Prevalence, determinants, and prognostic impact of polyvascular disease in patients hospitalised for atherosclerosis in Slovenia: a nationwide, retrospective cohort study

Kevin Pelicon,[a,*] Tjaša Furlan,[b] Vinko Boc,[a,c] Dalibor Gavrić,[d] Borut Jug,[a,c,f] and Petra Došenović Bonča[e,f]

[a]Department of Vascular Diseases, University Medical Centre Ljubljana, Slovenia
[b]General Hospital Trbovlje, Slovenia
[c]Faculty of Medicine, University of Ljubljana, Slovenia
[d]Department of Development and Analysis, The Health Insurance Institute of Slovenia, Slovenia
[e]School of Economics and Business, University of Ljubljana, Slovenia

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Summary

Background Polyvascular disease (PVD) is an increasingly recognised form of atherosclerotic cardiovascular disease (ASCVD) with heightened prognostic implications. This study aimed to comprehensively assess the prevalence, risk factors, and prognosis of PVD in Slovenia.

Methods We conducted an observational retrospective cohort study using national-level reimbursement data from The Health Insurance Institute of Slovenia between January 1, 2015, and December 31, 2023. The study considered all adults who were hospitalised for coronary, cerebrovascular, or lower extremity peripheral arterial disease with diagnoses defined using ICD-10 codes. Multivariate logistic regression was used to identify cardiovascular risk factors for PVD. Patients were grouped by the number of affected vascular beds. The primary outcomes were all-cause death, major adverse cardiovascular events (MACE), major adverse limb events (MALE), and major bleeding. In outcome analysis, a landmark of 90 days was considered. Cause-specific survival analysis was performed, and associations with the primary outcomes was assessed using univariate and multivariate Cox proportional hazards models, adjusting for demographics, cardiovascular risk factors, comorbidities, and prescribed medication.

Findings The study included 91,917 adults hospitalised for ASCVD. Of these, 85,703 (93.2%) had atherosclerosis in one vascular bed, 5878 (6.4%) in two, and 336 (0.4%) in three; the latter two groups (6214; 6.8%) were classified as having PVD. Traditional cardiovascular risk factors were strongly associated with PVD, with chronic kidney disease (odds ratio [OR] 1.96; 95% CI 1.81–2.11; $p < 0.0001$), diabetes (OR 1.57; 95% CI 1.48–1.66; $p < 0.0001$), and chronic obstructive pulmonary disease – a surrogate indicator of tobacco use (OR 1.56; 95% CI 1.40–1.74; $p < 0.0001$) emerging as the strongest predictors. Compared to patients with ASCVD in one vascular bed, patients with two affected beds had adjusted hazard ratios (HRs) of 1.24 (95% CI 1.09–1.42) for all-cause death, 1.51 (95% CI 1.24–1.83) for MACE, 2.52 (95% CI 2.08–3.05) for MALE, and 1.27 (95% CI 1.05–1.54) for major bleeding. Patients with three affected beds had adjusted HRs of 1.69 (95% CI 1.40–2.03), 2.70 (95% CI 2.23–3.28), 4.24 (95% CI 3.49–5.14), and 2.31 (95% CI 1.45–3.68), respectively.

Interpretation Patients with PVD face a high overall disease burden, with adverse event rates increasing in proportion to the number of affected vascular beds. Accurate assessment of individual risk profiles is essential, as patients with the highest baseline risk are most likely to benefit from intensified preventive strategies. Potential underreporting inherent in administrative claims data, along with our selective criteria for defining leading diagnoses, may have somewhat limited the number of identified patients with PVD. Nonetheless, even after adjusting for group size, comorbidities, and prescribed medication, PVD independently predicted not only all-cause death and ischaemic events but also major bleeding. Further research is needed to define optimal treatment strategies in this high-risk population.

*Corresponding author. Zaloška cesta 7, 1000, Ljubljana, Slovenia.
E-mail address: kevin.pelicon@kclj.si (K. Pelicon).
[f]Authors contributed equally to the final manuscript.

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Research in context

Evidence before this study

We performed a literature search in the PubMed database, covering a period from the database's inception until July 11th 2025, using search terms such as "atherosclerosis," "polyvascular," "coronary artery disease," "peripheral arterial disease," "cerebrovascular disease," "outcome," "MACE," "MALE," "mortality,", "death," "bleeding," and "haemorrhage" without language restrictions. We considered observational cohort studies, registry analyses, interventional trials, and review articles reporting on the prevalence, risk factors, or outcomes associated with polyvascular disease (PVD). PVD is consistently associated with an increased risk of adverse events, including all-cause and cardiovascular mortality, major adverse cardiovascular events (MACE), and major adverse limb events (MALE), with risks increasing in proportion to the number of affected vascular beds. However, existing evidence remains limited by comparatively small sample sizes, select trial populations, and restricted generalisability, with only two large-scale studies (based on Medicare data and the CRUSADE registry) addressing broader populations. Furthermore, the association between PVD and bleeding risk remains insufficiently explored, with conflicting findings across studies and limited adjustment for confounding variables such as comorbidities and prescribed medication.

Added value of this study

Our study adds population-level evidence from a large national cohort of over 91,000 patients, who were hospitalised for atherosclerotic cardiovascular disease (ASCVD) in Slovenia. We confirm the high overall disease burden of PVD with patients experiencing a stepwise increase in the risk of all-cause death, MACE, MALE, and major bleeding with each additional involved vascular bed. Importantly, this is the first study to show that PVD is a predictor of major bleeding even after adjusting for demographics, cardiovascular risk factors, comorbidities, and prescribed medication, highlighting a previously under-recognised risk in this population.

Implications of all the available evidence

Current and new evidence shows that patients with PVD constitute a particularly high-risk subgroup in the ASCVD population. The consistent association between the number of affected vascular beds and adverse clinical outcomes underscores the need for comprehensive and individualised risk stratification and management to prevent progression of ASCVD from one vascular bed to PVD. Although the nature of our dataset and methodology may have somewhat limited PVD subgroup sizes, this was carefully adjusted for. As a result, the role of PVD as an independent predictor of adverse ischaemic and bleeding events is strongly supported. Further research should explore the benefit of screening for PVD, as well as identify treatment strategies that effectively balance thrombotic and bleeding risks in this population.

Introduction

Polyvascular disease (PVD), the concurrent presence of clinically relevant atherosclerosis in at least two vascular beds, represents a distinct and increasingly recognised subset of atherosclerotic cardiovascular disease (ASCVD). While PVD has traditionally been acknowledged as an advanced stage of ASCVD, evidence suggests the presence of PVD itself carries heightened prognostic implications with patients experiencing a markedly increased risk for major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and cardiovascular death, as well as all-cause death.[1–9]

A growing body of evidence suggest that novel, intensified antithrombotic and lipid-lowering treatment approaches may offer benefits in patients with PVD,[7,10,11] however the value of identifying atherosclerosis in secondary and tertiary vascular beds remains unclear, particularly in asymptomatic individuals and in patients already receiving optimal medical therapy.[12] Current treatment guidelines thus give no clear recommendations on when to screen for PVD, with screening generally reserved for selected high-risk patients and patients undergoing surgical procedures, such as coronary artery bypass grafting or carotid endarterectomy.[13]

Given that patients with a high absolute risk of adverse events derive the greatest potential benefit from targeted treatment interventions, an accurate understanding of the disease burden associated with PVD in specific patient populations is essential for optimizing healthcare strategies. Furthermore, a comprehensive understanding of the determinants of PVD can help directly address modifiable risk factors and improve outcomes.

As is the case in other developed countries, ASCVD remains a leading cause of morbidity and mortality in Slovenia.[14] However, data on the prevalence and impact of PVD in the Slovenian population remain limited. The study had three objectives: provide an appraisal of the burden of PVD in Slovenia, identify its determinants, and assess its clinical outcomes in patients hospitalised for ASCVD.

Methods

Study design

We conducted an observational longitudinal study with a retrospective design, aggregating national-level reimbursement data obtained from The Health Insurance Institute of Slovenia, the country's single third-party public payer. The dataset, previously evaluated for conformance, completeness, and plausibility and shown to have high data quality,[15] included acute hospital admissions, categorised into diagnosis-related groups, data on comorbidities, patient demographics, performed procedures, prescribed medication within 90 days before or after discharge, and mortality records. The primary diagnosis and comorbidities were identified based on established diagnoses, coded using the 10th revision of the International Classification of Diseases (ICD-10). Prescribed medication was identified using Anatomical Therapeutic Chemical (ATC) Classification codes. Mortality data were obtained from insurance and hospital records, while other outcome data was obtained from subsequent hospitalisations.

Patients

We included all patients aged 18 years and older, who were hospitalised in Slovenia between January 1, 2015, and December 31, 2023 with a primary diagnosis of coronary artery disease (CAD), cerebrovascular disease (CVD), or lower extremity peripheral arterial disease (PAD). A patient's first admission with a relevant diagnosis during the study period was considered as the index hospitalisation while subsequent hospitalisations were considered in the outcome analysis. A selective approach was chosen for defining CAD, CVD, and lower extremity PAD, aiming to consider only ICD-10 codes which reflect atherosclerotic disease. Detailed definitions used to define leading diagnoses, as well as common comorbidities and outcomes, are provided in the Supplementary Materials.

Primary outcomes

Patients were followed for: all-cause death, MACE (defined as all-cause death, non-fatal myocardial infarction or ischaemic stroke), major adverse limb events—MALE (defined as surgical or endovascular revascularisation of the lower-limb arteries or major amputation), and major bleeding events (defined as gastrointestinal or intraccranial bleeding requiring hospitalisation).

Statistical methods

The presence of ASCVD in multiple vascular beds was determined using data on both the primary diagnosis of the index hospitalisation, as well as the comorbidities recorded during that hospitalisation. For comparative analysis, patients were grouped based on whether one, two, or all three of the specified vascular beds were affected with PVD defined as ASCVD in two or three vascular beds. The three groups' baseline characteristics were analysed using descriptive statistics, with categorical variables reported as frequencies and percentages, and continuous variables as medians and interquartile ranges (IQR). Group comparisons were performed using Pearson's χ^2 test for categorical variables and the Kruskal–Wallis rank sum test for continuous variables. Cause-specific survival analyses were performed and Kaplan–Meier curves were plotted for each of the four observed outcomes to visualise survival across patient groups, based on the number of involved vascular beds. A landmark of 90 days was considered to allow for clinical stabilisation after the index event. Patients without an outcome event were censored at the end of the observed period. Differences in survival were assessed using log-rank tests.

The predictive value of traditional cardiovascular risk factors for the presence of PVD was assessed using multivariate logistic regression. To assess the association of PVD with patient outcomes, a univariate Cox proportional hazards model was fitted. To account for potential clustering of patients within hospitals, a robust sandwich variance estimator was applied, using the hospital as the clustering variable. The proportional hazards assumption for the model was evaluated using the scaled Schoenfeld residuals test. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were calculated.

Multivariate Cox proportional hazard models were subsequently constructed for each outcome to adjust for demographic factors, traditional cardiovascular risk factors, comorbidities, and prescribed medication. As a sensitivity analysis, we conducted a weighted Cox proportional hazards regression analysis using inverse probability of treatment weights (IPTWs) for a multicategory exposure (i.e., involvement of one, two, or three vascular beds). IPTWs were estimated using multinomial logistic regression based on the following covariates: age group, sex, diabetes mellitus, hypertension, hyperlipidemia, heart failure, atrial fibrillation, chronic kidney disease (CKD), cancer, chronic obstructive pulmonary disease (COPD), dementia, depression, and the Charlson comorbidity index. Stabilised average treatment effect on the treated weights were calculated by multiplying the IPTWs with the predicted probability of belonging to the reference group (i.e., patients with ASCVD in three vascular beds). A 'double-robust' Cox proportional hazard regression model was fitted (i.e., weighted for inverse

probability of treatment and adjusted for all covariates, with robust standard errors estimation). A directed acyclic graph was plotted to demonstrate the rationale for including different groups of covariates in the various models and is available in the Supplementary Materials. The number of hospitalised patients with ASVD and the proportion of patients with PVD throughout the years was plotted and a linear trendline was calculated (Supplementary Materials).

Statistical analyses were performed using the R programming language version 4.4.1 (R Foundation for Statistical Computing, Austria).[16] All tests were two-tailed. The reported p-values are provided for descriptive purposes only, as the study includes national-level data on all hospitalised patients in the specified period. The study was conducted according to the Declaration of Helsinki. To ensure transparent reporting, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was followed.

Ethics

The study protocol was approved by the Medical Ethics Committee of the Republic of Slovenia (KME) no. 0120-223/2021/11. Informed consent was waived due to the use of anonymised administrative data and the study's retrospective nature. The analysis was conducted in compliance with the Slovenian and European Union regulations and legislative frameworks.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors had full access to the data, with K.P. and B.J. bearing final responsibility for the decision to submit the manuscript for publication.

Results

A total of 91,917 adult patients were hospitalised in Slovenia due to atherosclerosis of the coronary, carotid or lower-limb arteries between 2015 and 2023 (Fig. 1). When considering not only the leading diagnosis but also comorbidities, the most common manifestation of ASCVD was CAD (56,214 patients; 61.2%), followed by CVD (24,350 patients; 26.5%), and lower extremity PAD (17,903 patients; 19.5%). The patients' baseline characteristics, as well as characteristics of the respective patient groups, based on the number of affected vascular beds, are shown in Table 1.

Of the included patients, 6214 (6.8%) had polyvascular disease, meaning atherosclerosis in two or three vascular beds. Of those, 4323 (69.6%) had CAD, 4109 (66.1%) had CVD, and 4332 (69.7%) had lower extremity PAD. The area-proportional Venn diagram in Fig. 2 illustrates the distribution and overlap of patients with confirmed atherosclerosis across the three vascular beds, regardless of whether it was the leading diagnosis or a comorbidity.

Traditional cardiovascular risk factors were strongly associated with the presence of PVD. The included risk factors and their corresponding odds ratios (ORs), obtained from the multivariate logistic regression model, are shown in Fig. 3. The full results of the analysis are available in the Supplementary Materials.

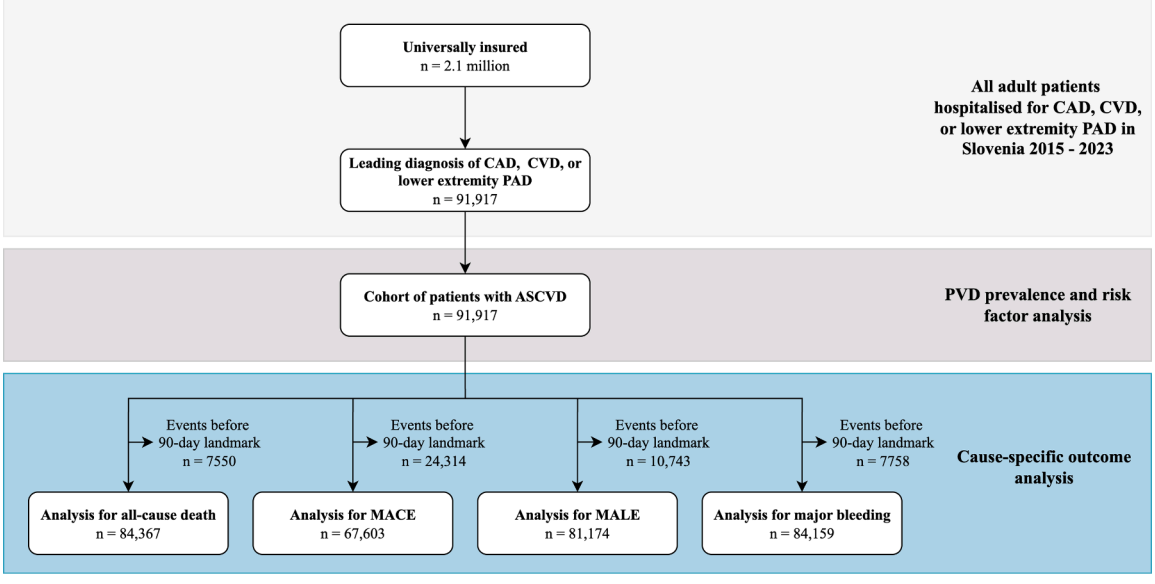

Fig. 1: Study flow diagram showing patient inclusion in different analyses. ASCVD, atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular event; MALE, major adverse limb event; PAD, peripheral arterial disease; PVD, polyvascular disease.

Characteristic	All patients N = 91,917	One vascular bed N = 85,703	Two vascular beds N = 5878	Three vascular beds N = 336	p-value
Leading diagnosis					
Coronary	54,121 (59%)	51,891 (61%)	2090 (36%)	140 (42%)	<0.0001
Cerebrovascular	22,413 (24%)	20,241 (24%)	2104 (36%)	68 (20%)	<0.0001
Lower extremity	15,383 (17%)	13,571 (16%)	1684 (29%)	128 (38%)	<0.0001
Demographics, cardiovascular risk factors, and comorbidities					
Age (Years)	70 (62–79)	70 (61–79)	74 (66–81)	72 (66–79)	<0.0001
Sex (Male)	55,042 (60%)	51,201 (60%)	3627 (62%)	214 (64%)	0.0044
Diabetes mellitus	17,712 (19%)	15,811 (18%)	1771 (30%)	130 (39%)	<0.0001
Arterial hypertension	46,457 (51%)	42,473 (50%)	3776 (64%)	208 (62%)	<0.0001
Dyslipidaemia	29,272 (32%)	26,841 (31%)	2292 (39%)	139 (41%)	<0.0001
Heart failure	7502 (8.2%)	6766 (7.9%)	689 (12%)	47 (14%)	<0.0001
Atrial fibrillation	14,009 (15%)	12,634 (15%)	1306 (22%)	69 (21%)	<0.0001
CKD	6317 (6.9%)	5367 (6.3%)	895 (15%)	55 (16%)	<0.0001
Cancer	2712 (3.0%)	2427 (2.8%)	267 (4.5%)	18 (5.4%)	<0.0001
COPD	3599 (3.9%)	3187 (3.7%)	385 (6.5%)	27 (8.0%)	<0.0001
Dementia	2631 (2.9%)	2363 (2.8%)	254 (4.3%)	14 (4.2%)	<0.0001
Depression	953 (1.0%)	887 (1.0%)	65 (1.1%)	1 (0.3%)	NA
Charlston index	0 (0–2)	0 (0–2)	1 (0–2)	1 (0–2)	<0.0001
Prescribed medication					
Aspirin	39,763 (43%)	36,939 (43%)	2649 (45%)	175 (52%)	<0.0001
$P2Y_{12}$ antagonist	23,326 (25%)	21,816 (25%)	1413 (24%)	97 (29%)	0.018
Anticoagulant medication	12,673 (14%)	11,567 (13%)	1047 (18%)	59 (18%)	<0.0001
Lipid-lowering therapy	43,568 (47%)	40,222 (47%)	3140 (53%)	206 (61%)	<0.0001

Data are presented as frequency (percentage; %) for categorical and as median (IQR) for continuous variables. Due to rounding or missing data, totals may differ from 100%. p-values are for descriptive purposes only as population-level data was considered. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NA, not available (due to the low number of patients).

Table 1: **Baseline characteristics of included patients.**

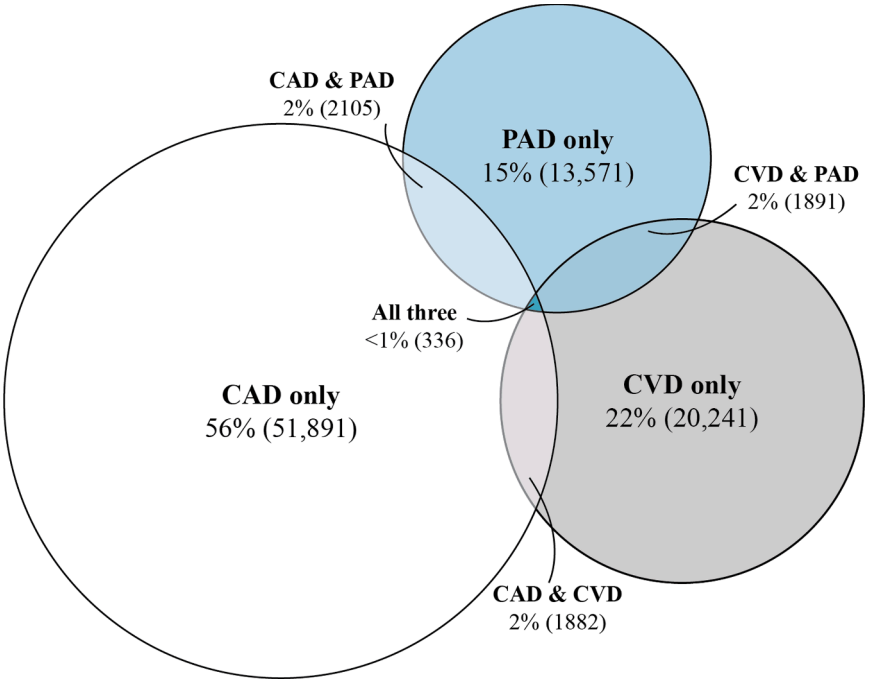

Fig. 2: Area-proportional Venn diagram of atherosclerosis in different vascular beds. CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, lower extremity peripheral arterial disease.

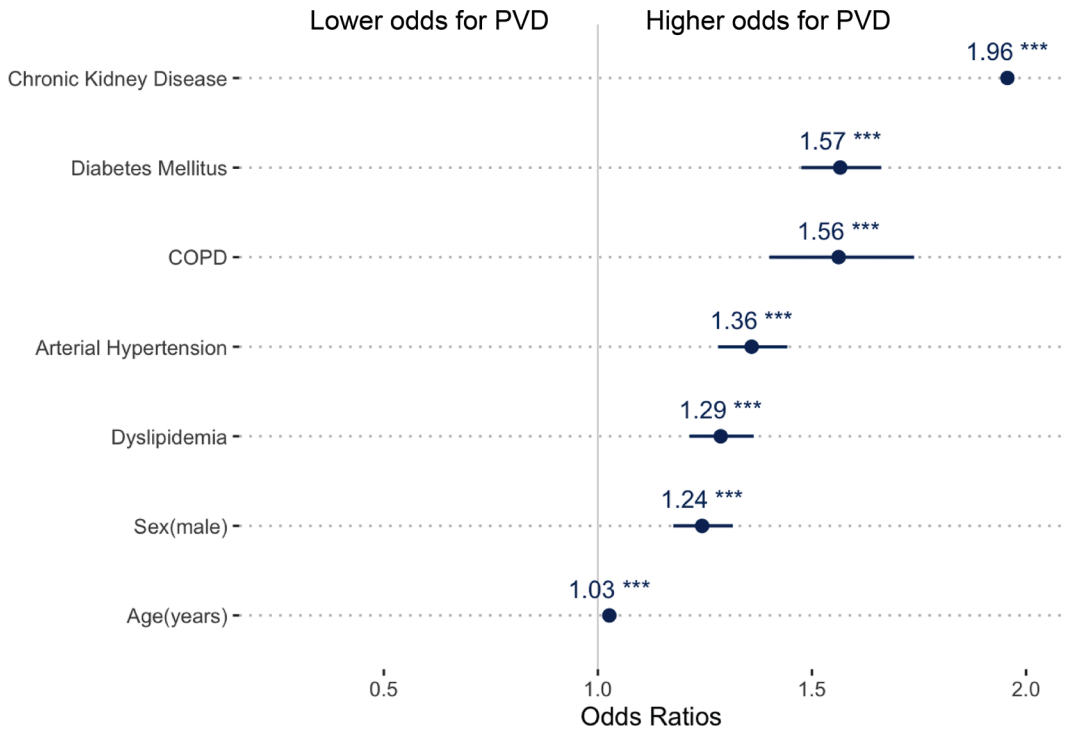

Fig. 3: Multiple logistic regression model of risk factors for the development of PVD. COPD, chronic obstructive pulmonary disease; PVD, polyvascular disease. Asterisks (***) denote a level of significance of $p \leq 0.0001$. COPD is used as a proxy for tobacco use.

Survival analysis was conducted using Kaplan–Meier curves for each of the four observed outcomes, with patients stratified according to the number of affected vascular beds. Patients who experienced the respective primary outcome within the 90-day landmark period were excluded (Fig. 1). The resulting survival distributions, along with the corresponding log-rank tests, are presented in Fig. 4.

With atherosclerosis in one vascular bed considered as the baseline, the HRs for all-cause death, MACE, MALE, and major bleeding in patients with two vascular beds affected were 1.59 (95% CI 1.52–1.67), 1.88 (95% CI 1.73–2.05), 2.63 (95% CI 2.46–2.80), and 1.59 (95% CI 1.29–1.96), respectively. For patients with three vascular beds affected, the HRs were 1.93 (95% CI 1.62–2.29), 3.05 (95% CI 2.33–3.99), 4.66 (95% CI 3.81–5.70), and 2.77 (95% CI 1.49–5.17), respectively.

Adjusted for age, sex, diabetes, arterial hypertension, dyslipidaemia, heart failure, atrial fibrillation, CKD, cancer, COPD, dementia, depression, the Charlson Comorbidity Index score, and prescribed antithrombotic and lipid-lowering medication the HRs for all-cause death, MACE, MALE, and major bleeding were 1.24 (95% CI 1.09–1.42), 1.51 (95% CI 1.24–1.83), 2.52 (95% CI 2.08–3.05), and 1.27 (95% CI 1.05–1.54) for patients with two vascular beds involved. In patients with ASCVD in three vascular beds, the HRs were 1.69 (95% CI 1.40–2.03), 2.70 (95% CI 2.23–3.28), 4.24 (95% CI 3.49–5.14), and 2.31 (95% CI 1.45–3.68), respectively. The Supplementary Materials include the full results of the main analysis along with the sensitivity analysis using IPTWs, both yielding similar findings.

Discussion

Patients with established PVD experienced significantly poorer outcomes compared to patients in whom only one vascular bed was affected. The results showed a proportional increase in event rates with each additional vascular bed involved. These findings persisted even when adjusting for traditional cardiovascular risk factors, other comorbidities, and medication, indicating that PVD itself is an independent predictor of all-cause death, MACE, and MALE, as well as major bleeding events.

Our findings align with previously published results, where a similar stepwise increase in adverse event rates was observed with the involvement of multiple vascular beds.[1–4,17] The observed proportional increase can likely be attributed to the fact that the presence of atherosclerosis in multiple vascular beds reflects a more widespread disease process, potentiating outcomes across all affected vascular beds. While atherosclerotic disease in a given vascular bed is most strongly associated with its respective endpoint, the presence of

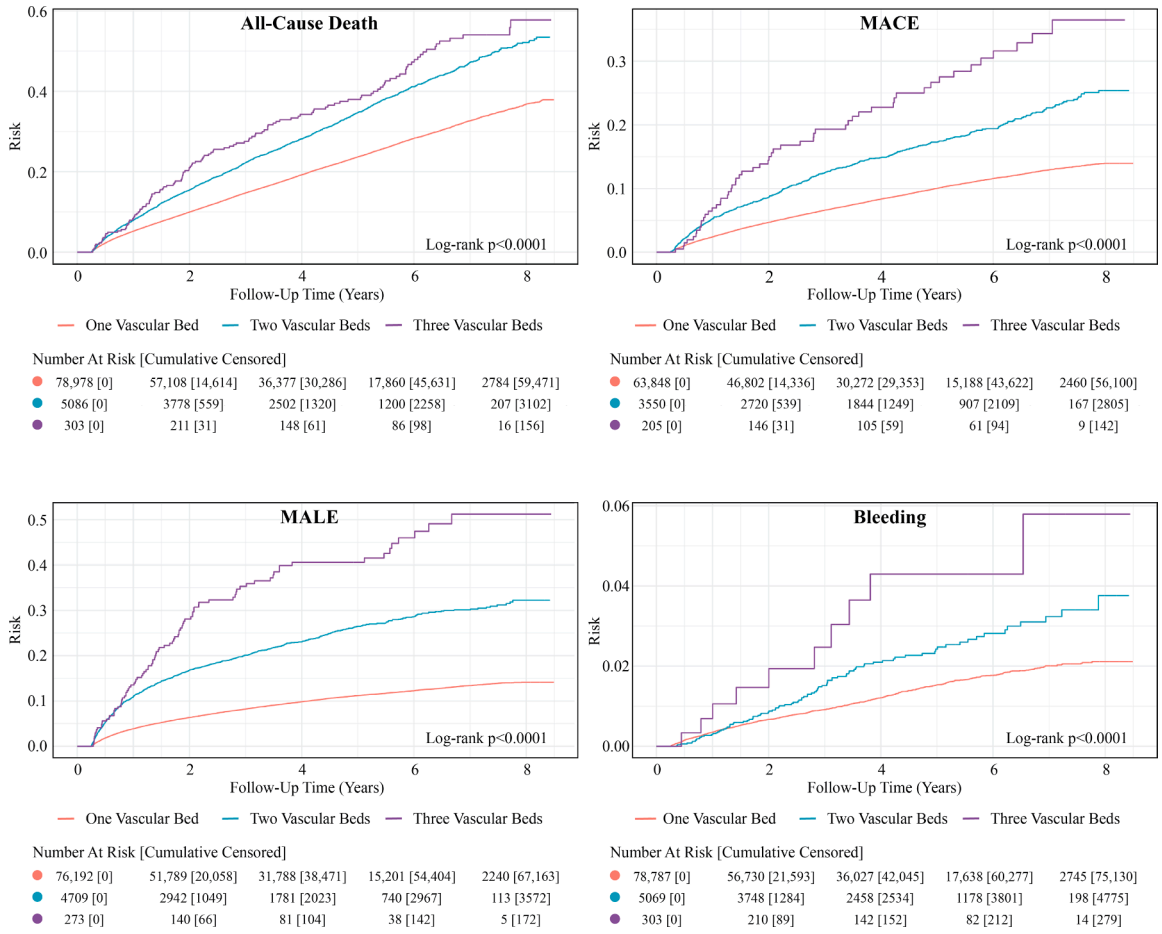

Fig. 4: Cause-specific Kaplan–Meier curves for the four observed outcomes, stratified by the number of vascular beds involved. MALE, major adverse limb events; MACE, major adverse cardiovascular event. Note the y axes are truncated for clarity. A landmark of 90 days was considered.

atherosclerosis itself also significantly elevates the risk of events in other vascular beds.[18] This indicates a systemic disease process that transcends individual anatomical sites. This is particularly true in patients with lower extremity PAD, which has been consistently linked to the highest rates of adverse limb events, MACE and all-cause death.[7,8,19–23] In our cohort, 24.2% (4332 of 17,903) of patients with lower extremity PAD had confirmed atherosclerosis in at least one additional vascular bed, compared to only 16.9% (4109 of 24,350) of patients with CVD, and 7.7% (4323 of 56,214) of patients with CAD. Patients who had PVD were also more likely to have been hospitalised with lower extremity PAD as the primary diagnosis, indicating that lower extremity PAD is more strongly associated with PVD than atherosclerosis in other vascular beds.

Although there is still no evidence that screening for PVD improves patient outcomes, recent research highlights potential treatment implications of identifying atherosclerosis in additional vascular beds.[7,10,11] As intense antithrombotic treatment in PVD has been shown to offer a similar relative risk reduction for ischaemic events as seen in patients without PVD, this translates to a greater absolute risk reduction in this high-risk population.[24] However, the potential benefits must be carefully weighed against the significantly increased bleeding risk associated with the routine use of antiplatelet agents or low-dose anticoagulants. Our study is the first to demonstrate that patients with PVD are at an increased bleeding risk, even after adjusting for cardiovascular risk factors, comorbidities, and medication. Our sensitivity analysis, which adjusted for differences in group sizes, confirms these findings. This highlights the importance of carefully tailoring antithrombotic strategies to individual patients. While previous research has shown that patients with PVD have a higher bleeding risk compared to patients with monovascular disease,[7,25] findings remained inconclusive when adjusting for factors such as comorbidities.[7,25,26] This may be

attributed to low absolute event rates and comparatively smaller sample sizes in prior studies.

Besides antithrombotic medication, aggressive lipid-lowering strategies are a key approach in reducing adverse outcomes in ASCVD. Current guidelines categorise all patients with established clinically relevant ASCVD as high-risk and thus give little specific treatment recommendations for patients with PVD as even patients with monovascular disease should be aggressively treated to prevent progression to PVD in the first place.[13,27] Intensive lipid-lowering treatment (including ezetimibe and PCSK-9 inhibitors) has been shown to confer comparable benefits in patients with PVD compared to monovascular disease,[28] despite statins being less effective in reducing atherosclerotic plaques in PVD patients.[29] Our data shows that patients with PVD were more likely to be prescribed lipid-lowering therapy, which is consistent with previous research[18] and suggests that prevention efforts are generally more focused on high-risk patients.

In our study, 6.8% of patients had PVD, which likely underestimates the actual prevalence. Multiple large studies on registry data based on extensive vascular diagnostic work-up have found the prevalence of PVD in patients with established ASCVD to be between 12.8 and 20.1%; however, the selected patient populations vary greatly, making direct comparisons between studies difficult. For instance, the CRUSADE registry only included patients after NSTEMI,[17] while the REACH[30] and SMART registries[1] enrolled not only patients with established atherosclerosis but also patients with ASCVD risk factors. Furthermore, the SMART registry also included abdominal aortic aneurysms, which were not considered in this study. On the other hand, we observed a steady decline in both the hospitalisation rates for ASCVD and the proportion of patients with PVD. The proportion of patients with PVD declined from 12% at the beginning of the observation period (i.e., comparable to the registry-based data available from studies carried out before 2015) to 4% at the end in 2023, possibly reflecting broader trends in decreasing ASCVD throughout Europe.[31]

In the multivariate logistic regression model, male sex, age, dyslipidaemia, hypertension, diabetes, and CKD were all predictors of PVD, which is in line with previous findings.[9] As our dataset lacked reliable information on prior or current tobacco use, we included COPD as a surrogate indicator of smoking exposure. As expected, COPD emerged as one of the three strongest predictors of PVD. However, it should be noted that COPD is not merely a proxy for tobacco use but is also independently associated with increased cardiovascular risk.[32] In the Cox proportional hazards model, traditional cardiovascular risk factors and comorbidities were also independently associated with higher adverse event rates, although not all reached significance. Interestingly, hypertension was not associated with all-cause death, MACE or major bleeding, while it appeared to be inversely associated with MALE. This counterintuitive finding may be explained by the blood pressure J-curve phenomenon, whereby both high and low (particularly diastolic) blood pressures are associated with increased adverse outcomes, while moderately elevated levels may confer a protective effect in certain patient populations.[33,34] The strong association between traditional cardiovascular risk factors and both PVD and adverse outcomes highlights the importance of targeted risk modification.

The current study has some limitations, mainly due to the nature of the administrative claims data, which was used. While the dataset used in this study has previously been assessed for quality using measures of conformance, completeness, and plausibility, and has demonstrated high data quality,[15] underreporting of diagnoses and events cannot be excluded. As a consequence, atherosclerosis of all vascular beds (i.e. aorta, splanchnic, etc.) was purposefully not included in the analysis as coding for these diagnoses is often inconsistent. Similarly, broad ICD-10 codes such as I24.x (other acute ischaemic heart diseases), I73.89 (other specified peripheral vascular diseases), I73.9 (peripheral vascular disease, unspecified), or I74.x (arterial embolism and thrombosis) were not considered, as they do not necessarily reflect atherosclerotic disease and may introduce heterogeneity in capturing embolic, vasospastic, or non-vascular pathologies. This pragmatic, selective approach to defining leading diagnoses may lead to an underestimation of PVD in patients with established atherosclerosis, somewhat limiting the absolute number of identified patients, particularly those with ASCVD in three vascular beds. Nonetheless, PVD remained an independent predictor of adverse events even after adjusting for group size, comorbidities, and prescribed medication, as was done in the sensitivity analysis.

Furthermore, we did not distinguish between symptomatic and asymptomatic atherosclerotic disease as these data were not available. While the primary diagnosis at hospitalisation was likely due to symptomatic ASCVD, the presence of atherosclerosis in secondary and tertiary vascular beds may have been detected incidentally through screening and could therefore have been asymptomatic. The lack of other clinical and laboratory data such as haemodynamic stability, haemoglobin levels, and transfusion requirements also meant a standardised major bleeding definition could not be applied. Instead, we defined major bleeding as hospitalisation due to gastrointestinal or intracranial bleeding, as these events can reliably be identified through ICD-10 codes.

A further limitation was that our data enabled us to consider only subsequent hospitalisations based on the primary diagnosis, meaning that patients, who were hospitalised for different causes, may have experienced one of the observed adverse events during

hospitalisation (excluding death), but this was not reflected in the data. All these factors increase the likelihood of a type II error. Finally, although Slovenia has a relatively small population, the inclusion of all hospitalised adult patients nationwide ensures comprehensive representation, provides adequate statistical power, and enables estimation of event rates with a high level of certainty.

In conclusion, this study provides important insights into the burden, determinants, and prognosis of PVD in patients hospitalised for ASCVD in Slovenia. As the number of affected vascular beds increases, patients face a stepwise increase in ischaemic event rates and mortality. Notably, patients with PVD also face a significantly increased risk of major bleeding. A strong focus must therefore be put on preventing the progression from monovascular atherosclerosis to PVD. While the benefits of aggressive lipid-lowering therapy are well-established, the use of intensive antithrombotic regimens remains uncertain due to their increased bleeding risk, which is particularly concerning in patients with PVD. The high absolute disease burden underscores the need for comprehensive risk management and an individualised treatment approach. Further research is needed to define optimal treatment approaches and evaluate the benefits of PVD screening in high-risk populations. Addressing these gaps in evidence is crucial in reducing the overall disease burden and improving long-term outcomes.

Contributors

B. J. was responsible for the initial conceptualisation of the study with the final study design being developed by K. P., B. J., and P. D. B. The data was collected by B. J., D. G., and P. D. B. The authors K. P., B. J., and P. D. B. have access to and have verified the underlying study data. Data analysis was performed by B. J. and K. P. The original draft of the manuscript was written by K. P. and subsequently reviewed and revised by T. F., V. B., B. J., D. G., and P. D. B., who contributed to all of its sections. All authors have read and approved the final version of the manuscript.

Data sharing statement

The underlying data used for this article were provided by Healthcare Insurance Institute of Slovenia. Restrictions apply to the availability of the data, which were used under licence for this study and can only be shared upon reasonable request to the corresponding author with permission of Healthcare Insurance Institute of Slovenia.

Declaration of interests

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103542.

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