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Low rate of revascularization procedures and poor prognosis particularly in male patients with peripheral artery disease — A propensity score matched analysis

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ABSTRACT

Background: Few data discuss the impact of sex on diagnostic and therapeutic procedures and outcome of patients with peripheral artery disease (PAD).
Methods: We obtained data on 41,873 PAD patients between 2009 and 2011 (including a 4-year follow-up) from the largest German public health insurance (BARMER GEK). Propensity Score Matching (PSM) was performed to evaluate the impact of sex on treatment, complications, in-hospital and long-term outcome.
Results: Of 41,873 PAD patients, there were 23,282 (55.6%) male and 18,591 (44.4%) female. Male patients were younger (69 ± 11 years vs. 75 ± 12 years in females; $p < 0.001$) but had higher obesity (8.0% vs 6.5%), dyslipidemia (33.2% vs 28.1%), smoking (12.9% vs 9.2%), coronary artery disease (29.4% vs 19.5%), or diabetes rates (35.8% vs 28.1%; each $p < 0.001$). Almost three in five revascularizations applied to minor clinical stages, revascularization rate in critical limb ischemia (CLI) was 49% at in-hospital and 58.8% inc. follow-up in both sexes (Rutherford 6). PSM accounting for risk factors and PAD stages showed lower use of endovascular and higher use of surgical revascularization in males compared to females. Male sex was associated with higher in-hospital amputation and was an independent risk factor during follow-up for both amputation (HR 1.284; $p < 0.001$) and death (HR 1.155; $p < 0.001$).
Conclusions: Data show low rates of revascularization procedures particularly at advanced PAD stages (CLI). Male sex is associated with higher use of surgical, but lower use of endovascular and overall procedures, and higher amputation and mortality during follow-up.

1. Introduction

The burden of peripheral artery disease (PAD) is worldwide increasing with a prevalence of 4–9%, in particular in consideration of rising morbidity and aging of the population [1–4]. Historically regarded as a disease predominantly affecting males, recent global data suggest a marked increase in female patients [5]. There is increasing evidence that women with PAD may differ from male patients in terms of risk constellation [6] and symptom presentation [7]. The percentage of women in asymptomatic stages of PAD is higher compared to men, however the cardiovascular risk correlates poorly with symptom presentation and is almost as high as in symptomatic patients with comparably reduced ankle-brachial index (ABI) values [5,8]. Once progressed to symptomatic PAD, women present at more advanced PAD stages [1,9,10], and thus may be disadvantaged in terms of successful treatment and outcome. Otherwise, PAD itself has been shown to be an independent predictor of cardiovascular and cerebrovascular morbidity and mortality, predominantly in men [11,12]. Albeit there is strong evidence for a general under-supply of end-stage PAD patients with guideline-based therapies [13], particularly women have been suggested to receive fewer invasive arterial diagnostic and therapy prior to amputation [14]. According to current knowledge, invasive endovascular and surgical therapeutic procedures lead each to comparable results in male and female patients [15–17]. Thus, current guideline recommendations do not distinguish between male and female patients. However, robust data investigating the effect of sex on revascularization procedures and outcome in patients with PAD are rare.

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; CLI, critical limb ischemia; EVR, endovascular revascularization; G-DRG, German Diagnosis Related Groups; HR, hazard ratio; ICD-10, the International Statistical Classification of Diseases and Related Health Problems 10th Revision; InEK, Institut für das Entgeltsystem im Krankenhaus; OD, odds ratio; OPS, Operationen und Prozedurenschlüssel (German procedure classification system); PAD, peripheral artery disease; PSM, propensity score match; SD, standard deviation; TEA, thromboendarterectomy.

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2. Methods

The BARMER GEK is the largest public German health insurance, currently providing for ~8 million people, respectively 10% of the entire German population. Data on 41,873 patients hospitalized with PAD with an index hospitalization between January 1st, 2009 and December 31st, 2011 were obtained from the BARMER GEK for further analysis. Data sets also cover a time span of 24 months before index hospitalization and a follow-up period until December 31st, 2012. As obligated by law, the data sets comprise all in- and outpatient data on patient characteristics, diagnoses, co-morbidities, procedures, and complications, including all major adverse events such as death, amputation, myocardial infarction, and stroke.

2.1. Selection of patients and PAD diagnosis

Diagnoses were documented by use of the German Modification of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Patients with lower limb PAD (ICD-10 codes I70.20–I70.24) as primary diagnosis or as secondary diagnosis combined with at least one of the following main diagnoses: diabetes with vascular complications, other peripheral vessel disease, arterial embolism and thrombosis, or ulcers were included in the analysis [for details see 13,18].

Patients with PAD diagnosis were further sub-classified in clinical Rutherford stages 1–3 (ICD I70.20 or I70.21; $n = 21{,}190$), 4 (ICD-10 I70.22; $n = 5352$), 5 (ICD-10 I70.23; $n = 6916$), and 6 (ICD-10 I70.24; $n = 8415$). Critical limb ischemia (CLI) was defined as PAD Rutherford stages 4–6. In addition, an unlimited number of secondary diagnoses could be encoded to display the level of complexity with regard to patient's co-morbidities or complications during the hospital length of stay. Similarly, all diagnostic, endovascular, and surgical procedures were encoded by use of the German procedure classification ('Operationen und Prozedurenschlüssel', OPS) system. All diagnostic and procedural codes used in the analysis are shown in Appendix Table A.1.

As required by the German remuneration system (German Diagnosis Related Groups; G-DRG), these diagnostic and procedural data are comprised and each case assigned into a specific DRG to further be transferred to the Institut für das Entgeltsystem im Krankenhaus (InEK) as previously described in detail [9]. The InEK processes these data for the purpose of a dynamic costing evaluation. All calculated costs include the entire in-hospital measures including medication, catheters, and blood products except for expenses resulting from outpatient care.

2.2. Statistics

Categorical variables are presented as absolute numbers (n) and percentages (%), continuous variables are presented as mean value with the corresponding standard deviation (SD). To allow for sex differences in treatment parameters, a propensity score match (PSM 1) has been calculated based on a logistic regression model predicting male sex. The following important outcome-related baseline variables that differ significantly between male and female patients are included in PSM 1: *age*, *Rutherford Category*, *hypertension*, *smoking*, *obesity*, *dyslipidemia*, *diabetes*, *chronic kidney disease*, *coronary artery disease*, *chronic heart failure*, and *malignancies*. A 1:1 PS matching is performed by means of SPSS extensions FUZZY and PSM ('Fuzzy Matching'). The resulting PSM 1 data set on $n = 30{,}978$ patients covers 83.3% of female patients and 66.5% of male patients. To allow for sex differences in outcome parameters, concordantly a propensity score match (PSM 2) has been calculated including the treatment variables *endovascular revascularization* (*EVR*), and *surgery* in addition to the aforementioned baseline variables. The resulting PSM 2 data set on $n = 30{,}954$ patients covers 83.2% of female patients and 65.7% of male patients. The balancedness in the matched datasets is controlled by statistical tests and standardized differences resulting in no or only negligible differences (standardized differences <0.1, see Austin et al. [19]). Bivariate statistical comparisons between sex categories are performed in the matched and unmatched dataset by calculating X^2 test, McNemar tests, or t-tests when appropriate. The influence of baseline parameters on in-hospital outcomes is analyzed by multivariate logistic regression models. The predictive value of sex on long-term outcomes is tested by multivariable cox regression models, of which we present hazard ratios (HRs) and 95% confidence intervals (CIs). All tests are performed two-sided, and p-values <0.05 are considered statistically significant.

3. Results

3.1. Baseline characteristics

We analyzed a total of 41,873 PAD patients, thereof 23,282 male and 18,591 female (44.4%). In the unadjusted data (before PSM), male patients were at average 5.5 years younger compared to females, and cardiovascular risk factors were more frequent in men than in women (Table 1): the ratio of co-morbidities such as diabetes (35.8% male vs. 28.1% female), dyslipidemia (33.2% vs. 28.1%), obesity (8.0% vs. 6.5%), and smoking (12.9% vs. 9.2%; all $p < 0.001$) was significantly higher in male PAD patients. Chronic kidney disease (22.1% vs. 21.6%) did not differ significantly between the sexes. Co-prevalence of coronary artery disease was significantly higher in men (29.4% vs. 19.5%, $p < 0.001$), while the presence of chronic heart failure (9.5% vs. 10.2%, $p = 0.019$) and hypertension (67.4% vs. 68.7%; $p = 0.004$) was slightly (but statistically significant) higher in female patients.

Table 1
Baseline characteristics and comorbidities in the complete unadjusted data set.

	Male	Female	Total	p[a]
Patients, n (% of all)	23,282 (55.6)	18,591 (44.4)	41,873 (100.0)	
Age, mean ± SD	69.0 ± 10.6	74.5 ± 11.7	71.4 ± 11.4	<**0.001**
Ruth 1–3, n (%)	12,425 (53.4)	8765 (47.1)	21,190 (50.6)	<**0.001**
4, n (%)	2655 (11.4)	2697 (14.5)	5352 (12.8)	
5, n (%)	3503 (15.0)	3413 (18.4)	6916 (16.5)	
6, n (%)	4699 (20.2)	3716 (20.0)	8415 (20.1)	
Hypertension, n (%)	15,698 (67.4)	12,781 (68.7)	28,485 (68.0)	**0.004**
Smoking, n (%)	2998 (12.9)	1705 (9.2)	4705 (11.2)	<**0.001**
Obesity, n (%)	1868 (8.0)	1205 (6.5)	3073 (7.3)	<**0.001**
Dyslipidemia, n (%)	7733 (33.2)	5220 (28.1)	12,954 (30.9)	<**0.001**
Diabetes, n (%)	8341 (35.8)	5218 (28.1)	13,561 (32.4)	<**0.001**
CKD, n (%)	5135 (22.1)	4019 (21.6)	9155 (21.9)	0.287
CAD, n (%)	6837 (29.4)	3626 (19.5)	10,465 (25.0)	<**0.001**
CHF, n (%)	2221 (9.5)	1902 (10.2)	4123 (9.8)	**0.019**
Malignancies, n (%)	483 (2.1)	291 (1.6)	774 (1.8)	<**0.001**

Ruth — Rutherford Category; CKD — chronic kidney disease; CAD — coronary artery disease; CHF — chronic heart failure; SD — standard deviation.
Bold values indicate significance at p < 0.05.
[a] Derived from χ^2 or t-tests. Unadjusted data.

Half of the patients were at advanced clinical PAD stages with CLI (Rutherford Categories 4–6) with 36.6% of the entire cohort having ischemic tissue loss (16.5% with ulcers and 20.1% with gangrene). CLI was more common in female than in male patients (53% vs. 47%, $p < 0.001$). After multivariate adjustment for baseline characteristics and age, male sex was negatively correlated with CLI (OR 0.837, 95%-CI 0.802–0.874; $p < 0.001$; Table A.2). Further, hypertension (OR 0.830, 95%-CI 0.791–0.872) and dyslipidemia (OR 0.599, 95%-CI 0.570–0.629) were associated with lower occurrence of CLI, whereas diabetes (OR 1.892, 95%-CI 1.802–1.986), chronic kidney disease (OR 1.722, 95%-CI 1.629–1.820), chronic heart failure (2.362, 95%-CI 2.177–2.561), and malignancies (OR 1.953, 95%-CI 1.674–2.280; all $p < 0.001$) increased the risk for CLI (Table A.2).

3.2. Diagnostic and therapeutic procedures

Diagnostic angiography was performed in 54.6% of male and 55.7% of female patients at any stage of PAD (Table 2). The overall rate of revascularization procedure (endovascular or surgical) did not differ significantly between men and women (65.2% vs. 65.9%; $p = 0.114$) in the unadjusted data. Compared to men, women were revascularized more often by endovascular (45.7% vs. 43.3%, $p < 0.001$), yet less often by surgical approach (24.5% vs. 25.9%, $p < 0.001$). In both sexes, rate of bypass surgery (13.0% male vs. 11.7% female; $p < 0.001$) was slightly higher compared to thromboendarterectomy (12.8% vs. 10.8%; $p < 0.001$). PSM accounting for the afore-mentioned baseline variables (PSM 1) showed significantly higher chance for angiography but also for overall revascularization in female patients (67.5% vs. 64.7%, $p < 0.001$). Further PSM adjustment substantiated the higher chance for an endovascular approach in females compared to males (47.7% vs. 42.8%, $p < 0.001$), who on the other hand receive more frequently surgical procedures such as thrombendartherectomy (12.8% vs. 11%, $p < 0.001$) or bypass surgery (13.1% vs. 12.0%, $p = 0.006$; Table 2).

About 58% of all revascularizations were applied in patients with mild to modest PAD stages (Rutherford Categories Ruth 1–3), with slightly higher treatment rate in female patients compared to males in the unadjusted data set (76.5% vs. 74.5%; $p < 0.001$; Table A.3). With increasing clinical stages, the chance for an attempt of revascularization steadily decreased: 71% at Ruth 4, 51% at Ruth 5, and 49% at Ruth 6 (Table A.3). There was again a slightly higher revascularization rate in women at Ruth 5 (52.2% vs. 49.5%; $p = 0.024$), however at CLI stages Ruth 4 and Ruth 6 no significant sex difference in the revascularization rate could be observed.

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