

Gender differences in risk factors and cardiovascular outcomes in symptomatic peripheral artery disease patients

Mislav Vrsalović^{*1,2}, Tonći Batinić¹, Nikola Kos¹

¹ Department of Cardiovascular Diseases, University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia

² School of Medicine, University of Zagreb, Zagreb, Croatia

ABSTRACT:

AIM: To compare the influence of gender on adverse cardiovascular events in patients with symptomatic peripheral artery disease (PAD) based on their clinical presentation (intermittent claudication or critical limb ischemia, CLI).

PATIENTS AND METHODS: A prospective, registry-based study involving patients with symptomatic peripheral artery disease was conducted. Patients were divided according to initial clinical presentation (intermittent claudication or CLI) and gender and were analyzed separately. Risk factors, prognosticators and longitudinal events (major adverse cardiovascular events, MACE: myocardial infarction, stroke, death) were collected. Data were obtained prospectively from hospital records and death certificates.

RESULTS: 1084 patients (35% women) with symptomatic PAD were included in the study. Mean follow-up period was 45 months, and 371 patients (34%) experienced MACE. Compared to males, females were older ($p < 0.001$) and were more likely to have CLI ($p = 0.006$) and impaired renal function ($p < 0.001$). Diabetes ($p = 0.043$) and smoking ($p < 0.001$) were more prevalent in men, as well as polyvascular disease ($p = 0.024$). No significant difference was found regarding the use of medications. No differences were observed in MACE-free survival between women and men, both in subgroups of patients with intermittent claudication (log-rank $p = 0.759$) and CLI (log-rank $p = 0.558$).

CONCLUSIONS: Our study showed no gender differences in the occurrence of MACE based on initial clinical presentations of PAD.

KEYWORDS: peripheral artery disease, critical limb ischemia, gender, cardiovascular outcomes

OPEN ACCESS

Correspondence:

Mislav Vrsalović
mislav.vrsalovic@gmail.com
orcid.org/0000-0002-8432-404X

This article was submitted to RAD
CASA - Medical Sciences
as the original article

Conflict of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 18 October 2021

Accepted: 18 November 2021

Published: 27 December 2021

Citation:

Vrsalović M, Batinić T, Kos N. Gender differences in risk factors and cardiovascular outcomes in symptomatic peripheral artery disease patients. RAD CASA - Medical Sciences. 548=56-57 (2021): 22-27. DOI: 10.21857/yrvqteq19

Copyright (C) 2021 Vrsalović M, Batinić T, Kos N. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

SAŽETAK:

SPOLNE RAZLIKE U RIZIČNIM ČIMBENICIMA I KARDIOVASKULARNIM ISHODIMA BOLESNIKA SA SIMPTOMATSKOM PERIFERNOM ARTERIJSKOM BOLESTI

CILJ: Usporediti utjecaj spola na učestalost neželjenih kardiovaskularnih događaja u bolesnika sa simptomatskom perifernom arterijskom bolesti (PAB) s obzirom na inicijalnu kliničku prezentaciju (intermitentne klauđikacije ili kritična ishemija ekstremiteta).

MATERIJALI I METODE: Provedeno je prospektivno kliničko istraživanje u koje su uključeni bolesnici sa simptomatskom perifernom arterijskom bolesti. Bolesnici su podijeljeni u skupine s obzirom na inicijalnu kliničku prezentaciju (intermitentne klauđikacije ili kritična ishemija ekstremiteta) te s obzirom na spol. Prikupljeni su podaci o rizičnim čimbenicima, prognostičkim faktorima i neželjenim kardiovaskularnim ishodima (infarkt miokarda, cerebrovaskularni inzult, smrtni ishod).

REZULTATI: U istraživanje je uključeno 1084 bolesnika (35% žena) sa simptomatskom PAB. Prosječan period praćenja iznosio je 45 mjeseci tijekom kojeg je u 371 bolesnika (34%) zabilježen neželjeni kardiovaskularni događaj. U usporedbi s muškarcima, žene su bile starije dobi ($p < 0,001$), češće su se prezentirale s kliničkom slikom kritične ishemije ekstremiteta ($p = 0,006$) i oštećenom bubrežnom funkcijom ($p < 0,001$). Muškarci su češće bolovali od šećerne bolesti ($p = 0,043$) i polivasku-

larne bolesti ($p=0,024$) te su češće bili pušači ($p < 0,001$). Među spolovima nije bilo razlike u primjeni statina niti inhibitora angiotenzin konvertirajućeg enzima i antagonista angiotenzinskih receptora. Nije bilo razlike u preživljenju bez neželjenog kardiovaskularnog događaja između žena i muškaraca, u bolesnika s intermitentnim klaudikacijama (log-rank $p=0,759$) i kritičnom ishemijom ekstremiteta (log-rank $p=0,558$).

ZAKLJUČAK: Naše istraživanje nije pokazalo značajan utjecaj spola na učestalost neželjenih kardiovaskularnih događaja u bolesnika sa simptomatskom perifernom arterijskom bolesti, u ovisnosti o inicijalnoj kliničkoj prezentaciji.

KLJUČNE RIJEČI: periferna arterijska bolest, kritična ishemija ekstremiteta, spol, kardiovaskularni ishodi

INTRODUCTION

Gender differences in the spectrum of cardiovascular diseases are associated with differences in biology between the sexes as well as various social factors that ultimately lead to an unequal approach to the diagnosis and treatment. (1–3) Peripheral artery disease (PAD), as one of the most significant markers of atherosclerotic disease extension, occurs with varying frequency and with different clinical manifestations among genders. (4) In women PAD occurs about 15 years later than in men, probably due to the protective effect of estrogen. (5) However, the prevalence of PAD in postmenopausal women is higher than in men. (6) The risk profile of patients with PAD differs between sexes: men are more likely to be smokers, while women more often suffer from dyslipidemia and diabetes. (7–9) Compared to men, in women with chronic renal failure, PAD occurs more often and at an earlier age. (10) In women, the frequency of subclinical, asymptomatic and atypical forms of PAD is higher, and when the disease becomes symptomatic, women tend to start the treatment at a more advanced stage of the disease, often in the phase of critical limb ischemia (CLI). (11–13)

Although some studies indicate that cardiovascular mortality is higher in women than in men, the results of available meta-analyses show contradictory results on the impact of gender on cardiovascular and overall outcomes in patients with PAD. (10, 14–16) There are insufficient data regarding outcomes between women and men, according to the clinical presentation of PAD. The aim of our study was to assess the influence of gender on risk factors in symptomatic PAD, and sex differences in cardiovascular outcomes according to the clinical presentation of the disease, i.e. intermittent claudication or CLI.

PATIENTS AND METHODS

The first Croatian prospective Peripheral Artery Disease registry (CRO-PAD) was created in 2010, with the aim to: collect, organise and analyse data about patients with PAD. (17–19) We planned to investigate risk factors, prognosticators and longitudinal events to improve patients' healthcare and disease outcomes. During hospital stay, demographic data and clinical

characteristics of the patients were recorded and included general information (age, gender, and anthropometric data), cardiovascular risk factors, laboratory data, comorbidities, and medications. The diagnosis of PAD was established by clinical examination, ankle brachial index measurement, duplex sonography, and/or computed tomography, magnetic resonance angiography or peripheral angiography using the criteria of the European Society of Cardiology. (1) Critical limb ischemia was defined as the presence of rest pain, ulcer or gangrene (Fontaine stages III and IV). Diabetes was defined according to the criteria of the American Diabetes Association and was considered to be present in all patients taking antidiabetic medication. (20) Hypertension was diagnosed in accordance with the European Society of Cardiology/ European Society of Hypertension 2017 guidelines. (21) Renal function was assessed by estimating the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease formula and $GFR < 60 \text{ mL/min/1.73 m}^2$ indicated impaired renal function. (22) Cardiovascular disease, in addition to confirmed PAD, was defined as a history of percutaneous coronary intervention, coronary artery bypass grafting, or myocardial infarction (MI), history of stroke or transient ischemic attack, carotid stenosis ($\geq 50\%$), or carotid revascularization. All patients were followed up through scheduled clinical visits, firstly three months after the index hospitalization and thereafter at 12-month interval. Outcomes were documented by reviewing hospital records or death certificates and the occurrence of major adverse cardiovascular events (MACE), defined as composite endpoint of MI, stroke, and death was assessed.

Differences between the groups were analysed with t-test for continuous variables and with chi-square test for categorical variables. Kaplan-Meier methods with log-rank tests were performed to compare the survival curves between women and men with intermittent claudication and CLI. The value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the MedCalc Statistical Software version 20.011, Ostend, Belgium. The investigation was performed in accordance with the Declaration of Helsinki and was approved by the University Hospital Ethics Committee (No. EP-7407/15-1).

RESULTS

In this prospective database 1084 consecutive patients with symptomatic PAD, admitted to the University Hospital between January 2010 and January 2020 were included. Baseline characteristics of the study population are shown in Table 1. During mean follow-up period of 45 months, 371 patients (34%) experienced MACE, with 77 MIs, 63 strokes, and 231 deaths.

The prevalence of women among symptomatic PAD patients was 35% and female gender was not associated with unfavourable outcomes. When compared with males, female patients were older (72 vs 69 years, $p < 0.001$), and were more likely to have CLI (42% vs 33%, $p = 0.006$) and impaired renal function (42%

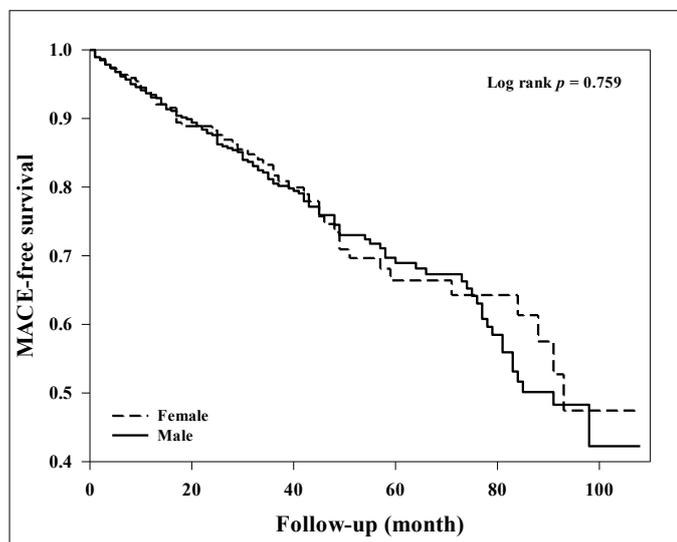
vs 31%, $p < 0.001$). Cardiovascular risk factors such as diabetes (53% vs 47%, $p = 0.043$) and smoking (58% vs 43%, $p < 0.001$) were more prevalent in men, as well as polyvascular disease (58% vs 51%, $p = 0.024$). No significant difference was found regarding the use of medications that improve cardiovascular outcomes, namely statins ($p = 0.289$) and angiotensin converting enzyme inhibitors/angiotensin receptor blockers ($p = 0.844$) (Table 1). Kaplan-Meier curves showed no differences in MACE-free survival between women and men, both in subgroup of patients with intermittent claudication (log-rank $p = 0.759$) and CLI (log-rank $p = 0.558$) (Figure 1).

Table 1. Baseline characteristics of the study population by gender (n=1084)

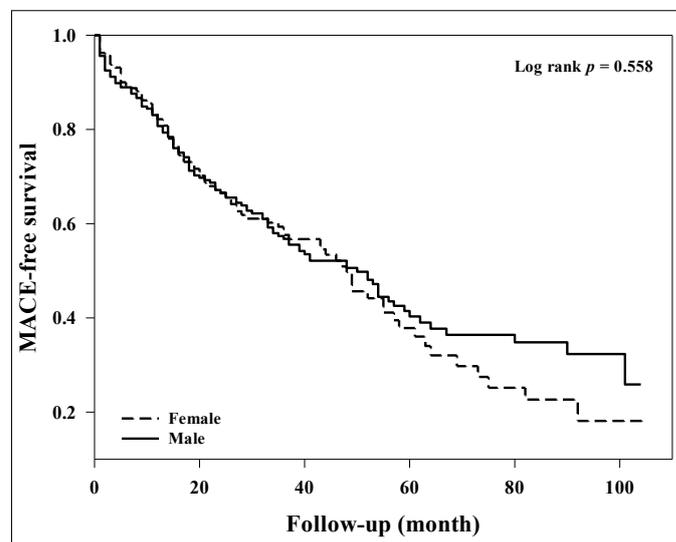
Characteristic	Female (n = 385)	Male (n = 699)	p-value
Age (years)*	72.3±9.4	68.5±9.7	<0.001
BMI (kg/m ²)*	26.8±4.4	27.5±3.9	0.016
Hypertension (%)	90	86	0.145
Diabetes mellitus (%)	47	53	0.043
Smoking (%)	43	58	<0.001
Dyslipidemia (%)	73	76	0.267
Polyvascular disease (%)	51	58	0.024
Critical limb ischemia (%)	42	33	0.006
Atrial fibrillation (%)	15	15	0.894
Impaired renal function (%)	42	31	<0.001
ACEi/ARB (%)	71	72	0.844
Statin (%)	77	80	0.289

* mean ± standard deviation

BMI, body mass index; ACEi/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.



A



B

Figure 1. Major adverse cardiovascular events (MACE) free survival according to gender in patients with (A) intermittent claudication ($n=694$) and (B) critical limb ischemia ($n=390$).

DISCUSSION

The aim of the study was to compare the influence of gender on adverse cardiovascular events in patients with symptomatic peripheral artery disease, based on their clinical presentation. The results of our prospective study showed no significant differences between women and men in adverse cardiovascular event rates, although there were differences in risk factors and initial clinical presentation.

Our results are in accordance with a meta-analysis of 16 population-based cohort studies by Fowkes et al. and the Medicare population-based cohort study. (23, 24) On the contrary, the results from meta-analysis of Parvar et al. have showed a higher rate of adverse cardiovascular outcomes in men with PAD. (25) Wand et al. reported that women had a lower rate of short-term outcomes, but no differences were noted when long-term outcomes were compared. (26) Of note, studies included in meta-analyses were heterogeneous regarding the initial presentation of PAD and treatment strategies.

Lo et al. compared in-hospital cardiovascular outcomes rates in patients with PAD, divided by gender and initial clinical presentation. They showed that women were significantly older and had a higher mortality rate. (27) The differences between the studies can be explained by the duration of follow-up period and treatment advancements during the last decades for PAD patients i.e.

more frequent prescription of cardiovascular outcome-modifying medications and use of modern endovascular materials and techniques.

Previous studies warned about significant undertreatment of women with PAD, especially with lipid-lowering drugs. (28) Our study demonstrated no gender differences in medication use, and about 80% of our study population was on statin therapy. Additionally, we showed that men with PAD suffered more frequently from diabetes and polyvascular disease, while women were significantly older and more often presented with CLI. The latter can be explained by biological differences, since women tend to have a higher threshold for ischemic pain and have smaller vessel diameters. (29, 30)

In conclusion, we found no differences in terms of adverse cardiovascular events between women and men with symptomatic PAD based on their initial clinical presentation. More research is needed to explain gender disparities across the peripheral vascular disease continuum.

Funding

This research was conducted with no grant support.

Competing interest

The authors declare no potential conflict of interests.

REFERENCES:

1. Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases. *Eur Heart J*. 2018 Mar 1;39(9):763–816.
2. Schramm K, Rochon PJ. Gender Differences in Peripheral Vascular Disease. *Semin Interv Radiol*. 2018 Mar;35(1):9–16.
3. Aboyans V, Vrsalovic M, Madaric J, Mazzolai L, De Carlo M, ESC Working Group on Aorta and Peripheral Vascular Diseases. The year 2018 in cardiology: aorta and peripheral circulation. *Eur Heart J*. 2019 Mar 14;40(11):872–9.
4. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg*. 2007 Jun;45(6):1185–91.
5. Nguyen L, Liles DR, Lin PH, Bush RL. Hormone replacement therapy and peripheral vascular disease in women. *Vasc Endovascular Surg*. 2004 Dec;38(6):547–56.
6. Gerhard M, Baum P, Raby KE. Peripheral arterial-vascular disease in women: prevalence, prognosis, and treatment. *Cardiology*. 1995;86(4):349–55.
7. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. *J Am Geriatr Soc*. 1985 Jan;33(1):13–8.
8. Vrsalovic M, Vucur K, Vrsalovic Presecki A, Fabijanec D, Milosevic M. Impact of diabetes on mortality in peripheral artery disease: a meta-analysis. *Clin Cardiol*. 2016 Dec 27;40(5):287–91.
9. Vrsalović M, Presečki AV. Atrial fibrillation and risk of cardiovascular events and mortality in patients with symptomatic peripheral artery disease: A meta-analysis of prospective studies. *Clin Cardiol*. 2017 Dec;40(12):1231–5.
10. Wang GJ, Shaw PA, Townsend RR, Anderson AH, Xie D, Wang X, et al. Sex Differences in the Incidence of Peripheral Artery Disease in the Chronic Renal Insufficiency Cohort. *Circ Cardiovasc Qual Outcomes*. 2016 Feb;9(2 Suppl 1):S86–93.
11. Higgins JP, Higgins JA. Epidemiology of peripheral arterial disease in women. *J Epidemiol*. 2003 Jan;13(1):1–14.
12. Jackson EA, Munir K, Schreiber T, Rubin JR, Cuff R, Gallagher KA, et al. Impact of sex on morbidity and mortality rates after lower extremity interventions for peripheral arterial disease: observations from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. *J Am Coll Cardiol*. 2014 Jun 17;63(23):2525–30.
13. Mazzeffi MA, Lin H-M, Flynn BC, O'Connell TL, DeLaet DE. Hypothyroidism and the risk of lower extremity arterial disease. *Vasc Health Risk Manag*. 2010 Oct 26;6:957–62.
14. Olinic D-M, Spinu M, Olinic M, Homorodean C, Tataru D-A, Liew A, et al. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. *Int Angiol*. 2018 Aug;37(4):327–34.
15. Mentias A, Vaughan-Sarrazin M, Saad M, Girotra S. Sex Differences in Management and Outcomes of Critical Limb Ischemia in the Medicare Population. *Circ Cardiovasc Interv*. 2020 Oct;13(10):009459.
16. Hussain MA, Lindsay TF, Mamdani M, Wang X, Verma S, Al-Omran M. Sex differences in the outcomes of peripheral arterial disease: a population-based cohort study. *CMAJ Open*. 2016 Mar;4(1):124–131.
17. Vrsalović M, Vučur K, Car B, Krčmar T, Vrsalović Presečki A. C-reactive protein, renal function, and cardiovascular outcome in patients with symptomatic peripheral artery disease and preserved left ventricular systolic function. *Croat Med J*. 2015 Aug;56(4):351–6.
18. Vrsalović M, Vučur K. Diabetes and Critical Limb Ischemia: The Deadly Duo in Patients with Symptomatic Peripheral Artery Disease. *Acta Clin Croat*. 2016 Jun;55(2):240–6.
19. Vrsalovic M, Vucur K, Jelakovic B. Atrial Fibrillation Predicts Cardiovascular Outcome in Hypertensive Patients with Symptomatic Peripheral Artery Disease and Preserved Ejection Fraction. *J Clin Hypertens (Greenwich)*. 2016 Sep;18(9):953–4.
20. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020 Jan 7;41(2):255–323.
21. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018 Sep 1;39(33):3021–104.
22. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999 Mar 16;130(6):461–70.
23. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008 Jul 9;300(2):197–208.
24. Mentias A, Vaughan-Sarrazin M, Saad M, Girotra S. Sex Differences in Management and Outcomes of Critical Limb Ischemia in the Medicare Population. *Circ Cardiovasc Interv*. 2020 Oct;13(10)
25. Parvar SL, Thiyagarajah A, Nerlekar N et al. A systematic review and meta-analysis of gender differences in long-term

- mortality and cardiovascular events in peripheral artery disease. *J Vasc Surg.* 2021 Apr;73(4):1456-1465.
26. Wang J, He Y, Shu C et al. The effect of gender on outcomes after lower extremity revascularization. *J Vasc Surg.* 2017 Mar;65(3):889-906.
 27. Lo RC, Bensley RP, Dahlberg SE et al. Presentation, treatment, and outcome differences between men and women undergoing revascularization or amputation for lower extremity peripheral arterial disease. *J Vasc Surg.* 2014 Feb;59(2):409-418.
 28. McDermott MM, Greenland P, Reed G et al. Gender differences in cholesterol-lowering medication prescribing in peripheral artery disease. *Vasc Med.* 2011 Dec;16(6):428-35.
 29. Keefe-McCarthy S. Women's experiences of cardiac pain: a review of the literature. *Can J Cardiovasc Nurs.* 2008;18(3):18-25.
 30. Pabbidi MR, Kuppusamy M, Didion SP, Sanapureddy P, Reed JT, Sontakke SP. Sex differences in the vascular function and related mechanisms: role of 17 β -estradiol. *Am J Physiol Heart Circ Physiol.* 2018 Dec 1;315(6):H1499-H1518.