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Cardioprotective Medication Is Associated With Improved Survival in Patients With Peripheral Arterial Disease

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OBJECTIVES We sought to investigate the effect of cardiac medication on long-term mortality in patients with peripheral arterial disease (PAD).

BACKGROUND Peripheral arterial disease is associated with increased cardiovascular morbidity and mortality. Treatment guidelines recommend aggressive management of risk factors and lifestyle modifications. However, the potential benefit of cardiac medication in patients with PAD remains ill defined.

METHODS In this prospective observational cohort study, 2,420 consecutive patients (age, 64 ± 11 years, 72% men) with PAD (ankle-brachial index ≤0.90) were screened for clinical risk factors and cardiac medication. Follow-up end point was death from any cause. Propensity scores for statins, beta-blockers, aspirin, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, nitrates, coumarins, and digoxin were calculated. Cox regression models were used to analyze the relation between cardiac medication and long-term mortality.

RESULTS Medical history included diabetes mellitus in 436 patients (18%), hypercholesterolemia in 581 (24%), smoking in 837 (35%), hypertension in 1,162 (48%), coronary artery disease in 1,065 (44%), and a history of heart failure in 214 (9%). Mean ankle-brachial index was 0.58 (±0.18). During a median follow-up of eight years, 1,067 patients (44%) died. After adjustment for risk factors and propensity scores, statins (hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.36 to 0.58), beta-blockers (HR 0.68, 95% CI 0.58 to 0.80), aspirins (HR 0.72, 95% CI 0.61 to 0.84), and ACE inhibitors (HR 0.80, 95% CI 0.69 to 0.94) were significantly associated with a reduced risk of long-term mortality.

CONCLUSIONS On the basis of this observational longitudinal study, statins, beta-blockers, aspirins, and ACE inhibitors are associated with a reduction in long-term mortality in patients with PAD. (J Am Coll Cardiol 2006;47:1182–7) © 2006 by the American College of Cardiology Foundation

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis and carries a poor prognosis as a result of the frequent association with cerebral, renal, and coronary artery disease (1–4). Although patients with PAD may present with symptoms ranging from pain on exertion that is relieved by rest (intermittent claudication) to pain at rest, ulceration, or gangrene (critical limb ischemia), most patients with PAD are asymptomatic (1). The prevalence of PAD ranges from 4% in patients aged 40 years and older to more than 20% in patients aged 70 years and older (5–10).

Peripheral arterial disease remains an underdiagnosed disease in the primary care, and patients with PAD are not treated as aggressively as are patients with other manifestations of atherosclerotic disease (7,11). The treatment of PAD focuses on walking exercise, aggressive management of risk factors, lifestyle modifications, and antiplatelet therapy (12,13). Cardiovascular events are a major cause of morbidity and mortality in patients with PAD. However, the potential benefit of cardiac medication therapy remains ill defined. Beta-adrenergic receptor blockers were considered relatively contraindicated in PAD; however, several studies have revealed that beta-blockers do not adversely affect walking capacity, symptoms of intermittent claudication, and peripheral skin microcirculation (14–16).

In this report, we sought to determine the effect of chronic treatment with cardiac medication, including statins, beta-blockers, aspirins, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, nitrates, coumarins, and digoxin on long-term mortality among patients with PAD. In this observational cohort study, we used propensity analysis to adjust for selection bias in the comparison of treatments.

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Abbreviations and Acronyms

ABI = ankle-brachial index
ACE = angiotensin-converting enzyme
CI = confidence interval
HR = hazard ratio
PAD = peripheral arterial disease

METHODS

Assessment of baseline characteristics. The Erasmus Medical Center serves a population of approximately 3 million people and acts as a tertiary referral center for approximately 30 affiliated hospitals. Patients with suspected or known PAD who were referred to the Erasmus Medical Center, Rotterdam, the Netherlands, between January 1983 and January 2005, for the diagnosis and management of PAD were evaluated. The ankle-brachial index (ABI) at rest was measured in each patient and patients with PAD (ABI ≤0.90) were included in the study.

On the basis of hospital records and personal interviews at the time of the visit, a medical history was recorded. Information on the presence of previous myocardial infarction, angina pectoris, previous coronary artery revascularization, congestive heart failure, previous stroke or transient ischemic attack, diabetes mellitus, hypertension, current smoking, hypercholesterolemia, and renal dysfunction were obtained. Diabetes mellitus was recorded if patients presented with a fasting glucose level of ≥7.0 mmol/l, or in those who required treatment. Hypertension was recorded if patients presented with a blood pressure ≥140/90 mm Hg or if patients were medically treated for hypertension. Hypercholesterolemia was recorded when patients presented with the diagnosis, made by the referring physician, or if patients were taking lipid-lowering agents. Renal dysfunction was recorded if patients presented with a serum creatinine level ≥2.0 mg/dl (177 μmol/l) or in those who required dialysis. A baseline 12-lead electrocardiography was obtained and was considered abnormal in the presence of one or more of the following: Q waves, ST-segment depression or elevation, left ventricular hypertrophy, right or left bundle branch block, and atrial fibrillation.

Use of medication. All prescription and over-the-counter medications were noted at the time of the visit and were classified as follows: statins, beta-blockers, aspirins, ACE inhibitors, calcium channel blockers (dihydropyridines or non-dihydropyridines), diuretics, nitrates, coumarins, and digoxin. To ascertain the long-term use of cardiovascular medication, medication had to be documented at least at two months after the visit.

Follow-up. Patients were followed during a median time of 8 years (interquartile range, 4 to 11 years) for the occurrence of all-cause death. End point was mortality. Information about the patient's vital status was obtained by approaching the Office of Civil Registry. For patients who died at our hospital during follow-up, hospital records and autopsy results were retrieved and reviewed. For patients who died outside our hospital, general practitioners were approached to ascertain the cause of death.

Statistical analysis. Continuous data with a normal distribution were expressed as mean and compared using the Student *t* test. Categorical data are presented as percent frequencies, and differences between proportions were compared using the chi-square test with Yates' correction. The Kaplan-Meier method with log-rank test was used to compare survival curves in two or more groups. We applied univariate and multivariate Cox proportional hazards regression analyses to study the relation between cardiac medication therapy and long-term survival. Cardiac medication use was not randomly assigned in these patients, and the impact of selection bias may profoundly distort the results of our study.

Propensity analyses are reliable tools to correct for selection bias and the rationale for using propensity scores has been previously described (17). Therefore, separate propensity scores were calculated and ranged from 0.04 to 0.92 for statins, 0.002 to 0.98 for beta-blockers, 0.05 to 0.92 for aspirin, 0.04 to 0.95 for ACE inhibitors, 0.08 to 0.76 for calcium channel blockers, 0.0001 to 0.87 for diuretics, 0.04 to 0.91 for nitrates, 0.35 to 0.91 for coumarins, and 0.15 to 0.77 for digoxin, which were constructed using multiple logistic regression analysis. Variables (including baseline characteristics as listed in Table 1 and medication use as listed in Table 2) that were independently associated with the decision to prescribe statins, beta-blockers, aspirin, ACE inhibitors, calcium channel blockers, diuretics, ni-

Table 1. Baseline Characteristics of the 2,420 Study Participants

Characteristic	Total Population (n = 2,420)
Demographics	
Age (yrs)	64 ± 11
Male gender	1,748 (72%)
Cardiovascular history	
Angina pectoris	567 (23%)
Previous myocardial infarction	923 (38%)
History of congestive heart failure	214 (9%)
History of cerebrovascular disease	195 (8%)
Previous coronary revascularization	464 (19%)
Clinical risk factors	
Diabetes mellitus	436 (18%)
Hypercholesterolemia	581 (24%)
Hypertension	1,162 (48%)
Current smoking	837 (35%)
Renal failure	127 (5%)
Chronic pulmonary disease	288 (12%)
Ankle brachial index >0.70 and ≤0.90	557 (23%)
Ankle brachial index ≤0.70	1,863 (77%)
Electrocardiography	
Q waves	630 (26%)
ST-segment changes	382 (16%)
Left ventricular hypertrophy	113 (5%)
Left bundle branch block	98 (4%)
Right bundle branch block	56 (2%)
Atrial fibrillation	54 (2%)

Values are expressed as n (%) or mean ± SD.

Table 2. Number of Patients (%) Receiving Cardiac Medication

Medications	Total Population (n = 2,420)
Statin	457 (19%)
Beta-blockers	602 (25%)
Selective beta-blockers	468 (19%)
Non-selective beta-blockers	134 (6%)
Aspirin	542 (22%)
ACE inhibitors	626 (26%)
Calcium channel blockers	677 (28%)
Dihydropyridines	460 (19%)
Non-dihydropyridines	217 (9%)
Coumarin	597 (25%)
Nitrates	568 (23%)
Diuretics	365 (15%)
Digoxin	159 (7%)

Values are expressed as n (%).
ACE = angiotensin-converting enzyme.

trates, coumarins, and digoxin ($p < 0.25$) were included in the multivariate propensity score. In multivariate analysis, we adjusted for baseline clinical variables, irrespective of the significance level in univariate analysis. Propensity scores were added in separate multivariate models. Hazard ratios are given with 95% confidence intervals (CIs). For all tests, a p value <0.05 (two-sided) was considered significant. All analyses were performed using SPSS-11.0 statistical software (SPSS Inc., Chicago, Illinois).

RESULTS

Baseline characteristics of the 2,420 study participants are presented in Table 1. The mean age was 64 ± 11 years, and 1,748 patients (72%) were men. Severe PAD (ABI ≤0.70) was identified in 1,863 patients (77%). The mean ABI was 0.58 ± 18. An abnormal electrocardiogram was observed in 1,127 patients (47%). Table 2 shows cardiac medication in the study population. As demonstrated in Figure 1, the prescription of ACE inhibitors, statins, aspirin, and beta-blockers increased from 12%, 13%, 15%, and 17%, respectively, in the periods 1983 to 1989 to 30%, 32%, 27%, and 40%, respectively, in the periods 2000 to 2004 (all $p < 0.001$). Propensity analysis demonstrated that patients were more likely ($p < 0.001$) to be prescribed statins if they had hypercholesterolemia, beta-blockers if they had coronary artery disease or hypertension, aspirin if they had coronary artery disease or a history of cerebrovascular disease, and ACE inhibitors if they had a history of congestive heart failure.

During follow-up, death occurred in 1,067 patients (44%). The unadjusted and adjusted associations between clinical variables and long-term mortality are presented in Table 3. In a multivariate model that mutually adjusted for clinical risk factors and propensity scores, statins, beta-blockers, aspirin, and ACE inhibitors were independently associated with a reduced incidence of long-term mortality (hazard ratio [HR] 0.46, 95% CI 0.36 to 0.58; HR 0.68, 95% CI 0.58 to 0.80; HR 0.72, 95% CI 0.61 to 0.84); and HR 0.80, 95% CI 0.69 to 0.94, respectively (Table 4).

Calcium channel blockers, diuretics, nitrates, coumarins, and digoxin, however, were not significantly and independently associated with long-term mortality. In patients using beta-blockers, no difference was observed between selective and non-selective beta-blockers on the long-term outcome (selective beta-blockers: HR 1.31, 95% CI 0.87 to 1.72).

DISCUSSION

In this cohort study of consecutive patients referred to our center for the evaluation of PAD, we found that statins, beta-blockers, aspirins, and ACE inhibitors were signifi-

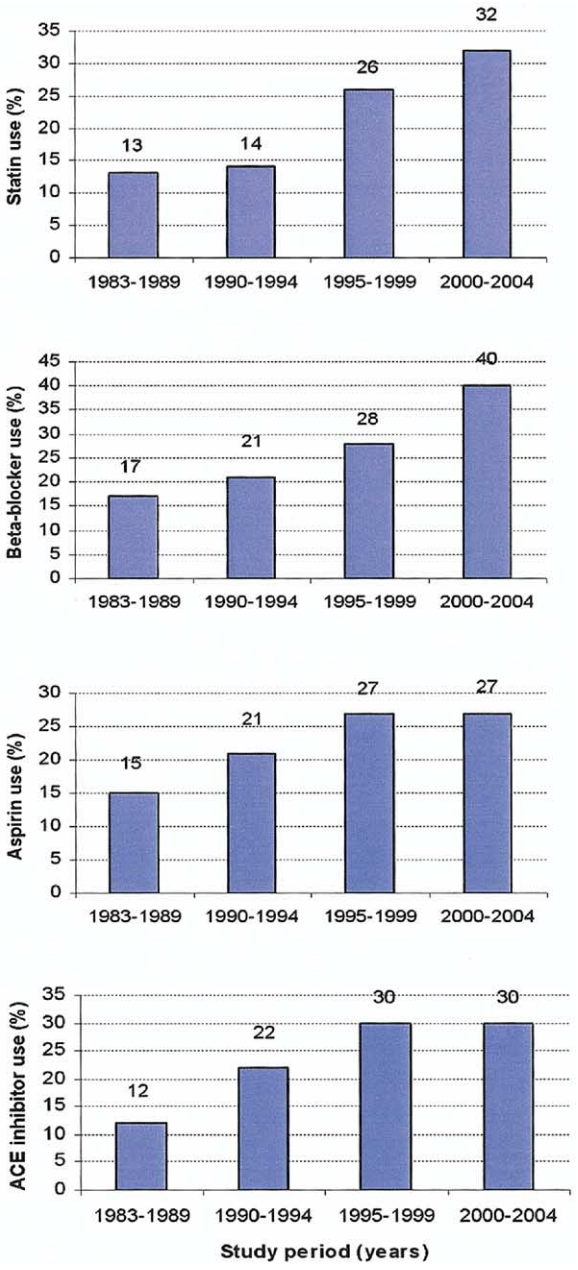

Figure 1. The prescription of statins, beta-blockers, aspirins, and angiotensin-converting enzyme (ACE) inhibitors in patients who were included in different periods of time.

Table 3. Univariate and Multivariate Associations of Clinical Variables and Overall Mortality

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR and 95% CI	p Value	HR and 95% CI	p Value
Age >70 yrs	1.75 (1.55–1.97)	<0.001	1.68 (1.48–1.91)	<0.001
Male gender	1.08 (0.94–1.24)	0.3	1.05 (0.91–1.22)	0.5
Coronary artery disease	1.59 (1.41–1.80)	<0.001	1.39 (1.19–1.62)	<0.001
History of heart failure	2.69 (2.26–3.19)	<0.001	1.73 (1.42–2.11)	<0.001
History of cerebrovascular accident	1.55 (1.26–1.90)	<0.001	1.28 (1.04–1.57)	0.02
Diabetes mellitus	1.42 (1.22–1.66)	<0.001	1.35 (1.15–1.60)	<0.001
Hypercholesterolemia	1.54 (1.29–1.84)	<0.001	1.77 (1.44–2.18)	<0.001
Hypertension	1.22 (1.08–1.38)	0.002	1.26 (1.10–1.45)	<0.001
Current smoking	1.25 (1.11–1.42)	<0.001	1.27 (1.12–1.44)	<0.001
Renal failure	3.81 (3.09–4.69)	<0.001	3.34 (2.68–4.16)	<0.001
Chronic pulmonary disease	1.52 (1.29–1.80)	<0.001	1.37 (1.15–1.65)	<0.001
Severe PAD (ABI ≤0.70)	1.40 (1.20–1.62)	<0.001	1.21 (1.05–1.41)	0.01
Abnormal electrocardiogram	1.71 (1.52–1.93)	<0.001	1.36 (1.17–1.59)	<0.001

ABI = ankle-brachial index; CI = confidence interval; PAD = peripheral arterial disease.

cantly associated with a reduction of all-cause mortality, independent of baseline clinical variables and independent of PAD severity.

Statins. 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor drugs (statins) have been shown to reduce cardiovascular morbidity and mortality in high-risk patients (18–22). The Medical Research Council and the British Heart Foundation (MRC/BHF) Heart Protection Study randomly allocated 20,536 patients adults with coronary disease, other occlusive arterial disease, or diabetes to receive either simvastatin or placebo and demonstrated in a subgroup analysis of 6,748 patients with PAD that statins were significantly associated with a reduction in the rate of major vascular events (22). The beneficial effect of statins may not only be the result of its lipid-lowering effect but may also be the result of the inhibition of the inflammatory processes of atherosclerosis (23). It has been shown that a reduction in the inflammatory component through the use of statins improved the clinical outcome in patients with coronary artery disease, regardless of the reduction in cholesterol levels (24,25). In patients with PAD, statin use has been demonstrated to favorably influence leg functioning, walking performance, ABI values, and symptoms of claudication (26–28). The association of statin use and superior leg functioning also was demonstrated in patients with an ABI of 0.90 to 1.49, which may reflect the favorable influence of statins on subclinical PAD (26). A recent study by Schillinger et al. (29) showed that statin therapy was associated with an improved survival of patients with severe PAD with elevated high-sensitivity C-reactive protein levels (>0.42 mg/dl). The observation that patients with low inflammatory activity had no survival benefit supports the view that statins may exert beneficial effect though anti-inflammatory properties.

Beta-blockers. Although beta-blockers were considered relatively contraindicated in patients with PAD, several studies showed that beta-blockers do not adversely affect walking capacity, symptoms of intermittent claudication, and peripheral skin microcirculation (14–16). Beta-blockers are effective antihypertensive agents and improve the prognosis of patients with ischemic heart disease and congestive heart failure and are thus indicated in a majority of patients with PAD. However, it seems that beta-blockers have been underused by vascular surgeons and primary care providers, perhaps because of concerns that beta-blockers will aggravate symptoms of intermittent claudication (30,31). Patients with PAD are at increased risk for cardiovascular morbidity and mortality, and recent studies have demonstrated the beneficial effect of beta-blockers in these patients. In a study cohort of 575 patients with symptomatic PAD and with a

Table 4. Univariate and Multivariate Association Between Cardiac Medication and Mortality

Model	Medication	HR and 95% CI for Overall Death, Univariate	p Value	HR and 95% CI for Overall Death, Multivariate*	p Value	HR and 95% CI for Overall Death, Multivariate†	p Value
1	Statin	0.65 (0.54–0.78)	<0.001	0.42 (0.34–0.53)	<0.001	0.46 (0.36–0.58)	<0.001
2	Beta-blocker	0.76 (0.65–0.88)	<0.001	0.64 (0.55–0.75)	<0.001	0.68 (0.58–0.80)	<0.001
3	Aspirin	0.87 (0.77–1.01)	0.08	0.78 (0.67–0.91)	0.002	0.72 (0.61–0.84)	<0.001
4	ACE inhibitors	1.13 (0.98–1.30)	0.08	0.80 (0.69–0.93)	0.004	0.80 (0.69–0.94)	0.005
5	Diuretics	1.22 (1.03–1.43)	0.02	0.82 (0.68–0.98)	0.03	0.85 (0.71–1.02)	0.09
6	Ca-antagonists	1.14 (1.01–1.30)	0.04	1.04 (0.91–1.19)	0.6	1.03 (0.90–1.18)	0.7
7	Nitrates	1.36 (1.19–1.56)	<0.001	1.00 (0.86–1.16)	1.0	1.00 (1.86–1.16)	1.0
8	Coumarins	1.15 (1.01–1.32)	0.03	1.13 (0.98–1.29)	0.08	1.13 (0.98–1.29)	0.08
9	Digoxin	1.91 (1.57–2.33)	<0.001	1.2 (1.01–1.57)	0.04	1.21 (1.95–1.53)	0.1

*Medication was adjusted for all baseline clinical variables. †Medication was adjusted for all baseline clinical variables and propensity scores.
ACE = angiotensin-converting enzyme, Ca-antagonists = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

previous myocardial infarction, Aronow and Ahn (32) demonstrated that beta-blocker therapy was associated with a 53% significant reduction in new coronary events, independent of other confounding variables (32). This was confirmed in a more recently published study demonstrating a three-fold reduction in cumulative cardiac mortality in 78 patients after infarction with intermittent claudication who were treated with beta-blocker therapy compared with patients not treated with beta-blocker therapy (33). It has been shown that hemodynamic forces (blood pressure and heart rate) are associated with the development of disruption of the vulnerable plaque, which consists of an atheromatous plaque core covered by a thin fibrous cap with ongoing inflammation (34). Beta-blockers may prevent plaque disruption by reducing heart rate and blood pressure. In addition, it can be hypothesized that anti-inflammatory properties of beta-blockers may limit the phased progression of cardiovascular disease (35).

Aspirin. Antiplatelet drugs are now established agents for preventing cardiovascular and cerebrovascular ischemic events. The meta-analysis of the Antithrombotic Trialists' Collaboration showed a proportional reduction of 23% in serious vascular events among 9,214 patients with PAD using antiplatelet therapy (primarily aspirin), compared with those using no antiplatelet therapy (5.8% vs. 7.1%, $p < 0.004$) (36). Limited information is available regarding the optimal antiplatelet treatment choice in patients with PAD. Potential adverse effects, including diarrhea, neutropenia, and thrombotic thrombocytopenic purpura, may limit the use of ticlopidine. On the basis of current evidence, aspirin or clopidogrel seem to be the first-line oral antiplatelet drugs of choice.

Use of ACE inhibitors. The use of ACE inhibitors have been shown to inhibit the atherosclerotic process and to improve peripheral blood pressure and blood flow in patients with PAD (37). The Heart Outcomes Prevention Evaluation (HOPE) study investigators showed that the use of ramipril significantly reduced the rate of mortality, myocardial infarction, and stroke in 9,297 high-risk patients without a low ejection fraction or heart failure (38). A recent randomized placebo-controlled study demonstrated the beneficial effect of ramipril in patients with clinical or subclinical PAD for preventing major cardiovascular events (39). Activation of the renin-angiotensin system seems to be associated with an increased risk of cardiovascular events. Growing evidence suggest that ACE inhibitors directly inhibit the atherosclerotic process and improve vascular endothelial function (40,41). In addition, the benefit of ACE inhibitors may be independent of the antihypertensive properties of these agents (42).

Study limitations. The results of our study are in accordance with previously published studies demonstrating the effect of statins, beta-blockers, aspirin, and ACE inhibitors for reducing complications in patients with PAD. Several limitations of our study should be addressed. The major limitation of this study is that the use of cardiac medication was not assigned randomly to patients with PAD. However, properly conducted observational studies might not produce misleading or biased results (43). Moreover, we used propensity analysis and in multivariate analysis we adjusted for known possible confounding factors. The strength of using propensity score methods lies in its ability to adjust for selection bias because subjects in an observational study have not been randomized to exposure groups. A propensity score generally is defined as the conditional probability of assignment to a particular treatment given a vector of observed covariates (44). To assess the effect of a treatment in a situation in which randomization is difficult or impossible, propensity scores are a useful method for matching members of different groups. Comparisons of different groups reveal reliable information on the impact of the treatment of interest with a small residual bias (17).

Conclusions. On the basis of this observational longitudinal study, statins, beta-blockers, aspirin, and ACE inhibitors are associated with a reduction in long-term mortality risk in patients with PAD that is independent of clinical risk factors and adjusted for propensity scores. The use of cardiac medications as therapeutic and preventive agents in patients with PAD seems to be promising in reducing long-term mortality and could be incorporated among other management strategies, including walking exercise and risk factor modification. Future studies should be conducted to determine which patients with PAD would mostly benefit from statins, beta-blockers, aspirin, and ACE inhibitor therapy.

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REFERENCES

1. Mohler ER 3rd. Peripheral arterial disease: identification and implications. Arch Intern Med 2003;163:2306–14.
2. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381–6.
3. Valentine RJ, Grayburn PA, Eichhorn EJ, Myers SI, Clagett GP. Coronary artery disease is highly prevalent among patients with premature peripheral vascular disease. J Vasc Surg 1994;19:668–74.
4. Hertzer NR, Beven EG, Young JR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223–33.
5. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW, for the Framingham study. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. Arch Intern Med 2003;163:1939–42.
6. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. Circulation 1985;71:510–5.
7. McDermott MM, Kerwin DR, Liu K, et al. Prevalence and significance of unrecognized lower extremity peripheral arterial disease in general medicine practice. J Gen Intern Med 2001;16:384–90.
8. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004;110:738–43.

9. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317–24.
10. Meijer WT, Grobbee DE, Hunink MG, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. Arch Intern Med 2000;160:2934–8.
11. Belch JJ, Topol EJ, Agnelli G, et al. Prevention of Atherothrombotic Disease Network. Critical issues in peripheral arterial disease detection and management: a call to action. Arch Intern Med 2003;163:884–92.
12. Creager MA, Jones DW, Easton JD, et al. American Heart Association. Atherosclerotic Vascular Disease Conference: Writing Group V: medical decision making and therapy. Circulation 2004;109:2634–42.
13. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. N Engl J Med 2001;344:1608–21.
14. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease. A meta-analysis of randomized controlled trials. Arch Intern Med 1991;151:1769–76.
15. Ubbink DT, Verhaar EE, Lie HK, Legemate DA. Effect of beta-blockers on peripheral skin microcirculation in hypertension and peripheral vascular disease. J Vasc Surg 2003;38:535–40.
16. Heintzen MP, Strauer BE. Peripheral vascular effects of beta-blockers. Eur Heart J 1994;15 Suppl C:2–7.
17. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757–63.
18. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003;107:1848–51.
19. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.
20. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. N Engl J Med 1996;335:1001–9.
21. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
22. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
23. Moreno PR, Fuster V. The year in atherothrombosis. J Am Coll Cardiol 2004;44:2099–110.
24. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.
25. Ridker PM, Cannon CP, Morrow D, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20–8.
26. McDermott MM, Guralnik JM, Greenland P, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003;107:757–61.
27. Mondillo S, Ballo P, Barbati R, et al. Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic patients with peripheral vascular disease. Am J Med 2003;114:359–64.
28. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation 2003;108:1481–6.
29. Schillinger M, Exner M, Mlekusch W, et al. Statin therapy improves cardiovascular outcome of patients with peripheral artery disease. Eur Heart J 2004;25:742–8.
30. Torella F, Khattak I, Edwards PR, de Cossart L. Cross-sectional survey of beta-blockers use in primary and secondary care for patients with arterial disease. Int J Clin Pract 2004;58:1159–61.
31. Ness J, Aronow WS, Newkirk E, McDanel D. Prevalence of symptomatic peripheral arterial disease, modifiable risk factors, and appropriate use of drugs in the treatment of peripheral arterial disease in older persons seen in a university general medicine clinic. J Gerontol A Biol Sci Med Sci 2005;60:255–7.
32. Aronow WS, Ahn C. Effect of beta-blockers on incidence of new coronary events in older persons with prior myocardial infarction and symptomatic peripheral arterial disease. Am J Cardiol 2001;87:1284–6.
33. Narins CR, Zareba W, Moss AJ, et al. Relationship between intermittent claudication, inflammation, thrombosis, and recurrent cardiac events among survivors of myocardial infarction. Arch Intern Med 2004;164:440–6.
34. Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 2001;104:1477–82.
35. Yeager MP, Fillinger MP, Hettleman BD, Hartman GS. Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. J Cardiothorac Vasc Anesth 2005;19:237–41.
36. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. BMJ 2002;324:71–86.
37. Hirsch AT, Duprez D. The potential role of angiotensin-converting enzyme inhibition in peripheral arterial disease. Vasc Med 2003;8:273–8.
38. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145–53.
39. Ostergren J, Sleight P, Dagenais G, et al. HOPE Study Investigators. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. Eur Heart J 2004;25:17–24.
40. Lonn EM, Yusuf S, Jha P, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. Circulation 1994;90:2056–69.
41. Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al. Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. Circulation 2000;101:1372–8.
42. Bosch J, Yusuf S, Pogue J, et al., for the HOPE Investigators. Heart outcomes prevention evaluation. Use of ramipril in preventing stroke: double blind randomised trial. BMJ 2002;324:699–702.
43. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–92.
44. Rosenbaum PR, Rubin DB. The bias due to incomplete matching. Biometrics 1985;41:103–16.