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.

Article history: Received 5 September 2012, Accepted 1 April 2013, Available online 6 May 2013

Keywords: Vascular surgery, Epidemiology, Beta blocker, Nationwide longtime follow-up

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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1078-5884/$ — see front matter

http://dx.doi.org/10.1016/j.ejvs.2013.04.006

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 Therapeutical 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

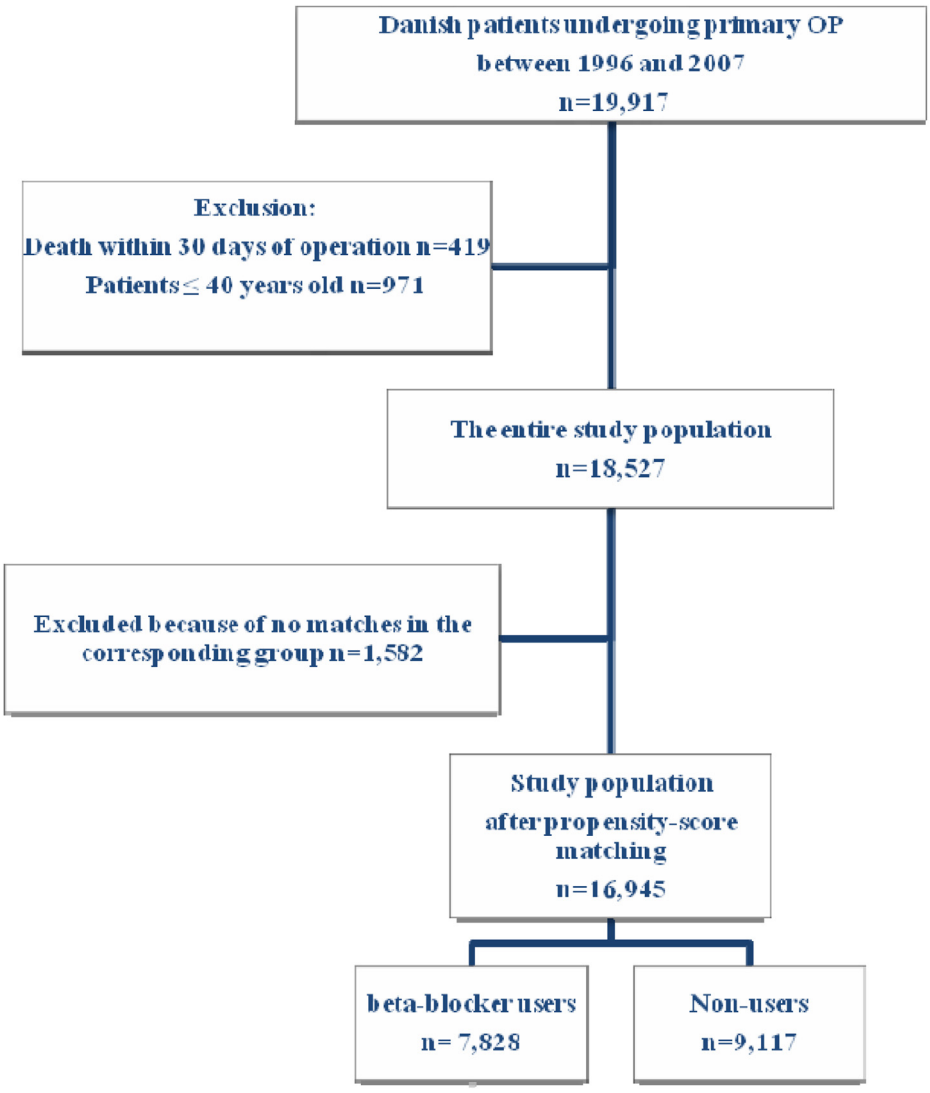

Figure 1. Flow diagram of the study population.

score to overcome or at least reduce the risk of confounding bias.[26,27]

Beta-blocker users were defined as those having filled at least one prescription 180 days before or after primary vascular reconstruction. Up to five non-users were matched to each beta-blocker user. Beta-blocker users not matched to a non-user were excluded (Fig. 1). Users were matched based on the following covariates: gender, age group, co-morbidity index, hospital history, operation type, marital status, employment, education level, gross income in quartiles, tobacco use, acute operation, patency at discharge and discharge destination. An absolute standardised difference of $<$10% and a variance ratio between 0.8 and 1.25 were considered to support the assumption of balance between the groups[28,29] (Figs. 2 and 3).

Cox regression analysis and the estimation of adjusted hazard ratios (adj. HRs) were performed after matching, which enabled us to adjust for potential residual confounders using non-users as references. The Cox regression analyses were conducted using a multivariant model based on competing risk analysis of the end points (all-cause mortality, MI, stroke, major amputation and/or recurrent vascular surgery) with an adjustment for baseline covariates and medications used during the follow-up period (angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, calcium antagonists, diuretics, anti-platelet drugs and lipid-lowering drugs).

We evaluated the robustness of our results by repeating the analyses after stratifying for previous MIs because the full balance between beta-blocker users and non-users was not achieved despite propensity score matching. Furthermore, we repeated the analyses using the entire study population, including the propensity score for beta-blocker use as a covariate after transforming it into cubic splines, which describe a continuous smooth function and provide a general and robust approach for adapting linear methods to the modelling of non-linear relationships.

All data analyses were performed using STATA version 11.2 (Statacorp) and SAS 9.2 (Rx64 2.13.0).

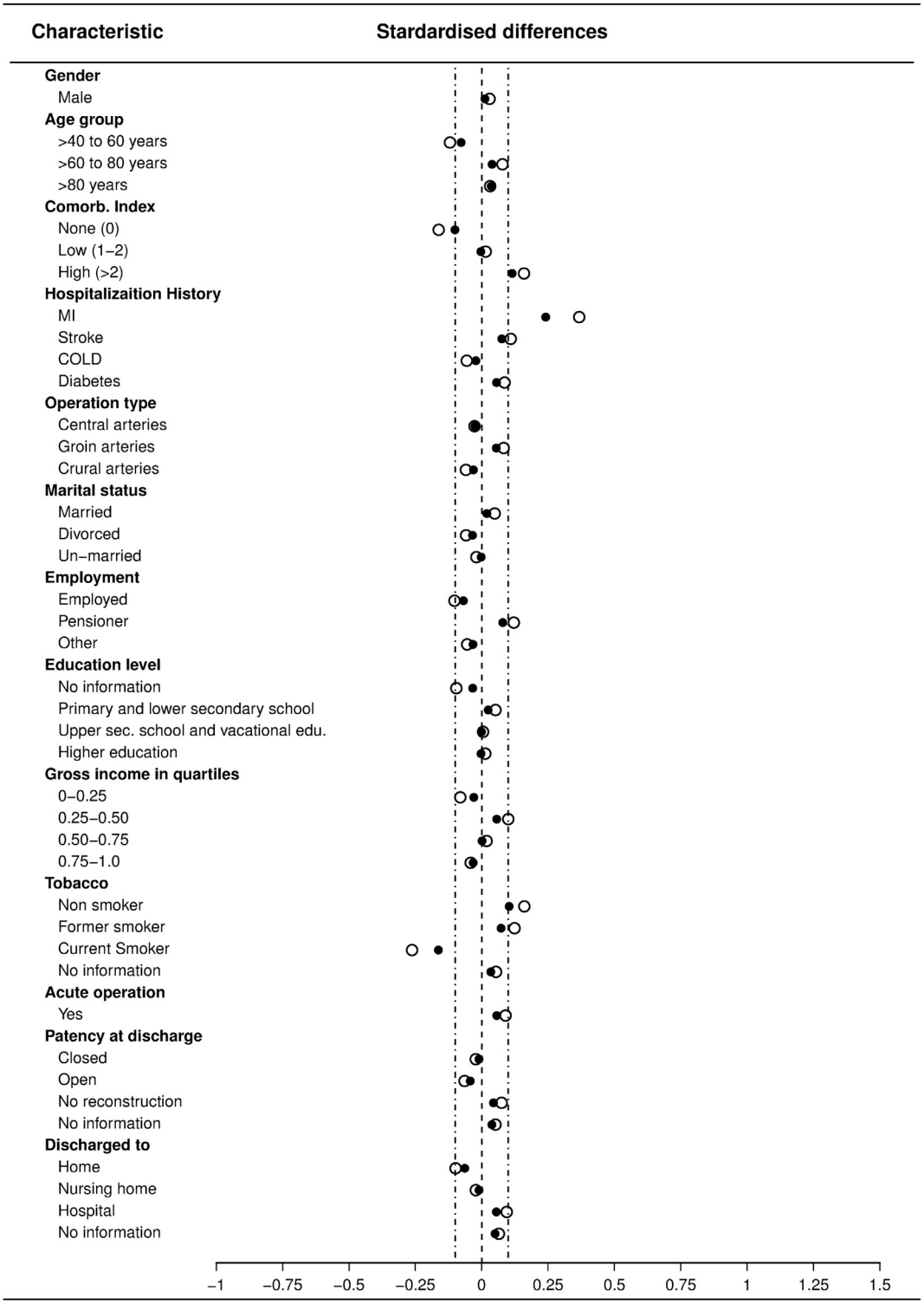

Figure 2. The standardised differences in variables included in the propensity score for the entire study population (○) and for the propensity score-matched patients (●).

RESULTS

Patient characteristics

Table 1 displays the characteristics of the study population according to beta-blocker use before and after propensity score matching. Beta-blocker users had a significantly higher risk of being admitted with a MI (16.4% vs. 5.4%) or stroke (12.2% vs. 9.2%) prior to primary vascular reconstruction. In contrast, we found no major differences in gender, operation type (central (abdominal aortic segments and iliac vessels), groin or peripheral arteries), indication for operation (acute, intermittent claudication, rest pain or tissue loss) or socio-economic variables between the two groups. The proportions of percutaneous transluminal angioplasty in the iliac system increased

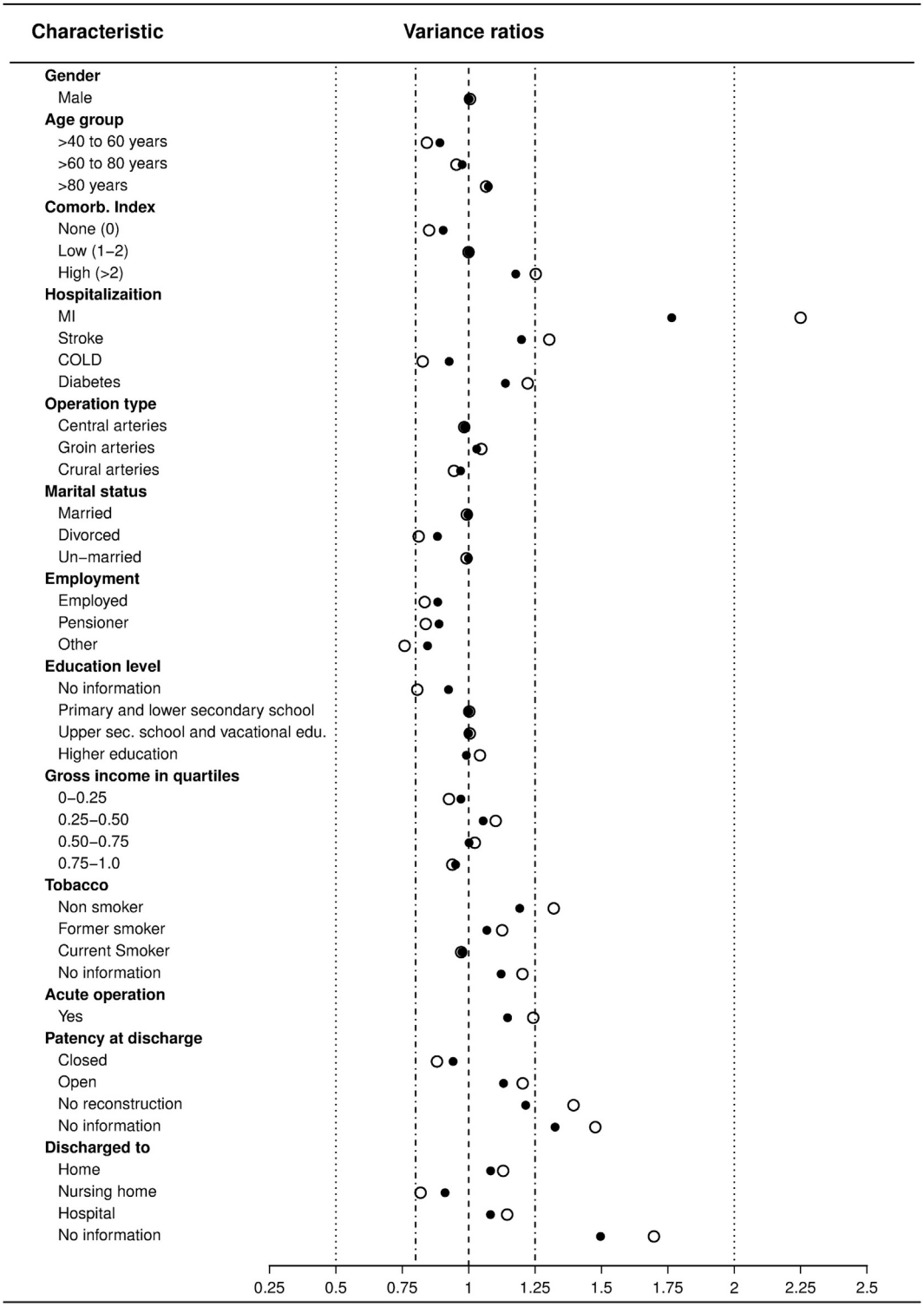

Figure 3. The variance ratios of variables, including the propensity score for the entire study population (○) and for the propensity score-matched patients (●).

during the study period from 18.3% of the reconstructions in the early period (1996—2000) to 30.9% in the late period (2001—7). A significantly lower proportion of current smokers were beta-blocker users (56.3% vs. 44.8%). After propensity score matching, an acceptable balance was achieved for all examined covariates with the exception of MI (Figs. 2 and 3).

Beta-blocker use and clinical outcomes

Patients were followed for a median of 582 days (range, 30—4379 days). Table 2 displays the absolute risk of the competing outcomes and the corresponding adjusted HRs with 95% CI; for the matched population, we used the non-users as a reference group.

Table 1. Descriptive characteristics.

	Before propensity score matching (n = 18,527)			After propensity score matching (n = 16,945)		
	+Beta-blockers (n = 8357)	−Beta-blockers (n = 1,0170)	p-Value	+Beta-blockers (n = 7828)	−Beta-blockers (n = 9117)	p-Value
Male	53.5	53.5%	.05	52.9%	54.3%	.18
Age group						
40–60 years	20.7	23.8	.02	20.1	22.1	.14
60–80 years	65.4	61.7	<.01	65.9	63.5	.01
> 80 years	13.9	14.6	.63	14.1	14.4	.93
Comorbidity index						
None (0)	27.1	32.3	<.01	26.9	30.8	<.01
Low (1–2)	51.1	50.4	.48	51.4	51.1	.77
High (>2)	21.8	17.4	<.01	21.7	18.1	.01
Medical history						
Myocardial infarction	16.4	5.4	<.01	15.1	6.0	<.01
Stroke	12.2	9.2	.04	12.3	9.8	.09
COPD	6.5	8.3	.20	6.2	7.5	.40
Diabetes	14.6	12.0	<.01	14.6	12.0	<.01
Socioeconomic status						
Marital status						
Married	55.0	51.0	<.01	55.1	52.3	.07
Divorced	14.5	16.2	.20	14.2	15.5	.22
Unmarried	5.9	7.9	.18	5.8	7.3	.04
Widowed	24.7	24.9	.86	24.9	24.9	1.00
Employment						
Employed	16.6	19.5	.033	16.2	18.4	.12
Pensioner	79.9	76.3	<.01	80.4	77.7	<.01
Other	3.5	4.2	.63	3.4	3.9	.74
Education level						
No information	11.5	15.5	<.01	11.2	13.5	.12
Primary and lower sec. school	49.6	47.0	.14	49.8	48.3	.17
Upper secondary school and vocational education	30.8	30.0	.53	30.7	30.4	.71
Higher education	8.2	7.6	.65	8.3	8.0	.75
Clinical data						
Operation type						
Abdominal aortic segments and iliac arteries	35.2	35.7	.66	35.3	36.0	.53
Groin arteries	36.4	34.4	.10	36.7	35.6	.36
Peripheral arteries	28.5	29.9	.26	28.1	28.4	.80
Indication						
Acute	10.9	11.0	.95	11.0	11.4	.79
Intermittent claudication	37.4	39.0	.17	37.5	39.1	.19
Rest pain	16.2	16.9	.63	16.2	16.6	.78
Tissue loss	24.1	25.0	.49	24.0	24.5	.65
Other	11.4	8.2	.02	11.3	8.3	.04
Tobacco use						
Non-smoker	18.5	13.4	<.01	18.7	14.7	<.01
Former smoker	29.7	24.3	<.01	30.5	26.4	<.01
Current smoker	44.8	56.3	<.01	43.7	52.4	<.01

Table 1-*continued*

	Before propensity score matching (n = 18,527)			After propensity score matching (n = 16,945)		
	+Beta-blockers (n = 8357)	−Beta-blockers (n = 1,0170)	p-Value	+Beta-blockers (n = 7828)	−Beta-blockers (n = 9117)	p-Value
No information	7.0	6.0	.48	7.1	6.5	.65
Patency at discharge						
Closed	2.6	3.2	.96	2.6	3.1	.76
Open	91.1	91.8	.13	91.1	91.4	.77
No reconstruction	4.6	3.6	.48	4.6	3.9	.68
No information	1.7	1.4	.88	1.7	1.6	.93
Discharged to						
Home	80.5	79.2	.05	80.3	79.2	.13
Nursing home	17.2	18.2	.50	17.4	18.1	.62
Hospital	2.3	2.7	.79	2.3	2.6	.83
No information	0.1	0.1	.00	0.1	0.1	1.00

COPD = chronic obstructive pulmonary disease. Data are presented as percentages.

The cumulative, all-cause mortality risk was 17.9%, and no significant association was found between beta-blocker use and all-cause mortality (adj. HR, 0.92; 95% CI, 0.84—1.02). In contrast, we found significant associations between beta-blocker use and the risk of MI or stroke. The adj. HRs were 1.52 (95% CI, 1.31—1.78) and 1.21 (95% CI, 1.03—1.43) for MI and stroke, respectively. The cumulative risk of major amputation was 9.1%, and beta-blocker use was associated with a significant risk reduction in this outcome (adj. HR 0.80; 95% CI, 0.70—0.93). Moreover, 23.1% of the population had recurrent vascular reconstruction, but no significant association with beta-blocker use was found (adj. HR, 0.99; 95% CI, 0.91—1.07).

After stratification according to prior MI and stroke, we repeated the analyses in the propensity-matched population (Table 3). After stratification by MI, the overall cumulative risk of major amputation was unchanged; however, after the adjustment, we found a stronger association between beta blocker use in patients without a prior MI and decreased rates of major amputation (adj. HR, 0.77; 95% CI, 0.66—0.90). No difference was seen among beta-blocker users with a prior MI (adj. HR, 1.05; 95% CI, 0.72—1.53).

The cumulative risk of MI during the follow-up period was twice as high among patients with a prior MI as in patients without a prior MI (4.6% vs. 11.3%). However, after the adjustment, we found an increased risk of MI among beta-blocker users without a prior MI (adj. HR, 1.58; 95% CI, 1.32—1.89). No differences were seen among beta-blocker users with a previous MI (adj. HR, 1.10; 95% CI, 0.80—1.52). Additionally, beta-blocker users with a previous MI were at increased risk of having a stroke (adj. HR, 1.63; 95% CI, 1.09—2.44), while beta-blocker users without a previous MI had an unchanged risk. Beta-blocker users with a prior stroke had a decreased cumulative risk of having a recurrent stroke compared with beta-blocker users without a prior stroke but an increased adj. HR compared with non-users (Table 3).

The use of other antihypertensive agents (angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, calcium antagonists, diuretics, antiplatelet drugs and lipid-lowering drugs) during the follow-up period has previously been described.[30]

DISCUSSION

In this nationwide follow-up study of all patients undergoing primary vascular reconstruction in Denmark over a 10-year period, we found that beta-blocker use was

Table 2. Adjusted hazard ratios with 95% CIs for competing adverse clinical outcomes according to beta-blocker use in the entire population (n = 18,527) and propensity score-matched population (n = 16,945). Patients not using beta-blockers serve as the reference group.

	Entire study population		Propensity score-matched population	
	Events (%)	Adjusted HR[a] (95% CI)	Events (%)	Adjusted HR[a] (95% CI)
All-cause mortality	18.2	0.95 [0.86;1.05]	17.9	0.92 [0.84;1.02]
MI	5.3	1.38 [1.18;1.60]	5.3	1.52 [1.31;1.78]
Stroke	5.5	1.16 [0.98;1.37]	5.6	1.21 [1.03;1.43]
Major amputation	9.1	0.83 [0.72;0.95]	9.2	0.80 [0.70;0.93]
Recurrent vascular surgery	23.3	1.00 [0.86;1.05]	23.1	0.99 [0.91;1.07]

[a] Adjusted for age, Charlson's comorbidity index, socioeconomic status (gross income, education level, marital status and employment), smoking, acute/non-acute surgery, operation type, indication for operation discharge destination, patency at discharge, and drug use during follow-up (angiotensin-converting enzyme/angiotensin II receptor antagonists, calcium antagonists, diuretics, antiplatelet drugs and lipid-lowering drugs).

Table 3. Adjusted hazard ratios with 95% CIs for competing adverse clinical outcomes according to beta-blocker use in the propensity score-matched population ($n = 16,945$) stratified to prior myocardial infarction (MI) or stroke.

	All-cause mortality	MI	Stroke	Major amputation	Recurrent vascular surgery
−MI[a,b] (%) ($n = 12,518$)	17.5	4.6	5.3	9.3	23.5
Adj. HR (95% CI)	0.92 [0.82;1.02]	1.58 [1.32;1.89]	1.15 [0.95;1.38]	0.77 [0.66;0.90]	1.00 [0.91;1.10]
+MI[a,b] (%) ($n = 1727$)	21.1	11.3	7.1	8.9	20.2
Adj. HR (95% CI)	0.79 [0.75;1.24]	1.10 [0.80;1.52]	1.63 [1.09;2.44]	1.05 [0.72;1.53]	1.02 [0.80;1.29]
−Stroke[a,b] (%)	17.6	5.1	5.1	8.8	26.2
($n = 15,087$)	0.93 [0.84;1.04]	1.59 [1.35;1.89]	1.25 [1.04;1.50]	0.80 [0.68;0.93]	1.02 [0.94;1.12]
Adj. HR (95% CI)					
+Stroke[a,b] (%)	19.9	6.5	8.6	12.3	22.8
($n = 1858$)	0.89 [0.67;1.18]	1.13 [0.74;1.73]	1.00 [0.68;1.49]	0.90 [0.63;1.28]	0.77 [0.60;0.99]
Adj. HR (95% CI)					

[a] Adjusted for age, Charlson's comorbidity index, socioeconomic status (gross income, education level, marital status and employment), smoking, acute/non-acute surgery, operation type, indication for operation discharge destination, patency at discharge, and drug use during follow-up (angiotensin-converting enzyme/angiotensin II receptor antagonists, calcium antagonists, diuretics, antiplatelet drugs and lipid-lowering drugs).

[b] Patients not using beta-blockers serve as the reference group.

significantly associated with a 20% lower risk of major amputation compared with the risk in non-users. European Society of Cardiology guidelines for 2011 state that beta-blockers are not contraindicated in PAD patients[11] based on previous reports concluding beta-blockers are safe in PAD patients despite their suspected negative effects on walking capacity and impairment of intermittent claudication[18–20] Our findings regarding the reduced risk of future major amputation support these reports, although, to our knowledge, the influence of beta-blocker use on the amputation rate has not been previously described.

Our finding that beta-blockers are associated with an increased risk of MI and/or stroke during the follow-up period is not in accordance with findings of previous studies, including those on symptomatic PAD patients with prior MI, that found beta-blocker use to be associated with a lower risk of MI.[31,32] These conflicting data might reflect residual confounding effects despite our attempt to minimise bias and confounding effects through statistical adjustment and study design. However, it should be noted that a recent systematic review reported that high-dose beta-blockers increased systolic blood pressure variability, a powerful risk factor for stroke.[33]

Randomised clinical trials have found that beta-blocker use following MI in symptomatic PAD patients is associated with a significant reduction in early and late mortality.[34,35] However, we were unable to confirm this finding in our study, which is likely an indicator of residual or unaccounted confounding variables.

Beta-blockers are effective antihypertensive agents and are prescribed for their cardiovascular effects, including the prevention of the disruption of vulnerable atherosclerotic plaques by reducing heart rate and blood pressure;[36] however, adverse effects and possible consequences of beta-blocker use in PAD patients have been described, including the undesirable change in cholesterol metabolism[37–41] due to the decrease in high-density lipoprotein concentrations and the increase in triglyceride concentrations. The long-term impacts of these effects are unknown but could theoretically increase the progression of PAD symptoms because of arterial occlusion impairment. Another disadvantage of beta-blockers is their lack of influence on arterial structure or function in contrast to angiotensin II antagonists.[42]

Strengths and limitations

The major strengths of our study include the population-based design; the availability of detailed, prospectively collected, individual-level data; and complete follow-up. To minimise the risk of confounding bias, we used propensity score matching and a multivariable model based on adjusted competing risk analysis. This two-step procedure makes the model-based inferences less model- dependent and more accurate.[27]

However, selection bias may be present because beta-blockers were not the drug of choice for hypertension in symptomatic PAD patients for the majority of the studied period. During the entire study period, an average of 45% of the patients in our study population were taking beta-blockers. Furthermore, confounding could arise from the lack of information on the contraindications for beta-blocker use in individual patients, including chronic obstructive pulmonary disease, atrioventricular block, severe congestive heart failure, hypotension, bradycardia and gangrene.[18,43] These contraindications occur frequently and may be associated with adverse clinical outcomes. For example, a previous study described adverse effects that caused the discontinuation of initiated beta-blocker use in 12% of patients with prior MI and symptomatic PAD.[31]

Additionally, we used prescriptions filled by the patients as a proxy for actual drug use, but we had no information regarding patient compliance. However, mandatory self-payment indicates that a purchased prescription is likely to reflect actual medication use.

Finally, our estimates depend on the accuracy of the data sources. The accuracy of the Danish Vascular Registry was previously described as good;[22] our study further confirmed

this classification (see Patients and methods). Furthermore, the Danish Patients Registry has high validity for many diagnoses including MI, cancer and diabetes.[44]

CONCLUSION

In a study population of patients who had primary vascular reconstruction surgery between 1996 and 2007, beta-blocker use was associated with a decrease in the risk of major amputation compared with the risk in non-users but an increase in the risk of recurrent MI and/or stroke. However, our results are not sufficient to alter the indication of beta-blocker use among symptomatic PAD patients.

ACKNOWLEDGEMENTS

The authors thank the Danish Heart Foundation and the Health Department of Viborg County for their financial support. We also thank the Danish Vascular Registry for providing the data.

CONFLICT OF INTEREST

None.

FUNDING

None.

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