonidine, % (No.)	Placebo, % (No.)	*P* Value	Clonidine, % (No.)	Placebo, % (No.)	*P* Value
Before admission	100 (125)	100 (65)	1.0	0	0	1.0	9 (11)	2 (1)	0.06
At discharge	98 (123)	94 (61)	0.18	0	0	1.0	18 (22)	8 (5)	0.12
At 6 months	95 (119)	91 (59)	0.34	0	0	1.0	17 (20)	12 (7)	0.51
At 12 months	88 (110)	77 (50)	0.059	0	0	1.0	16 (18)	8 (4)	0.32
At 24 months	85 (106)	71 (46)	0.034	0	0	1.0	0.8 (1)	0 (0)	1.0

ACE = angiotensin-converting enzyme.

noncardiac surgery demonstrated that clonidine reduced the incidence of perioperative myocardial ischemic episodes from 39% (59 of 152) to 24% (35 of 145) ($P < 0.01$).[7] No significant differences in myocardial infarctions or mortality were found. No long-term follow-up was performed. Clonidine has been studied in patients undergoing cardiac surgery with mixed results, and it cannot be recommended.[8,11–14] A meta-analysis of the 28 English-language studies published between 1980 and 1999 found 7 that could be included.[15] The pooled odds ratio was 0.49 (95% CI, 0.34–0.71) for the prevention of myocardial ischemia. Subgroup analysis revealed that clonidine reduced the incidence of myocardial ischemia in patients undergoing both cardiac and noncardiac surgery. α_2-Agonist therapy with mivazerol has been shown to reduce myocardial ischemia[16] and may reduce mortality[17] but it is not clinically available. Dexmedetomidine has been shown to be a coronary vasoconstrictor when given by rapid intravenous infusion in dogs.[18] No studies have been published that clarify its effects on the incidence of perioperative myocardial ischemia in humans.[19] Currently, the only clinically available α_2-agonist therapy that has been shown to reduce the incidence of perioperative myocardial ischemia and reduce mortality is clonidine.

It is clear that all patients identified with or at risk for coronary artery disease who undergo surgery should be considered for anti-ischemia prophylaxis with either β blockade or α_2 agonist. Unfortunately, this study does not indicate which therapy is superior. Patients treated with α_2-agonist therapy still experienced tachycardia, which may lead to myocardial ischemia.[20] β Blockade more effectively prevents tachycardia and may be superior for ischemia prophylaxis. β Blockers also have multiple effects not related to control of heart rate, including platelet effects, antiarrhythmic effects, and the control of blood pressure, which may affect perioperative outcome. Preventing central release of catecholamines may have multiple effects separate from the pure effect on heart rate. It is unknown whether combined β blockade and α_2-agonist therapy will be superior to either agent alone by blocking both release and effects of catecholamines or will result in an increased risk for side effects. The current study does not have significant power to detect an added benefit of coadministration of α_2-agonist therapy to β blockade.

How could a therapy applied for only 4 days affect 2-yr mortality? A single episode of perioperative myocardial ischemia detected by Holter electrocardiographic monitoring has been shown to increase the risk of 2-yr mortality in previous studies.[3,4] Reducing the incidence of episodes of perioperative myocardial ischemia reduces the risk of 2-yr mortality.[4] Two separate studies have demonstrated that perioperative administration of a drug that reduces the incidence of myocardial ischemia reduces the risk of 2-yr mortality.[4,21] The long-term benefit of short-term perioperative therapy has been shown in the current study and with β blockers.[4,5,21] Prevention of episodes of myocardial ischemia reduces the incidence of subsequent episodes of ischemia that may develop into a pattern of unstable angina and subsequent myocardial infarction. Prophylactic anti-ischemic therapy prevents the initiation of a chain of events leading to myocardial infarction and death. Perioperative anti-ischemia therapy with atenolol or clonidine reduces the overall mortality by reducing the incidence of ischemic events. Therapies that reduced the incidence of perioperative ischemic episodes are associated with a reduction in mortality after surgery. The current study clearly demonstrates a significant difference in 30-day and 2-yr mortality using a prophylactic anti-ischemic therapy.

This study has limitations. Because study patients were enrolled at a Veterans Affairs Medical Center, significant numbers of women were not available for inclusion. Results may be slightly different when prophylactic clonidine therapy is used in women with or at risk for coronary artery disease. Despite this limitation, women at risk for cardiac morbidity should receive anti-ischemia prophylaxis. This study used a single dose of clonidine (0.2-mg oral tablet and Catapres-TTS-2 patch). Higher doses may have reduced the risk even more but may have greater side effects. Only a single clonidine concentration measurement was performed on postoperative day 2. This concentration may or may not be representative of the average concentration during administration. After the oral dose or at the end of the duration of effect of the patch, the concentration may have been different. Prophylactic administration of clonidine to pa-

Table 11. Continued

Taking Calcium Channel Blockers			Taking Nitrates			Taking ACE Inhibitors		
Clonidine, % (No.)	Placebo, % (No.)	*P* Value	Clonidine, % (No.)	Placebo, % (No.)	*P* Value	Clonidine, % (No.)	Placebo, % (No.)	*P* Value
25 (31)	23 (15)	0.86	10 (12)	6 (4)	0.58	17 (21)	22 (14)	0.44
28 (35)	29 (19)	0.73	12 (15)	12 (8)	1.0	22 (28)	20 (13)	1.0
32 (38)	36 (21)	0.75	9 (11)	19 (11)	0.15	19 (23)	8 (10)	0.84
20 (22)	20 (10)	1.0	11 (12)	10 (5)	1.0	22 (24)	16 (8)	0.53
0.8 (1)	0 (0)	1.0	0 (0)	0 (0)	1.0	0.8 (1)	0 (0)	1.0

tients may cause hypotension preoperatively. Three patients experienced systolic blood pressures between 80 and 90 mmHg just before surgery. This hypotension responded to fluid administration; however, patients with critical aortic stenosis or who are hypotensive (systolic blood pressure $<$ 110 mmHg) should not be given prophylactic clonidine therapy without careful medical supervision. This study used CPK-MB isoenzyme concentrations to detect biochemical evidence of myocardial injury. Concentrations were determined on postoperative days 1, 3, and 5 and when clinically indicated to optimize the detection of myocardial injury. If a larger number of CPK-MB measurements were taken or troponin I or troponin T were used, more evidence of myocardial injury may have been evident. Using CPK-MB did not affect the results of the study because the test was used for both randomized groups. The trend toward more patients in the clonidine group having a history of preoperative β blocker use does not change the results because exclusion of these patients from the analysis has no effect on the results.

The cost of prophylactic perioperative anti-ischemic therapy with either clonidine or atenolol is trivial compared with the cost of managing the perioperative myocardial infarctions and deaths incurred by not using prophylaxis. This study demonstrated that prophylactic therapy with the α_2 agonist clonidine reduces incidence of myocardial ischemia and postoperative death and has efficacy similar to that of β-blocker therapy. Clonidine anti-ischemia prophylaxis provides an alternative therapy to prophylactic β blockade for patients undergoing noncardiac surgery.

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References

1. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 1990; 323:1781–8

2. Mangano DT, Goldman L: Preoperative assessment of patients with known or suspected coronary disease. N Engl J Med 1995; 333:1750–6

3. Mangano DT, Browner WS, Hollenberg M, Li J, Tateo IM: Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 1992; 268:233–9

4. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, Miller D, Mangano DT: Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. ANESTHESIOLOGY 1998; 88:7–17

5. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group [published erratum appears in N Engl J Med 1997; 336:1039]. N Engl J Med 1996; 335:1713–20

6. Poldermans D, Boersma E, Bax JJ, Thomson IR, Van de Ven LLM, Blankensteijn JD, Baars HF, Yo T-I, Trocino G, Vigna C, Roelandt JRTC, Van Urk H: The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341:1789–94

7. Stühmeier K-D, Mainzer B, Cierpka J, Sandmann W, Tarnow J: Small, oral dose of clonidine reduces the incidence of intraoperative myocardial ischemia in patients having vascular surgery. ANESTHESIOLOGY 1996; 85:706–12

8. Dorman BH, Zucker JR, Verrier ED, Gartman DM, Slachman FN: Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirement, and alters hemodynamic parameters in patients undergoing coronary artery bypass surgery. J Cardiothorac Vasc Anesth 1993; 7:386–95

9. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram in population studies: A classification system. Circulation 1960; 21: 1160–75

10. Ellis JE, Drijvers G, Pedlow S, Laff SP, Sorrentino MJ, Foss JF, Shah M, Busse JR, Mantha S, McKinsey JF, Osinski J, Tisted RA, Roizen MF: Premedication with oral and transdermal clonidine provides safe and efficacious postoperative sympatholysis. Anesth Analg 1994; 79:1133–40

11. Myles PS, Hunt JO, Holdgaard HO, McRae R, Buckland MR, Moloney J, Hall J, Bujor MA, Esmore DS, Davis BB, Morgan DJ: Clonidine and cardiac surgery: Haemodynamic and metabolic effects, myocardial ischaemia and recovery. Anaesth Intensive Care 1999; 27:137–47

12. Loick HM, Schmidt C, Van Aken H, Junker R, Erren M, Berendes E, Rolf N, Meissner A, Schmid C, Scheld HH, Mollhoff T: High thoracic epidural anesthesia, but not clonidine, attenuates the perioperative stress response via sympatholysis and reduces the release of troponin T in patients undergoing coronary artery bypass grafting. Anesth Analg 1999; 88:701–9

13. Boldt J, Rothe G, Schindler E, Doll C, Gorlach G, Hempelmann G: Can clonidine, enoximone, and enalaprilat help to protect the myocardium against ischaemia in cardiac surgery? Heart 1996; 76:207–13

14. Abi-Jaoude F, Brusset A, Ceddaha A, Schlumberger S, Raffin L, Dubois C, Guilmet D, Fischler M: Clonidine premedication for coronary artery bypass grafting under high-dose alfentanil anesthesia: Intraoperative and postoperative hemodynamic study. J Cardiothorac Vasc Anesth 1993; 7:35–40

15. Nishina K, Mikawa K, Uesugi T, Obara H, Maekawa M, Kamae I, Nishi N: Efficacy of clonidine for prevention of perioperative myocardial ischemia: A critical appraisal and meta-analysis of the literature. ANESTHESIOLOGY 2002; 96:323–9

16. McSPI-EUROPE Research Group: Perioperative sympatholysis. Beneficial effects of the alpha 2-adrenoceptor agonist mivazerol on hemodynamic stability and myocardial ischemia. ANESTHESIOLOGY 1997; 86:346–63

17. Oliver MF, Goldman L, Julian DG, Holme I: Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary heart disease: The European Mivazerol Trial (EMIT). ANESTHESIOLOGY 1999; 91:951–61

18. Jalonen J, Halkola L, Kuttila K, Perttila J, Rajalin A, Savunen T, Scheinin M, Valtonen M: Effects of dexmedetomidine on coronary hemodynamics and myocardial oxygen balance. J Cardiothorac Vasc Anesth 1995; 9:519–24

19. Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, Mangano DT: Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. ANESTHESIOLOGY 1995; 82:620–33

20. Leung JM, O'Kelly BF, Mangano DT: Relationship of regional wall motion abnormalities to hemodynamic indices of myocardial oxygen supply and demand in patients undergoing CABG surgery. The SPI Research Group. ANESTHESIOLOGY 1990; 73:802–14

21. Poldermans D, Boersma E, Bax JJ, Thomson IR, Paelinck B, van de Ven LL, Scheffer MG, Trocino G, Vigna C, Baars HF, van Urk H, Roelandt JR: Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. Eur Heart J 2001; 22:1353–8