

Beta-blocker Use and Clinical Outcomes after Primary Vascular Surgery: A Nationwide Propensity Score-Matched Study

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WHAT THIS PAPER ADDS

The use of beta-blockers has been considered controversial in patients with peripheral arterial disease (PAD). However, our data provide evidence that beta-blocker treatment is safe and effective in unselected symptomatic PAD patients in routine clinical settings. To our knowledge, the influence of beta-blocker use on the rate of major amputation has not been described previously.

We hope that our results will contribute to the continuous improvement in the use of secondary medical prevention and thereby reduce the burden of cardiovascular events for this high-risk population.

Objective: To explore the associations between beta-blocker use and clinical outcomes (death, hospitalisation with myocardial infarction (MI) or stroke, major amputation and recurrent vascular surgery) after primary vascular reconstruction.

Methods: Patients who had primary vascular surgical or endovascular reconstruction due to symptomatic peripheral arterial disease, in Denmark between 1996 and 2007 were included. We obtained data on filled prescriptions, clinical outcomes and confounding factors from population-based healthcare registries. Beta-blocker users were matched to non-users by propensity score, and Cox-regression was performed. All medications were included as time-dependent variables.

Results: We studied 16,945 matched patients (7828 beta-blocker users and 9117 non-users) with a median follow-up period of 582 days (range, 30–4379 days). The cumulative risks were as follows: all-cause mortality, 17.9%; MI, 5.3%; stroke, 5.6%; major amputation, 9.1%; and recurrent vascular surgery, 23.1%. When comparing beta-blocker users with non-users: adjusted hazard ratio: MI, 1.52 (95% CI, 1.31–1.78); stroke, 1.21 (95% CI, 1.03–1.43); and major amputation, 0.80 (95% CI, 0.70–0.93).

Conclusion: Beta-blocker use after primary vascular surgery was associated with a lower risk of major amputation but an increased risk of hospitalisation with MI and stroke. No associations were found between beta-blocker use and all-cause mortality or the risk of recurrent vascular surgery. However, our results are not sufficient to alter the indication for beta-blocker use among symptomatic peripheral arterial disease patients.

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INTRODUCTION

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis and is associated with a significant cumulative risk of cardiovascular events, including death, myocardial infarction (MI), stroke and major amputation.^{1–5} The prevalence of hypertension among PAD patients is higher than in the general population, and blood

pressure control is considered critical for secondary medical prevention in patients with PAD; however, the use of secondary medical prevention is generally insufficient for PAD patients^{2,6–10} when compared with clinical guidelines and recommendations.^{11–15}

Beta-adrenoceptor blocking agents (beta-blockers) are traditionally used to treat hypertension and are the primary treatment choice after MI or for chronic angina.^{16,17} However, beta-blocker treatment has been considered controversial in PAD patients because it is suspected that beta-blockers cause α -receptor-mediated peripheral vasoconstriction and reduced peripheral circulation, leading to intermittent claudication symptoms. Two meta-analyses disproved this hypothesis and concluded that beta-blockers are safe in PAD patients and do not affect

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walking capacity or cause symptoms of intermittent claudication.^{18–20} However, there are few data on the safety and efficacy of beta-blocker treatment among unselected symptomatic PAD patients in routine clinical settings.

The primary objective of this study was to examine clinical outcomes following beta-blocker treatment after primary vascular reconstruction in unselected symptomatic PAD patients in a population-based, long-term follow-up study.

PATIENTS AND METHODS

This study was based on data from nationwide Danish population-based healthcare and administrative databases. The linking of individual records across the registries is possible using civil registration numbers, which are unique 10-digit personal identification numbers given to all citizens (the Danish population consists of approximately 5.5 million people) and used in all Danish registries.²¹ The Danish National Health Service provides tax-supported healthcare with free access to hospital care, surgery, general practitioners and reimbursement for many prescribed medications.

Study population

We included all patients who had primary vascular surgical or endovascular reconstruction due to atherosclerotic disease between 1997 and 2007. The indications for surgery included moderate intermittent claudication, ischaemic rest pain, ulceration and gangrene. The patients were identified using the Danish Vascular Registry, which is a national clinical registry that has been used for prospective data collection since 1996 with mandatory reporting for all Danish vascular surgery departments ($n = 9$). The primary objectives of the registry are surveillance and quality improvement. The registry contains 65 variables, including indication for surgery, timing of surgery (acute/elective), patient characteristics, smoking habits, type of intervention, vascular patency at discharge and discharge destination.²² Patients were only included for their first vascular procedure during the study period. Patients who died within 30 days of discharge and patients less than 40 years old were excluded (Fig. 1).

We validated the Danish Vascular Registry by comparing it with a national random sample of 200 medical records and found discrepancies of less than 1% for operation-related data and vascular patency at discharge. Additionally, we found discrepancies of less than 3% for the type of surgery.

Prescription information

We identified the prescriptions filled by the included patients throughout the follow-up period (1997–2007); prescriptions were for antihypertensive drugs (beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium antagonists and diuretics), antiplatelet drugs (low-dose aspirin, dipyridamole and clopidogrel) and lipid-lowering drugs. The data were obtained

from the Medical Register of the Danish Medicines Agency and identified on the basis of Anatomical Therapeutic Chemical (ATC) classification system. In Denmark, secondary medical prevention is only available by prescription with the exception of low-dose aspirin; however, regular aspirin is available by prescription and reimbursed for pensioners and patients with chronic diseases.

Clinical outcomes

Five competing end points were assessed: major amputation, hospitalisation with MI or stroke, recurrent vascular surgery and all-cause mortality. Data from hospitalisations (MI, stroke and/or major amputation) were obtained from the Danish National Patient Register, which contains information on all discharges from Danish hospitals since 1977, including the date and the diagnosis at discharge encoded according to the International Classification of Diseases (8th revision until 1993 and 10th revision thereafter).²³ Data on recurrent vascular surgery were obtained from the Danish Vascular Registry as described earlier. Information on mortality during follow-up was obtained from the Danish Civil Registration System, which has maintained birth and death records for the entire population since 1968.²¹

Covariates

A complete hospitalisation history until the primary operation date was compiled for each patient based on data from the Danish National Patient Register. Additionally, a comorbidity index score based on the methods of Charlson et al.²⁴ was computed for each patient. Three levels of comorbidity were defined: no comorbidity (score 0), low comorbidity (score 1–2) and high comorbidity (score > 2). The comorbidity index has previously been adapted and validated for use in the analysis of hospital discharge registry data.²⁵ Information on socio-economic status was obtained from the Integrated Database for Labour Market Research, which is updated yearly. We classified patients according to marital status (single, married, widowed or divorced), employment status (employed, pensioner or other), gross income in quartiles and educational level (primary and lower secondary school, upper secondary school, vocational education and higher education). The Danish Vascular Register provided information on the following clinical and operative variables: acute or elective surgery, region of surgery (central [abdominal aortic segments and iliac vessels], groin or peripheral arteries), vascular patency at discharge, discharge destination and smoking habits at the time of surgery.

Statistics

Patient characteristics were compared using a two-sample test of proportions. A p value < .05 was considered statistically significant. Because beta-blocker use was not randomly assigned in the study population, we used the calliper method of propensity score matching with a .2 standard deviation of the logit of the estimated propensity

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