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# Impact of extracardiac vascular disease on outcomes of 1.4 million patients undergoing percutaneous coronary intervention

Hussein Bashar[1,2,3] | Andrija Matetić[3,4] | Nick Curzen[1,2] | Mamas A. Mamas[3]

[1]Faculty of Medicine, University of Southampton, Southampton, UK

[2]Coronary Research Group, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[3]Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, Keele, UK

[4]Department of Cardiology, University Hospital of Split, Split, Croatia

**Correspondence**
Mamas A. Mamas, Professor of Cardiology, Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, UK.
Email: mamasmamas1@yahoo.co.uk

## Abstract

**Objectives:** Extracardiac vascular disease (ECVD) is increasingly recognized as a cardiovascular risk factor, but its association with outcomes after percutaneous coronary intervention (PCI) has not been well characterized.

**Methods:** Using the National Inpatient Sample database, all patients undergoing PCI between October 2015 and December 2018 were stratified by the presence and organ-specific extent of extracardiac vascular comorbidity (cerebrovascular disease (CeVD), renovascular, aortic and peripheral arterial disease (PAD)). Primary outcome was all-cause mortality and secondary outcomes were (a) major adverse cardiovascular and cerebrovascular events (MACCE), (b) acute ischemic stroke and (c) major bleeding. Multivariable logistic regression was used to determine the adjusted odds ratios (aOR) and 95% confidence interval (95% CI).

**Results:** Of a total of 1,403,505 patients undergoing PCI during the study period, 199,470 (14.2%) had ECVD. Patients with ECVD were older (median of 72 years vs. 70 years, $p < 0.001$) and had higher comorbidity burden that their counterparts. All cause-mortality was 22% higher in patients with any ECVD compared to those without ECVD. PAD patients had the highest odds of all-cause mortality (aOR 1.48, 95% CI 1.40–1.56), followed by those with CeVD (aOR 1.15, 95% CI 1.10–1.19). Patients with extracardiac disease had increased odds of MACCE, ischemic stroke and bleeding, irrespective of the nature or extent ($p < 0.05$), compared to patients without ECVD.

**Conclusion:** ECVD is associated with worse outcomes in patients undergoing PCI including significantly higher rates of death and stroke. These data should inform our shared decision-making process with our patients.

KEYWORDS
cerebrovascular, mortality, PAD, PCI, renovascular, stroke

## 1 | INTRODUCTION

Patients with coronary artery disease often have atherosclerosis in other vascular beds, given the common pathophysiology and risk profile. Extracardiac vascular disease (ECVD) can contribute to increased morbidity and technical challenges for diagnosis and treatment of patients with coronary disease, especially those being considered for revascularisation because of factors including: vascular access, renal function, frailty and neurologic sequelae. Previous studies have investigated the association of extracardiac atherosclerosis disease and outcomes after acute myocardial infarction (MI),[1–3] including in PCI cohorts.[4–11] Further, polyvascular disease (i.e., involvement of two or more vascular beds) has been associated with higher long-term mortality in patients undergoing PCI.[8,9,11] However, these studies do not reflect contemporary practice and do not consider whether there is a differential impact according to the vascular bed involved.[8,11]

From the point of view of the vascular bed affected by ECVD, results are variable. Specifically, several studies demonstrate an association between peripheral arterial disease to increased short- and long-term mortality and adverse cardiovascular outcomes in PCI patients (38% increase in-hospital mortality risk in a recent study).[5–7,10] Other studies have described a similar association with cerebrovascular disease in patients undergoing PCI, although the results are inconsistent.[4,12] Aortic atherosclerosis has been implicated in PCI-related stroke but such association with other clinical outcomes is limited.[13,14] On the other hand, limited data suggested that renovascular disease could be indirectly linked to major adverse cardiovascular events after PCI.[15]

To our knowledge, there has been no prior literature that has comprehensively compared different vascular bed types to PCI outcomes in a single study. The aim of this study is to investigate the association between the presence and extent of ECVD and in-hospital outcomes in a large contemporary US population of PCI patients.

## 2 | METHODS

### 2.1 | National inpatient sample database

Sponsored by the Agency for Healthcare Research and Quality (AHRQ), the Healthcare Cost and Utilization Project (HCUP) developed a number of databases including the National Inpatient Sample, which is the largest publicly available inpatient healthcare database that contains the data for more than 7 million hospitalization episodes each year unweighted (35 million per year weighted). This study uses discharge data from the National Inpatient Sample (NIS).[16] The NIS is derived from all the states participating in HCUP and covers more than 97% of the US population. It does not include rehabilitation and long-term acute care hospitals, and it estimates a 20% stratified sample of discharges from community hospitals.

### 2.2 | Study sample

All hospitalizations with a discharge record of PCI in the period of October 2015 to December 2018 (inclusive) were detected and stratified by the presence of ECVD as defined by (i) cerebrovascular disease, (ii) renovascular disease, (iii) aortic disease and (iv) peripheral arterial disease (PAD). The sample was further stratified based on the presence of ECVD and its extent (labeled as: one, two, or three or more extracardiac vascular beds). Finally, a sensitivity analysis was conducted based on the indication for PCI (i.e., ST-elevation myocardial infarction [STEMI], non-ST-elevation acute coronary syndrome [NSTE-ACS], chronic coronary syndrome [CCS]).

All diagnoses and procedures were detected using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. A full list of ICD-10 codes used to identify morbidities and vascular disease beds including cerebrovascular (CVD), renovascular, aortic, and peripheral arterial disease (PAD) can be found in Table SI. A coronary vascular disease category was not used as all records in this study had PCI. Records with age less than 18 years, in addition to those with missing data, were excluded from the study (4115 cases − 0.3%) (Figure SI, study flow diagram).

### 2.3 | Outcomes

The primary clinical outcome of this analysis was all-cause in hospital mortality. Secondary clinical outcomes were (a) acute ischemic stroke, (b) major adverse cardiovascular and cerebrovascular events (MACCE; composite of all-cause mortality, acute ischemic stroke and reinfarction), and (c) major bleeding (defined as nontraumatic intracranial hemorrhage, haematemesis, melaena, gastrointestinal hemorrhage, and unspecified hemorrhage). Other outcomes of interest included were the length of stay and total charges.

### 2.4 | Statistical analysis

IBM SPSS statistics software version 25 was used for analysing the database. Total discharges were estimated using sample weighting as recommended by HCUP. Qualitative data are presented as percentages, while quantitative data are presented as median and interquartile range. Pearson's Chi-square or the Kruskal–Wallis test are used to compare the variables as appropriate. The association of the presence, number and type of vascular disease and outcomes were inspected using multivariable binomial logistic regression models adjusted for: age, sex, weekend admission, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dementia, diabetes, dyslipidemia, smoking, heart failure, atrial fibrillation/flutter, thrombocytopaenia, hypertension, anemia, chronic lung disease, coagulopathy, liver disease, chronic kidney disease (CKD), metastatic disease, valvular heart disease, cardiogenic shock, ventricular tachycardia (VT), ventricular fibrillation (VF), PCI indication, previous myocardial infarction, previous PCI, and previous

coronary artery bypass grafting. These are expressed as adjusted odds ratios (aOR) with their associated 95% confidence intervals (95% CI).

## 3 | RESULTS

Of the 1,403,505 PCI procedures analyzed in the study, 14.2% had concomitant ECVD. Isolated CeVD was the most common (7.8%), followed by PAD (3.0%), aortic disease (1.7%), and renovascular disease (0.3%) (Table 1). Cases with single extracardiac vascular bed involvement accounted for the majority (90.6%), followed by those with two diseased extracardiac vascular beds (8.7%), and those with three or more affected extracardiac circulatory areas (0.6%) (Table 2).

### 3.1 | Baseline characteristics

Baseline clinical characteristic are summarized in Tables 1–2 and S2. The presence of any degree of ECVD was associated with a higher proportion of older patients (median of 70 years vs. 64 years, $p < 0.001$), female patients (38.9% vs 32.1%, $p < 0.001$), presentation with NSTE-ACS and CCS (45.5% vs. 40.4%, $p < 0.001$% and 36% vs. 27%, $p < 0.001$) (Table SII). In addition, this group had higher prevalence of heart failure (40.5% vs. 25.3%, $p < 0.001$), valvular disease (13.4% vs 7.6%, $p < 0.001$), atrial fibrillation/flutter (23.8% vs. 14.7%, $p < 0.001$), diabetes (56% vs. 38%, $p < 0.001$), dyslipidaemia (78% vs. 70.7%, $p < 0.001$), chronic lung disease (28.3% vs. 17.9%, $p < 0.001$), anemia (22.3% vs. 12.3%, $p < 0.001$), thrombocytopaenia (4.4% vs. 3%, $p < 0.001$), coagulopathy (5.9% vs. 4.1%, $p < 0.001$) and CKD (33.2% vs. 16.9%, $p < 0.001$) when compared to those with no ECVD.

Those with known CeVD had the highest prevalence of hypertension (49.7% vs. 31.9%-47.4%, $p < 0.001$), dyslipidaemia (78.7% vs. 74.9%–76.1%, $p < 0.001$), and dementia (5.4% vs. 3.1%–3.6%, $p < 0.001$) while those with identified renovascular disease had the highest prevalence of CKD (49.3% vs. 26%–42%, $p < 0.001$) compared to other extracardiac vascular groups. Heart failure (49.4% vs. 35.5%–48.5%, $p < 0.001$), diabetes (85.3% vs. 31.5%–48.9%, $p < 0.001$), and anemia (29.6% vs. 18.6%–27.2%, $p < 0.001$) were most prevalent in patients with diagnosed PAD. Meanwhile, aortic disease patients had the highest burden of comorbidities like valvular heart disease (17.6% vs. 11%–16.5%, $p < 0.001$), atrial fibrillation/flutter (24.6% vs. 22.1%–23.8%, $p < 0.001$), chronic lung disease (31.5% vs. 26.1%–29.1%, $p < 0.001$), thrombocytopaenia (5.7% vs. 3.5%–5.2%, $p < 0.001$), coagulopathy (7.3% vs. 5%–7%, $p < 0.001$), and chronic liver disease (3.2% vs. 1.9%–2.7%, $p < 0.001$) in comparison to other extracardiac vascular groups (Table 1).

Patients with isolated single extracardiac vascular bed involvement were generally older (median of 70 years vs. 64 years, $p < 0.001$), had more female patients (38.7% vs. 32.1%, $p < 0.001$), and were more likely to present with NSTE-ACS and CCS (45.2% vs. 40.4%, $p < 0.001$, and 35.7% vs. 27%, $p < 0.001$, respectively), than patients without ECVD. Patients with isolated single extracardiac vascular bed involvement generally had higher comorbidity burden, including higher prevalence of heart failure (39.7% vs. 25.3%, $p < 0.001$), valvular heart disease (13% vs. 7.6%, $p < 0.001$), atrial fibrillation/flutter (23.5% vs. 14.7%, $p < 0.001$), diabetes (54.9% vs. 38%, $p < 0.001$), dyslipidaemia (77.6% vs. 70.7%, $p < 0.001$), chronic lung disease (27.6% vs. 17.9%, $p < 0.001$), anemia (21.6% vs. 12.3%, $p < 0.001$), thrombocytopaenia (4.2% vs. 3%, $p < 0.001$), coagulopathy (5.8% vs. 4.1%, $p < 0.001$), dementia (4.5% vs. 2%, $p < 0.001$), chronic liver disease (2.3% vs. 1.8%, $p < 0.001$) and CKD (32.1% vs. 16.9%, $p < 0.001$) (Table 2).

In patients with two or more involved vascular beds, there was an increased prevalence of older patients (median of 72 years vs. 70 years, $p < 0.001$), female patients (40.9%–41.9% vs. 38.7%, $p < 0.001$), presentation for NSTE-ACS (48.1%–53.4% vs. 45.2%, $p < 0.001$), and the prevalence of comorbidities such as heart failure (48.1%–48.2% vs. 39.7%, $p < 0.001$), valvular heart disease (17%–17.2% vs. 13%, $p < 0.001$), atrial fibrillation/flutter (25.3%–26.3% vs. 23.5%, $p < 0.001$), diabetes (59.3%–67.6% vs. 54.9%, $p < 0.001$), dyslipidaemia (79.4%–82.6% vs. 77.6%, $p < 0.001$), chronic lung disease (34.3%–45.5% vs. 27.6%, $p < 0.001$), anemia (28.9%–36% vs. 21.6%, $p < 0.001$), thrombocytopaenia (5.7%–6.7% vs. 4.2%, $p < 0.001$), coagulopathy (7.2%–9.1% vs. 5.8%, $p < 0.001$), and CKD (41.5%–43.9% vs 32.1%, $p < 0.001$) compared to those with single ECVD (Table 2).

### 3.2 | Clinical outcomes based on extracardiac vascular involvement

ECVD was independently associated with increased risk of mortality (aOR 1.22, 95% CI 1.18–1.26), MACCE (aOR 1.44, 95% CI 1.41–1.47), acute ischemic stroke (aOR 2.23, 95% CI 2.15–2.32), and major bleeding (aOR 1.17, 95% CI 1.13–1.21) after adjusting for the baseline characteristics (Table SIII) compared with those with no ECVD. In addition, those with ECVD had longer hospital stay (median of 3–5 days vs. 2 days, $p < 0.001$) and higher total charges (median of $91,167–181,263 vs. $81,263, <0.001).

### 3.3 | Clinical outcomes based on organ of extracardiac vascular bed involvement

When comparing the crude rates of clinical outcomes among patient with single extracardiac bed involvement, patients with PAD had the highest rates of mortality and MACCE (4.9% and 6.7%, respectively). Acute ischemic stroke was highest in the CeVD group (2.5%) while major bleeding occurred more frequently in those with renovascular disease (3.3%) (Table SIV and Figure 1).

After adjusting for the baseline characteristics and in contrast to those with no ECVD, PAD patients had the highest odds of all-cause

**TABLE 1** Characteristics of patients with one extracardiac vascular bed involvement (stratified by involved organ site)

| Characteristics | No extracardiac vascular disease (*N* = 1,204,035; 85.8%) | One extracardiac vascular bed involvement (*N* = 180,805; 12.9%) | | | | *p*-value |
|---|---|---|---|---|---|---|
| | | Cerebrovascular disease (*N* = 110,040; 7.8%) | Renovascular disease (*N* = 4120; 0.3%) | Aortic disease (*N* = 24,265; 1.7%) | Peripheral artery disease (*N* = 42,380; 3.0%) | |
| Age (years), median (IQR) | 64 (56–73) | 71 (62–79) | 73 (64–80) | 72 (65–79) | 68 (60–75) | <0.001 |
| Females, % | 32.1 | 41.2 | 56.4 | 29.7 | 35.5 | <0.001 |
| Ethnicity, % | | | | | | <0.001 |
| White | 76.3 | 76.7 | 81.1 | 80.8 | 69.8 | |
| Black | 9.8 | 11.4 | 9.8 | 6.3 | 14.2 | |
| Hispanic | 7.4 | 6.7 | 5.1 | 6.6 | 9.7 | |
| Asian/Pacific Islander | 2.5 | 1.9 | 1.8 | 3.4 | 1.9 | |
| Native American | 0.5 | 0.5 | 0.5 | 0.5 | 0.7 | |
| Other | 3.5 | 2.8 | 1.8 | 2.4 | 3.7 | |
| Indication type, % | | | | | | <0.001 |
| STEMI | 32.6 | 19.3 | 15.4 | 22.6 | 17.0 | |
| NSTE-ACS | 40.4 | 44.7 | 47.6 | 45.0 | 46.5 | |
| CCS | 27.0 | 36.0 | 37.0 | 32.4 | 36.5 | |
| Cardiac arrest | 3.0 | 2.3 | 2.4 | 3.1 | 3.6 | <0.001 |
| Ventricular fibrillation | 3.9 | 2.6 | 2.1 | 3.5 | 3.7 | <0.001 |
| Ventricular tachycardia | 7.5 | 6.4 | 7.4 | 8.1 | 8.1 | <0.001 |
| Cardiogenic shock | 5.6 | 4.6 | 6.8 | 6.6 | 8.3 | <0.001 |
| Comorbidities, % | | | | | | |
| Heart failure | 25.3 | 36.6 | 48.5 | 35.5 | 49.4 | <0.001 |
| Valvular disease | 7.6 | 12.6 | 16.5 | 17.6 | 11.0 | <0.001 |
| Atrial fibrillation/flutter | 14.7 | 23.8 | 22.1 | 24.6 | 22.4 | <0.001 |
| Hypertension | 53.5 | 49.7 | 31.9 | 47.4 | 33.1 | <0.001 |
| Diabetes | 38.0 | 48.9 | 40.4 | 31.5 | 85.3 | <0.001 |
| Dyslipidaemia | 70.7 | 78.7 | 75.7 | 74.9 | 76.1 | <0.001 |
| Smoking | 2.2 | 1.6 | 2.8 | 1.7 | 1.4 | <0.001 |
| Chronic lung disease | 17.9 | 26.1 | 29.1 | 31.5 | 29.1 | <0.001 |
| Anemia | 12.3 | 19.0 | 27.2 | 18.6 | 29.6 | <0.001 |
| Thrombocytopaenia | 3.0 | 3.5 | 4.0 | 5.7 | 5.2 | <0.001 |
| Coagulopathy | 4.1 | 5.0 | 5.6 | 7.3 | 7.0 | <0.001 |
| Dementia | 2.0 | 5.4 | 3.6 | 3.3 | 3.1 | <0.001 |
| Chronic liver disease | 1.8 | 1.9 | 1.9 | 3.2 | 2.7 | <0.001 |
| Chronic kidney disease | 16.9 | 29.1 | 49.3 | 26.0 | 42.0 | <0.001 |
| Homelessness | 0.2 | 0.2 | 0.2 | 0.1 | 0.2 | <0.001 |
| Metastatic cancer | 0.5 | 0.5 | 0.7 | 0.9 | 0.5 | <0.001 |

Abbreviations: CCS, chronic coronary syndrome; IQR, interquartile range; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

**TABLE 2** Patient characteristics stratified by extracardiac vascular bed involvement

| Characteristics | No extracardiac vascular involvement (*N* = 1,204,035; 85.8%) | Extracardiac vascular involvement (*N* = 199,470; 14.2%) | | | *p*-value |
|---|---|---|---|---|---|
| | | One vascular bed (*N* = 180,805; 12.9%) | Two vascular beds (*N* = 17,400; 1.2%) | Three or more vascular beds (*N* = 1265; 0.1%) | |
| Age (years), median (IQR) | 64 (56–73) | 70 (62–78) | 72 (65–79) | 72 (67–78) | <0.001 |
| Females, % | 32.1 | 38.7 | 40.9 | 41.9 | <0.001 |
| Ethnicity, % | | | | | <0.001 |
| White | 76.3 | 75.7 | 77.2 | 81.6 | |
| Black | 9.8 | 11.3 | 10.4 | 8.6 | |
| Hispanic | 7.4 | 7.4 | 6.7 | 7.4 | |
| Asian/Pacific Islander | 2.5 | 2.1 | 2.1 | 1.6 | |
| Native American | 0.5 | 0.5 | 0.8 | 0.4 | |
| Other | 3.5 | 2.9 | 2.8 | 0.4 | |
| Indication type, % | | | | | <0.001 |
| STEMI | 32.6 | 19.1 | 12.3 | 11.1 | |
| NSTE-ACS | 40.4 | 45.2 | 48.1 | 53.4 | |
| CCS | 27.0 | 35.7 | 39.6 | 35.6 | |
| Cardiac arrest | 3.0 | 2.7 | 2.3 | 4.3 | <0.001 |
| Ventricular fibrillation | 3.9 | 3.0 | 2.6 | 3.2 | <0.001 |
| Ventricular tachycardia | 7.5 | 7.1 | 7.2 | 7.1 | <0.001 |
| Cardiogenic shock | 5.6 | 5.8 | 5.7 | 5.5 | <0.001 |
| Comorbidities, % | | | | | |
| Heart failure | 25.3 | 39.7 | 48.1 | 48.2 | <0.001 |
| Valvular disease | 7.6 | 13.0 | 17.2 | 17.0 | <0.001 |
| Atrial fibrillation/flutter | 14.7 | 23.5 | 26.3 | 25.3 | <0.001 |
| Hypertension | 53.5 | 45.1 | 35.3 | 34.4 | <0.001 |
| Diabetes | 38.0 | 54.9 | 67.6 | 59.3 | <0.001 |
| Dyslipidemia | 70.7 | 77.6 | 82.6 | 79.4 | <0.001 |
| Smoking | 2.2 | 1.6 | 0.9 | 2.4 | <0.001 |
| Chronic lung disease | 17.9 | 27.6 | 34.3 | 45.5 | <0.001 |
| Anemia | 12.3 | 21.6 | 28.9 | 36.0 | <0.001 |
| Thrombocytopenia | 3.0 | 4.2 | 5.7 | 6.7 | <0.001 |
| Coagulopathy | 4.1 | 5.8 | 7.2 | 9.1 | <0.001 |
| Dementia | 2.0 | 4.5 | 4.7 | 4.0 | <0.001 |
| Chronic liver disease | 1.8 | 2.3 | 2.6 | 3.6 | <0.001 |
| Chronic kidney disease | 16.9 | 32.1 | 43.9 | 41.5 | <0.001 |
| Homelessness | 0.2 | 0.2 | 0.3 | 0 | 0.001 |
| Metastatic cancer | 0.5 | 0.5 | 0.5 | 1.2 | 0.002 |

Abbreviations: CCS, chronic coronary syndrome; IQR, interquartile range; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

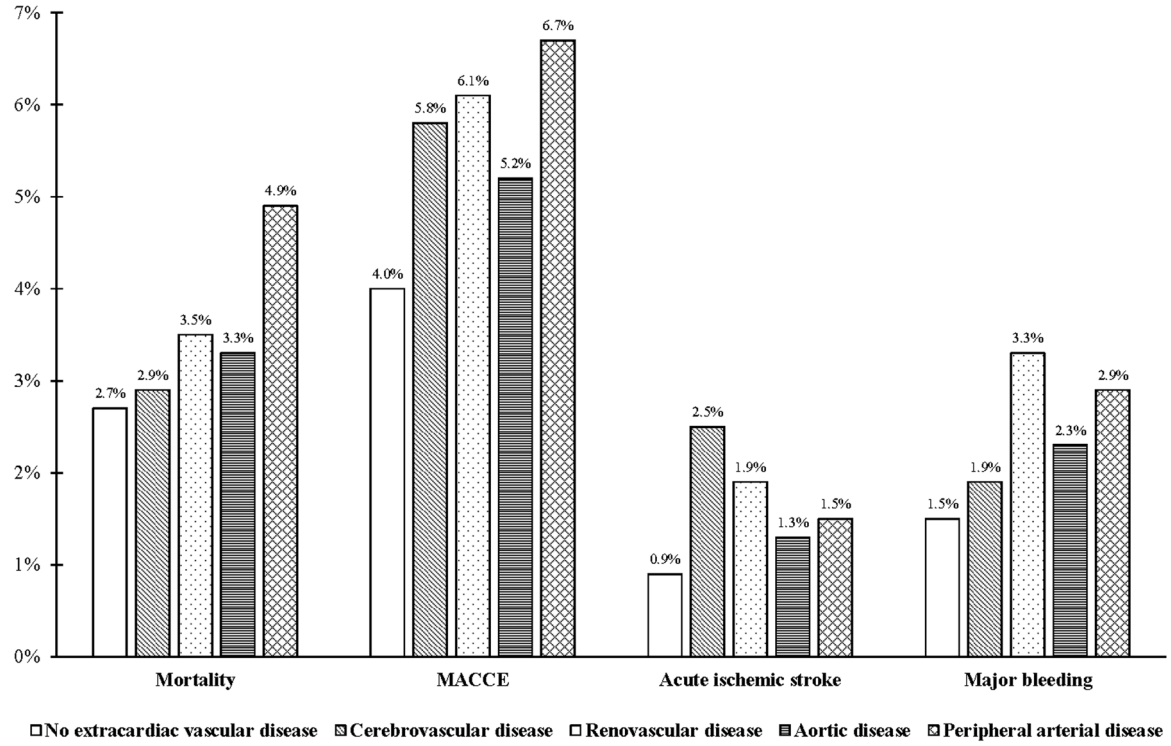


**FIGURE 1** In-hospital clinical outcomes in group with one extracardiac vascular bed involvement (stratified by involved organ site). MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke, and reinfarction).

**TABLE 3** Adjusted odds ratios (aOR) of in-hospital clinical outcomes in patients with one extracardiac vascular bed involvement (stratified by involved organ site)

| Clinical outcomes | Cerebrovascular disease | | Renovascular disease | | Aortic disease | | Peripheral artery disease | |
|---|---|---|---|---|---|---|---|---|
| | aOR [95% CI] | *p*-value | aOR [95% CI] | *p*-value | aOR [95% CI] | *p*-value | aOR [95% CI] | *p*-value |
| Mortality | 1.15 [1.10–1.19] | <0.001 | 1.09 [0.91–1.32] | 0.340 | 0.95 [0.87–1.03] | 0.212 | 1.48 [1.40–1.56] | <0.001 |
| MACCE | 1.54 [1.50–1.59] | <0.001 | 1.30 [1.13–1.49] | <0.001 | 1.09 [1.02–1.16] | 0.010 | 1.34 [1.28–1.40] | <0.001 |
| Acute ischemic stroke | 2.79 [2.67–2.91] | <0.001 | 1.87 [1.49–2.34] | <0.001 | 1.32 [1.18–1.48] | <0.001 | 1.35 [1.24–1.47] | <0.001 |
| Major bleeding | 1.11 [1.05–1.16] | <0.001 | 1.57 [1.31–1.87] | <0.001 | 1.14 [1.04–1.24] | 0.005 | 1.28 [1.21–1.36] | <0.001 |

*Note*: Multivariable analysis – the following variables were adjusted for: age, sex, weekend admission, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dementia, diabetes, dyslipidaemia, smoking, heart failure, atrial fibrillation/flutter, thrombocytopaenia, hypertension, anemia, chronic lung disease, coagulopathy, liver disease, chronic kidney disease, metastatic disease, valvular heart disease, cardiogenic shock, VT, VF, PCI indication, previous myocardial infarction, previous PCI, and previous coronary artery bypass grafting.

Abbreviations: aOR, adjusted odds ratios; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke, and reinfarction).

*Reference group: group with no extracardiac vascular involvement.

mortality (aOR 1.48, 95% CI 1.40–1.56), followed by those with CeVD (aOR 1.15, 95% CI 1.10–1.19) (Table 3 and Figure 2). Likewise, CeVD and PAD patients had the highest likelihood of MACCE (aOR 1.54, 95% CI 1.50–1.59; aOR 1.34, 95% CI 1.28–1.40, respectively). Not surprisingly, patients with CeVD, were more than twice likely to suffer an acute ischemic stroke (aOR 2.79, 95% CI 2.67–2.91) followed by those with renovascular disease (aOR 1.87, 95% CI 1.49–2.34). The odds of having major bleeding were similarly the highest in the renovascular disease group (aOR 1.57, 95% CI 1.31–1.87) and followed by those with the PAD (aOR 1.28, 95% CI 1.21–1.36) (Table 3).

## 3.4 | Clinical outcomes based on number of extracardiac vascular bed involvement

Patients with single ECVD had higher rates of all-cause mortality (3.4% vs. 2.7%, $p < 0.001$), MACCE (5.9% vs. 4%, $p < 0.001$), ischemic

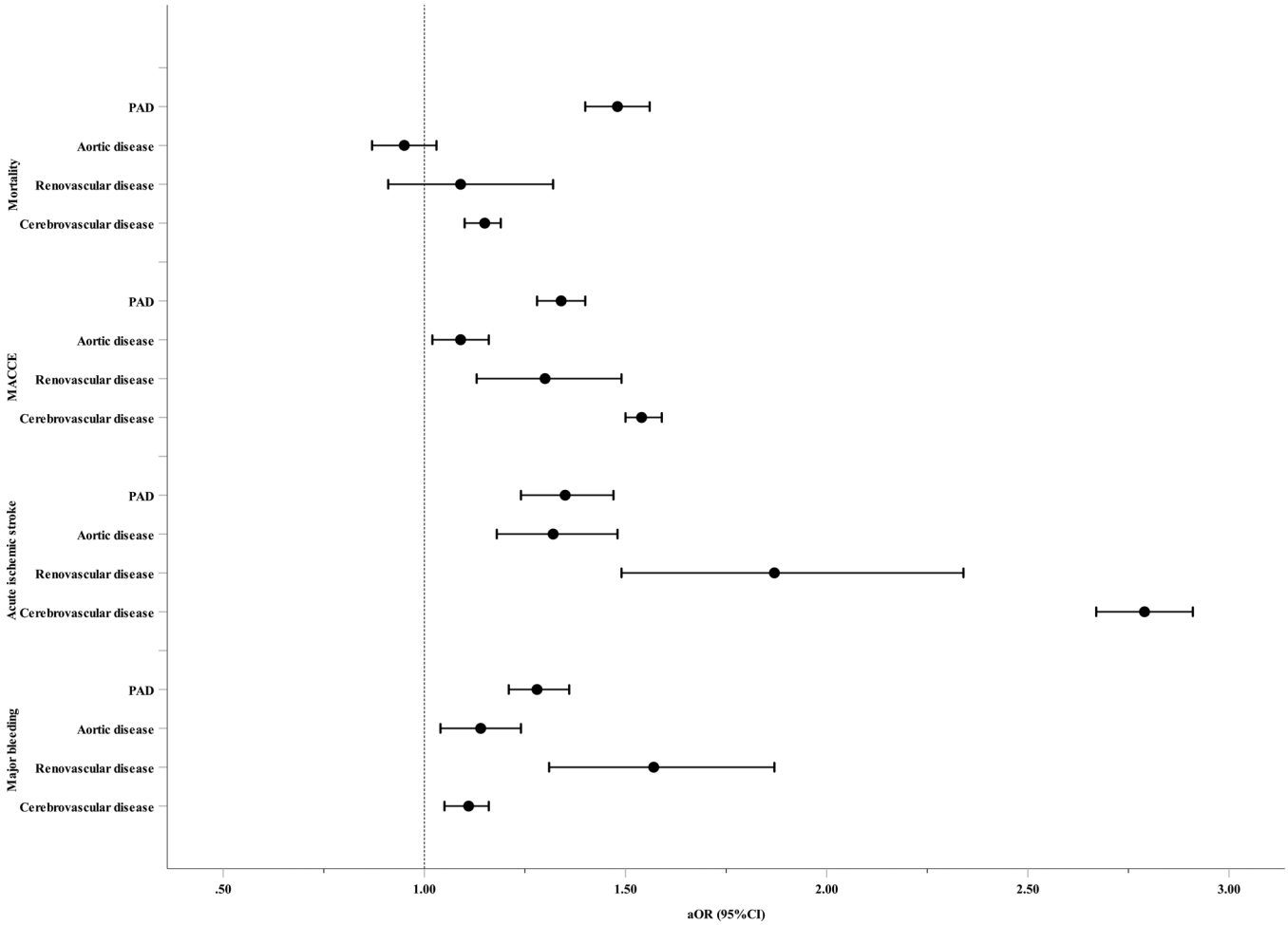


**FIGURE 2** Adjusted odds ratios (aOR) of in-hospital clinical outcomes in group with one extracardiac vascular bed involvement (stratified by involved organ site). aOR, adjusted odds ratios; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke, and reinfarction); PAD, peripheral artery disease.

stroke (2.1% vs 0.9%, $p < 0.001$), and major bleeding (2.2% vs. 1.5%, $p < 0.001$), than patients without ECVD (Table SV).

In addition, clinical outcome including mortality, MACCE, acute ischemic stroke, and major bleeding, also demonstrated increased frequency in a step ladder fashion with the higher number of involved vascular bed (up to 5.9%, 9.5%, 2.8%, and 3.6%, respectively in those with three or more involved vascular areas). A similar trend of increase length of stay and total charges was demonstrated (Table SV).

The odds of all-cause mortality increased as the number of affected extracardiac vascular areas increased (aOR 1.20, 95% CI 1.16–1.24; aOR 1.38, 95% CI 1.27–1.51; aOR 2.38, 95% CI 1.83–3.09; for one, two, and three or more vascular beds, respectively). A similar trend was seen for MACCE (aOR 1.42, 95% CI 1.38–1.45; aOR 1.63, 95% CI 1.52–1.74; aOR 2.42, 95% CI 1.98–2.96) and acute ischemic stroke (aOR 2.19, 95% CI 2.10–2.27; aOR 2.70, 95% CI 2.45–2.98; aOR 2.76, 95% CI 1.96–3.87) (Table 4 and Figure 3).

## 4 | DISCUSSION

This nationwide analysis provides an insight into the effect of concomitant ECVD on in-hospital outcomes of a contemporary cohort of patients undergoing PCI. The strengths of this study include a comprehensive evaluation of various ECVD, dose–response association, and rarely studied ECVD types such as renovascular disease. There are several important findings. First, pre-existent ECVD is common, observed in one out of seven patients undergoing PCI. Second, the presence of ECVD was associated with worse clinical outcomes, irrespectively of the organ involved and number of vascular beds. Third, the strongest association with mortality was present among patients with PAD, which is associated with a 48% increase in the odds of in hospital mortality.

Several studies have previously reported on the association of PAD and in-hospital mortality following PCI. Data from the German registry reported higher rates of inpatient death following PCI for myocardial infarction in this group of patients.[17] Similarly, a recent

**TABLE 4** Adjusted odds ratios (aOR) of in-hospital clinical outcomes according to extracardiac vascular bed involvement

| Clinical outcomes | One vascular bed | | Two vascular beds | | Three or more vascular beds | |
|---|---|---|---|---|---|---|
| | aOR [95% CI] | *p*-value | aOR [95% CI] | *p*-value | aOR [95% CI] | *p*-value |
| Mortality | 1.20 [1.16–1.24] | <0.001 | 1.38 [1.27–1.51] | <0.001 | 2.38 [1.83–3.09] | <0.001 |
| MACCE | 1.42 [1.38–1.45] | <0.001 | 1.63 [1.52–1.74] | <0.001 | 2.42 [1.98–2.96] | <0.001 |
| Acute ischemic stroke | 2.19 [2.10–2.27] | <0.001 | 2.70 [2.45–2.98] | <0.001 | 2.76 [1.96–3.87] | <0.001 |
| Major bleeding | 1.17 [1.13–1.21] | <0.001 | 1.17 [1.06–1.29] | 0.002 | 1.41 [1.04–1.92] | 0.027 |

*Note*: Multivariable analysis – the following variables were adjusted for: age, sex, weekend admission, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dementia, diabetes, dyslipidaemia, smoking, heart failure, atrial fibrillation/flutter, thrombocytopaenia, hypertension, anemia, chronic lung disease, coagulopathy, liver disease, chronic kidney disease, metastatic disease, valvular heart disease, cardiogenic shock, VT, VF, PCI indication, previous myocardial infarction, previous PCI, previous coronary artery bypass grafting.

Abbreviations: aOR, adjusted odds ratios; CI, confidence interval; MACCEm major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke, and reinfarction).

*Reference group: group with no extracardiac vascular involvement.

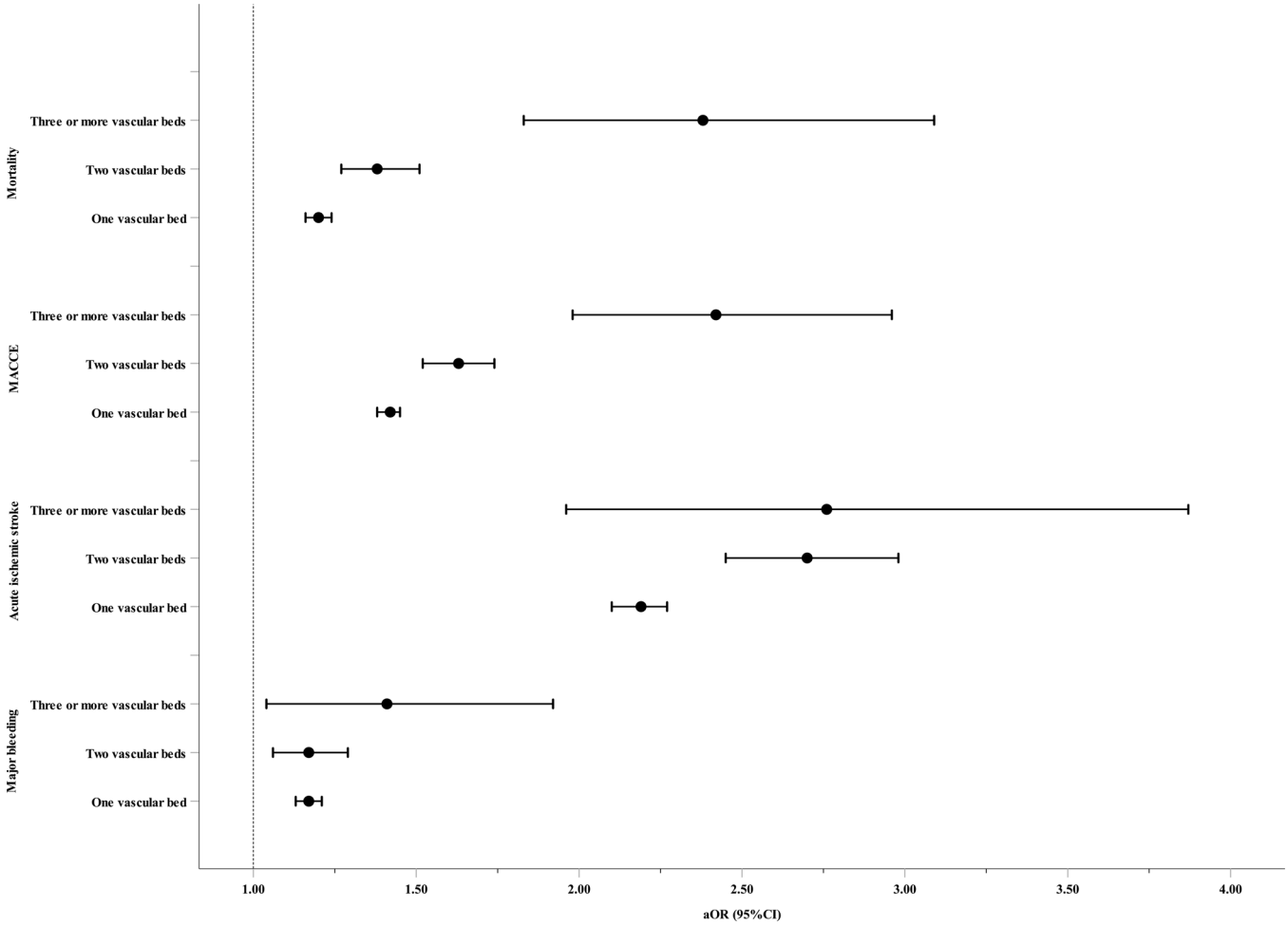


**FIGURE 3** Adjusted odds ratios (aOR) of in-hospital clinical outcomes according to extracardiac vascular bed involvement. aOR, adjusted odds ratios; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events (composite of mortality, acute stroke, and reinfarction).

analysis from the J-PCI (universal nationwide registration system in Japan) reported a 38% increased risk of in-hospital mortality following coronary revascularisation with PCI in patients with concomitant PAD.[6] Another smaller, single US centre study also showed higher unadjusted in hospital mortality in patients with peripheral vascular disease after PCI (1.8% vs. 0.1%; $p = 0.006$).[7] Our results, based upon a much larger population are broadly consistent with these, although the relative risk of death in our study was much higher than previously reported. Specifically,

this risk seems to have at least doubled since it was previously reported more than a decade ago.[7] This increase is counterintuitive, given the improved and more aggressively administered range of medical therapy available, but may be related to the improved identification of PAD and the generally better population life expectancy, leading to a rising prevalence of PAD.[18]

It is of no surprise that the presence of CeVD in our PCI population was associated with almost three times the risk of subsequent acute ischemic stroke, a finding which was consistent across all three PCI indications and also drove the highest risk of MACCE in this group. While a prior history of stroke is known to be a risk factor for recurrent stroke, the current data highlight the risk specific to PCI patients, a factor that could be important in the shared decision-making process.[19,20] It is also possible that a subset of patients with CeVD had atherosclerotic involvement of the aorta and brachiocephalic trunk which could have been the substrate for emboli during catheter and wire manipulation.[21]

Another potentially clinically important observation from our study is patients with additional extracardiac renovascular disease had more than 50% increased risk of major bleeding. While this group is well recognized to have higher rates of acute kidney injury, adverse coronary events, cardiovascular morbidity and mortality,[22–24] its association with major bleeding is not well documented. This association persisted even despite adjusting for the higher rate of CKD in this cohort, which is indeed a known risk factor for bleeding.[25] This could be secondary to the presence of underlying fibromuscular dysplasia in a proportion of the patients in this subgroup, which is associated with an increase the bleeding risk in other organs.[26] In addition, those with renovascular disease often have treatment resistant/oscillating blood pressure which increase their vascular complication risk after PCI.[27–29] It is also conceivable that this subset of patients has more fragile blood vessels more prone to rupture, although this is speculative at present.[30]

The presence of any degree of extracardiac atherosclerosis was associated with more than doubling the risk of in-hospital stroke post PCI, and this is again a potentially important observation when counseling patients. This is above and beyond the more than 40% increase in the risk of MACCE and more than 20% higher risk of in-hospital death. This is consistent with previous studies which describe and association between ECVD and worse inpatient outcome following PCI.[31,32] Furthermore, we demonstrated a dose response association between the number of extracardiac vascular beds involved and worse outcomes following PCI.

Our findings could impact practice in few various ways. First, these data should facilitate accurate counseling for patients with extracardiac atherosclerosis about their risk before PCI and thereby assist them in making an informed decision. Second, these data should encourage identification of those with more extensive atherosclerosis to guide optimization of disease-modifying medical therapies and closer monitoring of modifiable risk factors. Third, it raises the question whether the diagnosis of atherosclerosis in one territory should promote the screening for the disease in other vascular beds to guide possible prognostic interventions and to provide more accurate procedural risk stratification.

This study also has limitations. First, NIS is based on hospital discharge records and ICD-10 coding system that are prone to inadequate data entries and miscoding, which are unquantifiable for this cohort. Second, the analysis only tracks short term in-hospital outcomes and it is not possible to describe post-discharge events. Third, extracardiac atherosclerotic disease as described in this population represents only those in whom it has been diagnosed: undoubtedly there will be a subclinical and under-reported prevalence of which we cannot take account in this analysis. Fourth, the NIS doesn't capture pre-hospital medical treatments, chronic medications, laboratory parameters, left ventricular function, and the extent/severity of each ECVD and comorbidity that could influence the outcomes. Fifth, this study used a non-standard definition of major bleeding due to inherent limitations of the NIS data set. Sixth, other predictors of PCI outcome such as the timing to PCI, volume of PCI in the centre/operator, vascular access, anatomy and extent of coronary disease, PCI complications, the completeness of revascularisation, and the use of coronary physiology and other procedures were not accounted for in this analysis.[33–37] Finally, the design of this study does not allow the measurement of any causal relationship, but only association between ECVD and in-hospital outcomes.

## 5 | CONCLUSIONS

ECVD is highly prevalent in patients undergoing PCI and is associated with worse in-hospital outcomes including mortality after PCI. These data should inform our shared decision-making process with our patients.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

Data are available upon reasonable request to the corresponding author.

### ORCID

*Hussein Bashar* http://orcid.org/0000-0001-8256-5168
*Andrija Matetić* http://orcid.org/0000-0001-9272-6906

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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