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Relation of Extracardiac Vascular Disease and Outcomes in Diabetic Patients (1.1 Million) Hospitalized for Acute Myocardial Infarction

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Abstract:	The association between vascular disease and outcomes of acute myocardial infarction (AMI) patients has not been well-defined in the diabetes mellitus (DM) population. All DM patients presenting with AMI between October 2015 and December 2018 in the National Inpatient Sample database were stratified by number and site of extra-cardiac vascular comorbidity (cerebrovascular (CeVD), renovascular, neural, retinal and peripheral (PAD)). Multivariable logistic regression was used to determine the adjusted odds ratios (aOR) of in-hospital adverse outcomes and procedures. Of 1,116,670 patients with DM hospitalized for AMI, 366,165 (32.8%) had ≥1 extra-cardiac vascular comorbidity. Patients with vascular disease had increased aOR of mortality (aOR 1.05, 95%CI 1.04-1.07), major adverse cardiovascular and cerebrovascular events (MACCE) (aOR 1.19, 95%CI 1.18-1.21), stroke (aOR 1.72, 95%CI 1.68-1.76) and major bleeding (aOR 1.11, 95%CI 1.09-1.13), and had lower odds of receiving coronary angiography (CA) (aOR 0.90, 95%CI 0.90-0.91) and percutaneous coronary intervention (PCI) (aOR 0.82, 95%CI 0.82-0.83) compared to patients without extra-cardiac vascular disease. Patients with PAD had the highest odds of mortality (aOR 1.29, 95%CI 1.27-1.32) whereas CeVD patients had the greatest odds of MACCE, stroke and major bleeding (aOR 1.82, 95%CI 1.78-1.87, aOR 4.25, 95%CI 4.10-4.40, and aOR 1.51, 95%CI 1.45-1.57, respectively). Patients with DM presenting with AMI and concomitant extra-cardiac vascular disease were more likely to develop clinical outcomes and less likely to undergo CA or PCI. PAD patients had the highest risk of mortality, while CeVD patients had the greatest risk of MACCE, stroke and major bleeding.

Relation of Extracardiac Vascular Disease and Outcomes in Diabetic Patients (1.1 Million) Hospitalized for Acute Myocardial Infarction

Running title: Vascular impact on outcomes of acute myocardial infarction

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Abstract

The association between vascular disease and outcomes of acute myocardial infarction (AMI) patients has not been well-defined in the diabetes mellitus (DM) population. All DM patients presenting with AMI between October 2015 and December 2018 in the National Inpatient Sample database were stratified by number and site of extra-cardiac vascular comorbidity (cerebrovascular (CeVD), renovascular, neural, retinal and peripheral (PAD)). Multivariable logistic regression was used to determine the adjusted odds ratios (aOR) of in-hospital adverse outcomes and procedures. Of 1,116,670 patients with DM hospitalized for AMI, 366,165 (32.8%) had ≥1 extra-cardiac vascular comorbidity. Patients with vascular disease had increased aOR of mortality (aOR 1.05, 95%CI 1.04-1.07), major adverse cardiovascular and cerebrovascular events (MACCE) (aOR 1.19, 95%CI 1.18-1.21), stroke (aOR 1.72, 95%CI 1.68-1.76) and major bleeding (aOR 1.11, 95%CI 1.09-1.13), and had lower odds of receiving coronary angiography (CA) (aOR 0.90, 95%CI 0.90-0.91) and percutaneous coronary intervention (PCI) (aOR 0.82, 95%CI 0.82-0.83) compared to patients without extra-cardiac vascular disease. Patients with PAD had the highest odds of mortality (aOR 1.29, 95%CI 1.27-1.32) whereas CeVD patients had the greatest odds of MACCE, stroke and major bleeding (aOR 1.82, 95%CI 1.78-1.87, aOR 4.25, 95%CI 4.10-4.40, and aOR 1.51, 95%CI 1.45-1.57, respectively). Patients with DM presenting with AMI and concomitant extra-cardiac vascular disease were more likely to develop clinical outcomes and less likely to undergo CA or PCI. PAD patients had the highest risk of mortality, while CeVD patients had the greatest risk of MACCE, stroke and major bleeding.

Keywords: diabetes mellitus; acute myocardial infarction; vascular disease; outcomes.

Introduction

The prevalence of diabetes mellitus (DM) is greater than 420 million patients worldwide, and is a leading cause of death in the United States (US) [1]. DM has numerous direct and indirect pathophysiological effects including the development of vascular disease. Previous studies reveal that the presence of polyvascular disease in the setting of DM is associated with increased cardiovascular risk [2,3]. Due to the high atherosclerotic burden in patients with longstanding DM, patients with significant extra-cardiac vascular disease are increasingly encountered in acute cardiovascular presentations [4]. In a nationwide sample of patients with acute myocardial infarction (AMI) including diabetic and non-diabetic patients, we have previously demonstrated that nearly half of these patients had concomitant vascular disease (cardiac, cerebrovascular (CeVD), renal, aortic and peripheral artery disease (PAD)) [5]. However, whether manifested extra-cardiac vascular disease influences the management and outcomes of DM patients presenting with acute myocardial infarction (AMI) has not been well-investigated and therefore represents an important knowledge gap. We utilized a large national database to investigate management and outcomes of AMI patients with diabetes, stratified by number of extra-cardiac vascular comorbidities as well as by site of vascular comorbidity including five major organ systems.

Methods

The National Inpatient Sample (NIS) is the largest publicly available all-payer inpatient healthcare database in the US, developed by the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS covers more than 97% of the US population and contains anonymized data for more than 7 million hospital stays each year, approximating a 20-percent stratified sample of all US community hospitals [6].

Data of all adult (≥18 years) patients with type 1 and type 2 DM hospitalized for type 1 AMI between October 2015 and December 2018 were extracted using discharge data from the NIS database, HCUP, AHRQ. The study sample was stratified by number of extra-cardiac vascular comorbidities into four groups: 1) reference group: patients without extra-cardiac vascular disease, 2) group with extra-cardiac vascular disease: patients with 1, 2, ≥3 extra-cardiac vascular comorbidities. Patients with one extra-cardiac vascular comorbidity were stratified by site of vascular comorbidity into five groups: 1) CeVD, 2) renovascular disease, 3) neuropathy, 4) retinopathy, and 5) PAD. Patient characteristics, study groups, in-hospital procedures and clinical outcomes were all identified using the International Classification of Diseases, 10th revision (ICD-10) and Clinical Classification Software (CCS) codes (**Table S1**). We excluded cases with missing data for the following variables: age, gender, length of stay, primary expected payer, mortality status, elective admission, and total charges (n=48,590 [1.6%]). Patients with type 2 AMI or elective admissions were also excluded. We used Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) checklist to assess the reporting quality of our study (**Appendix A**). A flowchart showing the process of selecting the study sample is illustrated in **Figure S1**.

Our study aimed to investigate AMI outcomes and management in patients with DM, stratified by number and site of extra-cardiac vascular comorbidity, including CeVD, renovascular disease, diabetic neuropathy, retinopathy and PAD. The primary clinical outcome investigated was in-hospital all-cause mortality. Secondary clinical outcomes included in-hospital adverse events, including major adverse cardiovascular and cerebrovascular events (MACCE), acute ischemic stroke and major bleeding. Receipt of in-hospital invasive procedures was measured, including coronary angiography (CA), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

MACCE was defined as a composite of all-cause mortality, acute ischemic stroke or transient ischemic attack and reinfarction.

We used chi-square test to compare categorical variables, while Kruskal-Wallis test was used for continuous variables. Categorical data were presented as numbers (percentages) and continuous data were reported as median (interquartile range). Adjusted odds ratios (aOR [95% confidence interval (CI)]) of clinical outcomes and in-hospital procedures were calculated using binominal multivariable logistic regression analysis. We adjusted the analysis for the following variables due to their possible impact on the outcomes: *age, sex, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dyslipidaemia, smoking, heart failure, atrial fibrillation, dementia, thrombocytopenia, hypertension, anaemia, chronic renal failure, chronic lung disease, coagulopathy, liver disease, metastatic disease, valvular heart disease, previous myocardial infarction, previous PCI, previous CABG*. Sensitivity analyses were performed to examine differences between specific subgroups. All analyses were weighted. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 25 software (IBM Corp, Armonk, NY).

Results

Of a total of 1,116,670 patients with DM who were hospitalized for AMI, 67.2% had no diagnosed extra-cardiac vascular disease while 32.8% had at least one extra-cardiac vascular comorbidity. 24.8% of patients had one vascular comorbidity, 6.8% had two vascular comorbidities and 1.2% had three or more vascular comorbidities (**Table 1**). PAD was the most common extra-cardiac vascular disease (10.8%) followed by neuropathy (8.4%), CeVD (4.0%), retinopathy (1.3%) and renovascular disease (0.2%) (**Table 2**).

Patients with extra-cardiac vascular disease were older compared to patients without extra-cardiac vascular disease and had a higher prevalence of comorbidities including heart failure, valvular heart disease, atrial fibrillation/flutter, chronic lung disease, chronic renal failure, anemia, thrombocytopenia, coagulopathy, dementia, chronic liver disease, ventricular tachycardia and cardiogenic shock (P<0.001). Notably, metastatic cancer and ventricular fibrillation were more common in patients without extra-cardiac vascular disease (**Table S2**). The greater the number of diseased vascular beds, the more likely that patients presented with non-ST-elevation AMI (**Table 1**).

Patients with renovascular disease, CeVD and PAD were older than patients with other extra-cardiac vascular comorbidities. Heart failure, cardiac arrest, ventricular tachycardia and cardiogenic shock were more common in patients with PAD (**Table 2**).

Patients with extra-cardiac vascular disease had lower odds of receiving CA (aOR 0.90, 95% CI 0.90-0.91), PCI (aOR 0.82, 95% CI 0.82-0.83), higher odds of undergoing CABG (aOR 1.16, 95% CI 1.14-1.18) and increased aOR of all in-hospital outcomes, including mortality (aOR 1.05, 95% CI 1.04-1.07), MACCE (aOR 1.19, 95% CI 1.18-1.21), stroke (aOR 1.72, 95% CI 1.68-1.76) and major bleeding (aOR 1.11, 95% CI 1.09-1.13) compared to patients without extra-cardiac vascular disease (**Table S3**).

Patients with extra-cardiac vascular comorbidity were less likely to receive CA or PCI and more likely to undergo CABG compared to patients without extra-cardiac vascular disease (**Table 3**). When accounting for the baseline differences, patients with extra-cardiac vascular disease were consistently less likely to receive CA (aOR for: 1 bed 0.90, 95% CI 0.89-0.91, 2 beds 0.91, 95% CI 0.90-0.93, ≥3 beds 0.93, 95% CI 0.90-0.96). The greater the number of extra-cardiac vascular comorbidities, the lower the odds of receipt of PCI (aOR for: 1 bed 0.84, 95% CI 0.83-0.84, 2 beds 0.79, 95% CI 0.78-0.81, ≥3 beds 0.73, 95% CI

0.70-0.77). However, a positive dose response based on the number of extra-cardiac vascular comorbidities was evident for CABG (aOR for: 1 bed 1.13, 95% CI 1.11-1.15, 2 beds 1.26, 95% CI 1.22-1.29, ≥3 beds 1.28, 95% CI 1.20-1.36) (**Table 4**).

MACCE, acute ischemic stroke and major bleeding were more common in patients with extra-cardiac vascular disease (P<0.001) (**Table 3**). When accounting for the baseline differences, only patients with one extra-cardiac vascular comorbidity had significant greater odds of mortality (aOR 1.07, 95% CI 1.05-1.08) and major bleeding (aOR 1.14, 95% CI 1.12-1.17) while MACCE (aOR for: 1 bed 1.18, 95% CI 1.17-1.20, 2 beds 1.23, 95% CI 1.20-1.26, ≥3 beds 1.15, 95% CI 1.08-1.21) and acute ischemic stroke were increased across all subgroups (aOR for: 1 bed 1.64, 95% CI 1.59-1.68, 2 beds 2.06, 95% CI 1.98-2.14, ≥3 beds 1.83, 95% CI 1.67-2.00) (**Table 4 and Figure 1**).

Among patients with one extra-cardiac vascular comorbidity, patients with CeVD were the least likely to receive CA or PCI and had the highest likelihood of undergoing CABG (**Table 5**). After multivariable adjustment, patients with CeVD were consistently the least likely to receive CA or PCI (CA: aOR 0.69, 95% CI 0.68-0.70, PCI: aOR 0.56, 95% CI 0.55-0.58) and the most likely to undergo CABG (aOR 1.46, 95% CI 1.41-1.51) (**Table 6**).

Patients with PAD had the highest rate of in-hospital mortality while patients with CeVD had the highest crude rates of MACCE, acute ischemic stroke and major bleeding (**Table 5 and Figure 2**). After multivariable adjustment, patients with CeVD and PAD had increased odds of mortality, MACCE, stroke and major bleeding (P<0.001). The highest aOR of mortality was in patients with PAD (aOR 1.29, 95% CI 1.27-1.32) while the highest aOR of MACCE, acute ischemic stroke and major bleeding were in patients with CeVD (aOR 1.82, 95% CI 1.78-1.87, aOR 4.25, 95% CI 4.10-4.40, aOR 1.51, 95% CI 1.45-1.57, respectively). Patients with retinopathy did not have a significant increased risk of MACCE

or stroke while patients with neuropathy had significant higher risk of all clinical outcomes except major bleeding (**Table 6** and **Figure 3).** When evaluating only type 1 DM patients, there was no significant difference in invasive management and in-hospital clinical outcomes, except for the lower odds of receiving PCI compared to patients without extra-cardiac vascular disease (**Table S4**). Moreover, when looking at the type of AMI, the findings were consistent to those in the overall cohort, irrespectively of the AMI type (**Table S5**).

Discussion

Our study investigated the association between extra-cardiac vascular disease and the management and outcomes of more than 1 million DM patients hospitalized for AMI. We report that around third of all patients with diabetes presenting with AMI had one or more extra-cardiac vascular comorbidities with PAD being the most common. Patients with increasing vascular disease burden were less likely to undergo CA or PCI and more likely to receive CABG whereas mortality, MACCE, stroke and major bleeding were more prevalent in patients with vascular disease compared to their counterparts, with significant differences observed amongst the different anatomical sites of extra-cardiac vascular disease.

It has been well-established that vascular disease resulting from DM incorporates both microvascular and macrovascular complications. Microvascular abnormalities involve nephropathy, retinopathy and neuropathy, while macrovascular complications include atherosclerotic events in coronary artery disease (CAD), CeVD and PAD [7-10]. The pathophysiology of atherosclerosis in DM is multifactorial. Increased levels of proinflammatory markers such as C-reactive protein and cytokines have been shown to directly and indirectly affect vascular homeostasis. Nitric oxide, which normally inhibits platelet aggregation and modulates vascular tone, is inhibited by elevated free fatty acids, insulin resistance and hyperglycemia. Furthermore, functional impairments in coagulation

cascade and fibrinolytic pathways increase the susceptibility to atherosclerosis and thrombosis [11]. Several factors contribute to the mechanism of diabetic neuropathy and retinopathy, including duration and severity of hyperglycemia, metabolic dysregulation which implies glycation and increased protein kinase C, polyol, cytokines and oxidative stress which could cause abnormalities in the microvasculature of nerves and retina leading to axonal and retinal damage [9,12-15]. A previous meta-analysis also declared diabetic retinopathy as a predicator of cardiac death in DM patients [16] and another study found that it is associated with both systolic and diastolic dysfunction [17].

We report that patients with a greater number of diseased vascular beds were significantly less likely to undergo an invasive management with CA or PCI and more likely to receive CABG, with CeVD patients being the least likely to undergo CA or PCI. It is possible that patients with higher number of extracardiac vascular disease had more complex coronary artery disease, and were therefore more treated with surgical management. However, other factors could mediate the lower utilization of CA and PCI in these patients such as challenging vascular access, impaired renal function, concerns for periprocedural bleeding or stroke, or differences in clinical presentation [18,19]. Finally, worse comorbid profile in patients with higher vascular burden could potentiate the 'risk-treatment' paradox in which patients with higher risk are paradoxically less invasive managed.

Our study also revealed that in DM patients admitted with AMI, patients with extra-cardiac vascular disease had higher risk of death, MACCE, acute ischemic stroke and major bleeding in comparison to patients without extra-cardiac vascular disease. We have previously reported similar findings among all AMI patients (regardless of diabetes status), nearly half of whom had concomitant vascular disease and worse outcomes [5]. Meer at al. have previously demonstrated that among patients undergoing PCI, polyvascular disease was associated with increased mortality and morbidity, and this risk increased with the increase in

number of vascular beds diseased [20]. A post-hoc analysis of the EMPA-REG OUTCOME trial showed that polyvascular disease is associated with a greater risk of heart failure and cardiovascular events in DM patients [2]. IMPROVE-IT trial also showed that patients with type 2 DM and polyvascular disease had greater cardiovascular risk (60%) compared to patients with either polyvascular disease or type 2 DM alone who had almost similar risks (~40%) [3]. Additionally, our study showed that patients with vascular involvement had increased major bleeding, and particularly in patients with CeVD and PAD. This could be attributed to the probable higher risk profile of patients with vascular disease as they are more likely to be older [21] and have more comorbidities, which altogether could increase the bleeding risk. It could also be a result of concomitant therapy or drug interactions [22]. Problems with vascular access during CA or PCI in PAD patients might also increase the possibility of bleeding [23]. Notably, we found the highest adjusted in-hospital mortality among patients with concomitant PAD. These patients are at increased risk of ischemic events [24]. More specifically in the AMI population, presence of concomitant PAD has been shown to be an independent predictor of all-cause and cardiovascular mortality [25]. These findings highlight the importance of aggressive risk factor modification, primary and secondary prevention efforts and screening for occult atherosclerosis in other vascular beds among DM patients [26,27].

There are some several limitations to this study. Firstly, even though ICD-10 codes have been validated previously in this setting, there is possibility of undercoding or misclassification which is inherent to the dataset [28,29]. Additionally, the NIS does not capture data on severity of vascular disease, functional disabilities or pharmacological therapy where the previous use of statin, antiplatelet agents, oral anticoagulants and anti-hypertensive drugs may influence the results as they could impact the prognosis. Moreover, the NIS does not register specific cause of death which prevented from analysing the cardiovascular mortality.

Different risk scores for patient stratification are also not captured in the dataset due to a lack of some data such as laboratory parameters. Finally, this analysis is restricted to in-hospital outcomes and we were unable to assess longitudinal long-term results.

In conclusion, patients with DM presenting with AMI and concomitant extra-cardiac vascular disease had higher rates of in-hospital mortality, MACCE, acute ischemic stroke and major bleeding, as well as were less likely to receive CA or PCI, compared to patients without extra-cardiac vascular disease. Our findings emphasize the importance of early diagnosis and management of extra-cardiac vascular disease in patients with DM, particularly in certain vascular beds, to improve their prognosis and management.

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Figure titles and legends:

Figure 1. Adjusted odds ratios (aOR) of in-hospital clinical outcomes according to number of extra-cardiac vascular comorbidities.

Abbreviations: aOR – Adjusted Odds Ratios; CI – Confidence Interval; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and reinfarction).

Multivariable analysis – the following variables were adjusted for: age, sex, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dyslipidaemia, smoking, heart failure, atrial fibrillation, dementia, thrombocytopenia, hypertension, anaemia, chronic lung disease, chronic renal failure, coagulopathy, liver disease, metastatic disease, valvular heart disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting.

Figure 2. In-hospital clinical outcomes in group with one extra-cardiac vascular comorbidity (stratified by site of vascular comorbidity).

Abbreviations: MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and reinfarction); PAD – Peripheral Artery Disease.

Figure 3. Adjusted odds ratios (aOR) of in-hospital clinical outcomes in group with one extra-cardiac vascular comorbidity (stratified by site of vascular comorbidity).

Abbreviations: aOR – Adjusted Odds Ratios; CI – Confidence Interval; MACCE – Major Adverse Cardiac and Cerebrovascular Events (composite of mortality, acute stroke/transient ischemic attack and reinfarction); PAD – Peripheral Artery Disease.

Multivariable analysis – the following variables were adjusted for: age, sex, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dyslipidaemia, smoking, heart failure, atrial fibrillation, dementia, thrombocytopenia, hypertension, anaemia, chronic lung disease, chronic renal failure, coagulopathy, liver disease, metastatic disease, valvular heart disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting.

Figure S1. Flow diagram of study population.

Table 1: Characteristics of included patients stratified by number of extra-cardiac vascular comorbidities.

Characteristics	Number of vascular beds involved				
	0	1	2	≥3	P value
Number of weighted records	750,505	276,550	76,190	13,425	
Age (years), median (interquartile range)	69 (59, 78)	70 (62, 78)	69 (61, 77)	67 (60, 74)	<0.001
Females	41.4%	43.1%	43.4%	42.9%	<0.001
					<0.001
White	68.2%	69.8%	70.7%	67.9%	
Black	14.1%	14.9%	14.3%	13.1%	
Hispanic	10.3%	9.3%	9.3%	12.4%	
Asian/Pacific Islander	3.4%	2.7%	2.6%	3.4%	
Native American	0.6%	0.6%	0.8%	1.0%	
Other	3.4%	2.6%	2.3%	2.3%	
Hospital location					<0.001
Northeast	20.7%	19.7%	18.3%	18.8%	
Midwest	22.9%	25.9%	29.8%	33.7%	
South	42.1%	40.3%	35.6%	26.3%	
West	14.4%	14.1%	16.2%	21.2%	
Hospital bed size					<0.001
Small	17.3%	16.9%	16.1%	15.3%	
Medium	30.0%	29.3%	29.1%	29.3%	
Large	52.7%	53.8%	54.8%	55.4%	
Hospital location/ teaching status					<0.001
Rural	8.7%	7.9%	6.9%	4.7%	
Urban non-teaching	24.7%	22.9%	21.5%	19.6%	
Urban teaching	66.6%	69.2%	71.7%	75.8%	
Weekend admission	26.6%	25.6%	25.0%	24.4%	<0.001
Median household income (quartile)					<0.001
1st	33.7%	34.2%	32.1%	30.2%	
2nd	27.8%	27.7%	28.0%	27.8%	
3rd	22.3%	22.6%	23.9%	24.7%	
4th	16.1%	15.5%	16.0%	17.3%	
Expected primary payer					<0.001
Medicare	63.0%	72.8%	74.6%	77.1%	
Medicaid	9.7%	9.1%	9.1%	8.4%	
Private	20.5%	13.7%	12.7%	12.6%	
Uninsured	3.8%	2.0%	1.4%	0.6%	
No charge	0.4%	0.2%	0.1%	<0.1%	
Other	2.6%	2.3%	2.2%	1.3%	
Homelessness	0.3%	0.3%	0.2%	0.2%	0.002
Record Characteristics					
ST-elevation myocardial infarction	19.6%	13.1%	10.3%	8.3%	<0.001
Cardiac arrest	3.7%	3.7%	3.4%	3.4%	<0.001
Ventricular fibrillation	2.3%	1.9%	1.7%	1.9%	<0.001
Ventricular tachycardia	5.6%	5.8%	5.4%	5.5%	<0.001
Cardiogenic shock	5.9%	6.0%	5.8%	5.9%	<0.001
Length of stay (days), median (interquartile range)	3 (2, 7)	5 (2, 9)	5 (3, 10)	6 (3, 10)	<0.001

Total charges, $, median (interquartile range)	63238 (33189, 114869)	66404 (33956, 126962)	71623 (36749, 140077)	73883 (36557, 143991)	<0.001
Comorbidities					
Heart failure	43.9%	55.1%	60.3%	64.3%	<0.001
Valvular disease	9.7%	11.9%	13.2%	12.7%	<0.001
Atrial fibrillation/flutter	18.7%	21.3%	20.9%	21.5%	<0.001
Hypertension	88.1%	91.1%	92.9%	93.8%	<0.001
Dyslipidaemia	68.1%	71.1%	73.9%	77.1%	<0.001
Smoking	1.5%	1.2%	1.1%	0.6%	<0.001
Chronic lung disease	23.9%	29.5%	29.6%	28.0%	<0.001
Chronic renal failure	33.7%	48.4%	58.7%	68.4%	<0.001
Anaemia	25.7%	35.5%	43.7%	49.2%	<0.001
Thrombocytopenia	6.3%	7.3%	7.5%	8.2%	<0.001
Coagulopathy	8.2%	9.6%	9.9%	10.8%	<0.001
Dementia	7.3%	8.1%	7.5%	6.2%	<0.001
Chronic liver disease	3.3%	3.6%	3.4%	3.5%	<0.001
Metastatic cancer	1.4%	1.1%	0.6%	0.9%	<0.001

Table 2: Characteristics of included patients with one extra-cardiac vascular comorbidity (stratified by site of vascular comorbidity).

Characteristics	No vascular disease (N=750,505)	One vascular bed (N=276,550)					P value
		Cerebrovascular disease (N=45,045)	Renovascular disease (N=2,410)	Neuropathy (N=94,160)	Retinopathy (N=14,720)	Peripheral artery disease (N=120,215)	
Age (years), median (interquartile range)	69 (59, 78)	72 (64, 80)	72 (64, 79)	67 (58, 76)	67 (58, 76)	71 (63, 79)	<0.001
Females	41.4%	46.5%	51.7%	45.0%	48.9%	39.5%	<0.001
							<0.001
White	68.2%	63.6%	69.7%	73.7%	61.1%	70.1%	
Black	14.1%	19.0%	14.5%	13.5%	17.4%	14.3%	
Hispanic	10.3%	9.2%	9.8%	7.8%	13.7%	10.0%	
Asian/Pacific Islander	3.4%	4.0%	3.2%	2.0%	4.7%	2.4%	
Native American	0.6%	0.5%	0.2%	0.6%	0.9%	0.6%	
Other	3.4%	3.6%	2.6%	2.3%	2.2%	2.5%	
Hospital region							<0.001
Northeast	20.7%	19.4%	17.4%	18.8%	22.3%	20.3%	
Midwest	22.9%	23.6%	23.4%	27.7%	29.8%	24.9%	
South	42.1%	42.6%	44.4%	39.4%	29.7%	41.2%	
West	14.4%	14.4%	14.7%	14.1%	18.2%	13.6%	
Hospital bedsize							<0.001
Small	17.3%	16.6%	15.1%	17.5%	16.0%	16.8%	
Medium	30.0%	28.7%	29.0%	28.5%	26.0%	30.5%	
Large	52.7%	54.7%	55.8%	54.0%	58.1%	52.7%	
Hospital location/ teaching status							<0.001
Rural	8.7%	7.9%	8.9%	8.2%	5.8%	7.9%	
Urban non-teaching	24.7%	22.4%	23.4%	22.8%	17.1%	23.9%	
Urban teaching	66.6%	69.6%	67.6%	69.0%	77.2%	68.2%	
Weekend admission	26.6%	25.7%	28.6%	25.4%	25.3%	25.6%	<0.001
Median household income (quartile)							<0.001
1st	33.7%	35.4%	36.0%	34.1%	30.1%	34.4%	
2nd	27.8%	27.0%	27.4%	28.3%	26.6%	27.6%	
3rd	22.3%	22.0%	19.9%	22.9%	25.2%	22.2%	
4th	16.1%	15.6%	16.7%	14.7%	18.1%	15.7%	
Expected primary payer							<0.001
Medicare	63.0%	76.4%	73.9%	67.3%	66.8%	76.4%	
Medicaid	9.7%	8.2%	7.1%	11.3%	10.3%	7.6%	
Private	20.5%	11.2%	13.1%	16.2%	19.3%	12.0%	
Uninsured	3.8%	2.0%	2.7%	2.4%	2.0%	1.7%	

No charge	0.4%	0.1%	<0.1%	0.2%	<0.1%	0.1%	
Other	2.6%	2.1%	3.3%	2.6%	1.6%	2.3%	
Homelessness	0.3%	0.2%	0.2%	0.4%	0.2%	0.3%	<0.001
Record Characteristics							
ST-elevation myocardial infarction	19.6%	12.0%	12.0%	13.7%	13.8%	13.0%	<0.001
Cardiac arrest	3.7%	3.7%	3.5%	3.0%	3.6%	4.3%	<0.001
Ventricular fibrillation	2.3%	1.8%	2.1%	1.5%	1.6%	2.2%	<0.001
Ventricular tachycardia	5.6%	5.6%	6.0%	4.8%	4.9%	6.7%	<0.001
Cardiogenic shock	5.9%	5.4%	6.0%	4.8%	5.5%	7.3%	<0.001
Length of stay (days), median (interquartile range)	3 (2, 7)	5 (3, 10)	5 (3, 10)	4 (2, 8)	5 (2, 8.75)	4 (2, 8)	<0.001
Total charges, $, median (interquartile range)	63238 (33189, 114869)	69116 (35052, 137170)	76736 (39522, 150339)	64034 (33457, 120105)	63717 (32624, 126605)	67534 (34128, 129030)	<0.001
Comorbidities							
Heart failure	43.9%	50.0%	56.2%	52.3%	55.4%	59.2%	<0.001
Valvular disease	9.7%	12.4%	16.4%	9.9%	11.8%	13.2%	<0.001
Atrial fibrillation/ flutter	18.7%	23.2%	26.1%	18.7%	18.0%	23.0%	<0.001
Hypertension	88.1%	91.9%	87.3%	90.0%	92.6%	91.7%	<0.001
Dyslipidaemia	68.1%	69.2%	69.3%	70.5%	72.8%	72.1%	<0.001
Smoking	1.5%	1.0%	1.5%	1.2%	0.8%	1.4%	<0.001
Chronic lung disease	23.9%	23.5%	26.1%	29.2%	18.3%	33.4%	<0.001
Chronic renal failure	33.7%	41.7%	56.2%	45.7%	64.4%	50.8%	<0.001
Anaemia	25.7%	34.4%	39.8%	33.1%	44.0%	36.6%	<0.001
Thrombocytopenia	6.3%	7.6%	6.8%	7.0%	7.4%	7.4%	<0.001
Coagulopathy	8.2%	10.0%	10.2%	9.0%	9.3%	9.8%	<0.001
Dementia	7.3%	14.8%	5.4%	6.1%	5.5%	7.6%	<0.001
Chronic liver disease	3.3%	2.7%	3.7%	4.3%	3.3%	3.4%	<0.001
Metastatic cancer	1.4%	1.1%	2.3%	1.2%	0.7%	1.0%	<0.001

Table 3: In-hospital procedures and clinical outcomes stratified by number of extra-cardiac vascular comorbidities.

Procedures and outcomes	Number of vascular beds involved				P value
	0 (N=750,505)	1 (N=276,550)	2 (N=76,190)	≥3 (N=13,425)	
Procedures					
Coronary angiography	50.9%	45.4%	45.4%	46.2%	<0.001
Percutaneous coronary intervention	34.7%	27.2%	25.3%	23.7%	<0.001
Coronary artery bypass grafting	7.3%	8.3%	9.9%	10.7%	<0.001
Outcomes					
Mortality	7.4%	8.1%	7.5%	7.1%	<0.001
Major adverse cardiac and cerebrovascular events	10.1%	11.9%	12.0%	11.0%	<0.001
Acute ischemic stroke	2.4%	3.7%	4.4%	3.8%	<0.001
Major bleeding	3.8%	4.8%	4.5%	5.0%	<0.001

Legend: Major Adverse Cardiac and Cerebrovascular Events is a composite of mortality, acute stroke/transient ischemic attack and reinfarction.

Table 4: Adjusted odds ratios (aOR) of in-hospital procedures and clinical outcomes according to number of extra-cardiac vascular comorbidities relative to no extra-cardiac vascular disease.

Procedures and outcomes	One Vascular Bed (N=276,550)		Two Vascular Beds (N=76,190)		≥Three Vascular Beds (N=13,425)	
	aOR [95% CI]	P value	aOR [95% CI]	P value	aOR [95% CI]	P value
Procedures						
Coronary angiography	0.90 [0.89, 0.91]	<0.001	0.91 [0.90, 0.93]	<0.001	0.93 [0.90, 0.96]	<0.001
Percutaneous coronary intervention	0.84 [0.83, 0.84]	<0.001	0.79 [0.78, 0.81]	<0.001	0.73 [0.70, 0.77]	<0.001
Coronary artery bypass grafting	1.13 [1.11, 1.15]	<0.001	1.26 [1.22, 1.29]	<0.001	1.28 [1.20, 1.36]	<0.001
Outcomes						
Mortality	1.07 [1.05, 1.08]	<0.001	1.01 [0.98, 1.04]	0.366	0.98 [0.91, 1.05]	0.498
Major adverse cardiac and cerebrovascular events	1.18 [1.17, 1.20]	<0.001	1.23 [1.20, 1.26]	<0.001	1.15 [1.08, 1.21]	<0.001
Acute ischemic stroke	1.64 [1.59, 1.68]	<0.001	2.06 [1.98, 2.14]	<0.001	1.83 [1.67, 2.00]	<0.001
Major bleeding	1.14 [1.12, 1.17]	<0.001	1.00 [0.96, 1.03]	0.789	1.08 [0.99, 1.17]	0.078

***Reference group:** group with no vascular involvement.
Abbreviations: aOR – Adjusted Odds Ratios; CI – Confidence Interval; Major Adverse Cardiac and Cerebrovascular Events is a composite of mortality, acute stroke/transient ischemic attack and reinfarction.
Multivariable analysis – the following variables were adjusted for: age, sex, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dyslipidaemia, smoking, heart failure, atrial fibrillation, dementia, thrombocytopenia, essential hypertension, anaemia, chronic lung disease, chronic renal failure, coagulopathy, liver disease, metastatic disease, valvular heart disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting.

Table 5: In-hospital procedures and clinical outcomes in patients with one extra-cardiac vascular comorbidity (stratified by site of vascular comorbidity).

Procedures and outcomes	No vascular disease (N=750,505)	One vascular site (N=399,890)					P value
		Cerebrovascular disease (N=45,045)	Renovascular disease (N=2,410)	Neuropathy (N=94,160)	Retinopathy (N=14,720)	Peripheral artery disease (N=120,215)	
Procedures							
Coronary angiography	50.9%	38.3%	49.4%	47.4%	48.1%	46.0%	<0.001
Percutaneous coronary intervention	34.7%	20.1%	28.4%	29.2%	29.9%	28.1%	<0.001
Coronary artery bypass grafting	7.3%	10.4%	8.9%	8.4%	8.8%	7.5%	<0.001
Outcomes							
Mortality	7.4%	8.9%	8.9%	5.8%	6.7%	9.8%	<0.001
Major adverse cardiac and cerebrovascular events	10.1%	18.1%	12.9%	8.7%	9.6%	12.4%	<0.001
Acute ischemic stroke	2.4%	10.1%	4.8%	2.4%	2.5%	2.4%	<0.001
Major bleeding	3.8%	6.3%	4.8%	4.0%	3.7%	5.1%	<0.001

Legend: Major Adverse Cardiac and Cerebrovascular Events is a composite of mortality, acute stroke/transient ischemic attack and reinfarction

Table 6: Adjusted odds ratios (aOR) of in-hospital procedures and clinical outcomes in patients with one extra-cardiac vascular comorbidity relative to no extra-cardiac vascular disease (stratified by site of vascular comorbidity).

Procedures and outcomes	Cerebrovascular disease (N=45,045)		Renovascular disease (N=2,410)		Neuropathy (N=94,160)		Retinopathy (N=14,720)		Peripheral artery disease (N=120,215)	
	aOR [95% CI]	P value	aOR [95% CI]	P value	aOR [95% CI]	P value	aOR [95% CI]	P value	aOR [95% CI]	P value
Procedures										
Coronary angiography	0.69 [0.68, 0.70]	<0.001	1.18 [1.08, 1.28]	<0.001	0.90 [0.89, 0.91]	<0.001	0.95 [0.92, 0.98]	0.003	0.98 [0.97, 0.995]	0.007
Percutaneous coronary intervention	0.56 [0.55, 0.58]	<0.001	0.98 [0.90, 1.08]	0.732	0.84 [0.83, 0.85]	<0.001	0.91 [0.88, 0.95]	0.001	0.94 [0.93, 0.96]	<0.001
Coronary artery bypass grafting	1.46 [1.41, 1.51]	<0.001	1.18 [1.02, 1.37]	0.030	1.13 [1.10, 1.16]	<0.001	1.06 [1.00, 1.13]	0.064	1.02 [0.99, 1.05]	0.131
Outcomes										
Mortality	1.10 [1.06, 1.14]	<0.001	1.04 [0.90, 1.20]	0.632	0.78 [0.76, 0.80]	<0.001	0.91 [0.85, 0.97]	0.006	1.29 [1.27, 1.32]	<0.001
Major adverse cardiac and cerebrovascular events	1.82 [1.78, 1.87]	<0.001	1.16 [1.02, 1.31]	0.019	0.86 [0.84, 0.89]	<0.001	0.96 [0.91, 1.02]	0.190	1.23 [1.20, 1.25]	<0.001
Acute ischemic stroke	4.25 [4.10, 4.40]	<0.001	1.99 [1.64, 2.40]	<0.001	1.05 [1.01, 1.10]	0.030	1.10 [0.99, 1.22]	0.078	1.10 [1.06, 1.15]	<0.001
Major bleeding	1.51 [1.45, 1.57]	<0.001	1.00 [0.83, 1.21]	0.998	0.98 [0.95, 1.02]	0.372	0.82 [0.75, 0.90]	<0.001	1.16 [1.13, 1.20]	<0.001

***Reference group:** group with no vascular involvement.

Abbreviations: aOR – Adjusted Odds Ratios; CI – Confidence Interval; Major Adverse Cardiac and Cerebrovascular Events is a composite of mortality, acute stroke/transient ischemic attack and reinfarction.

Multivariable analysis – the following variables were adjusted for: age, sex, hospital bed size, hospital location/teaching status, hospital region, primary expected payer, dyslipidaemia, smoking, heart failure, atrial fibrillation, dementia, thrombocytopenia, essential hypertension, anaemia, chronic lung disease, chronic renal failure, coagulopathy, liver disease, metastatic disease, valvular heart disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting.

Figure 1

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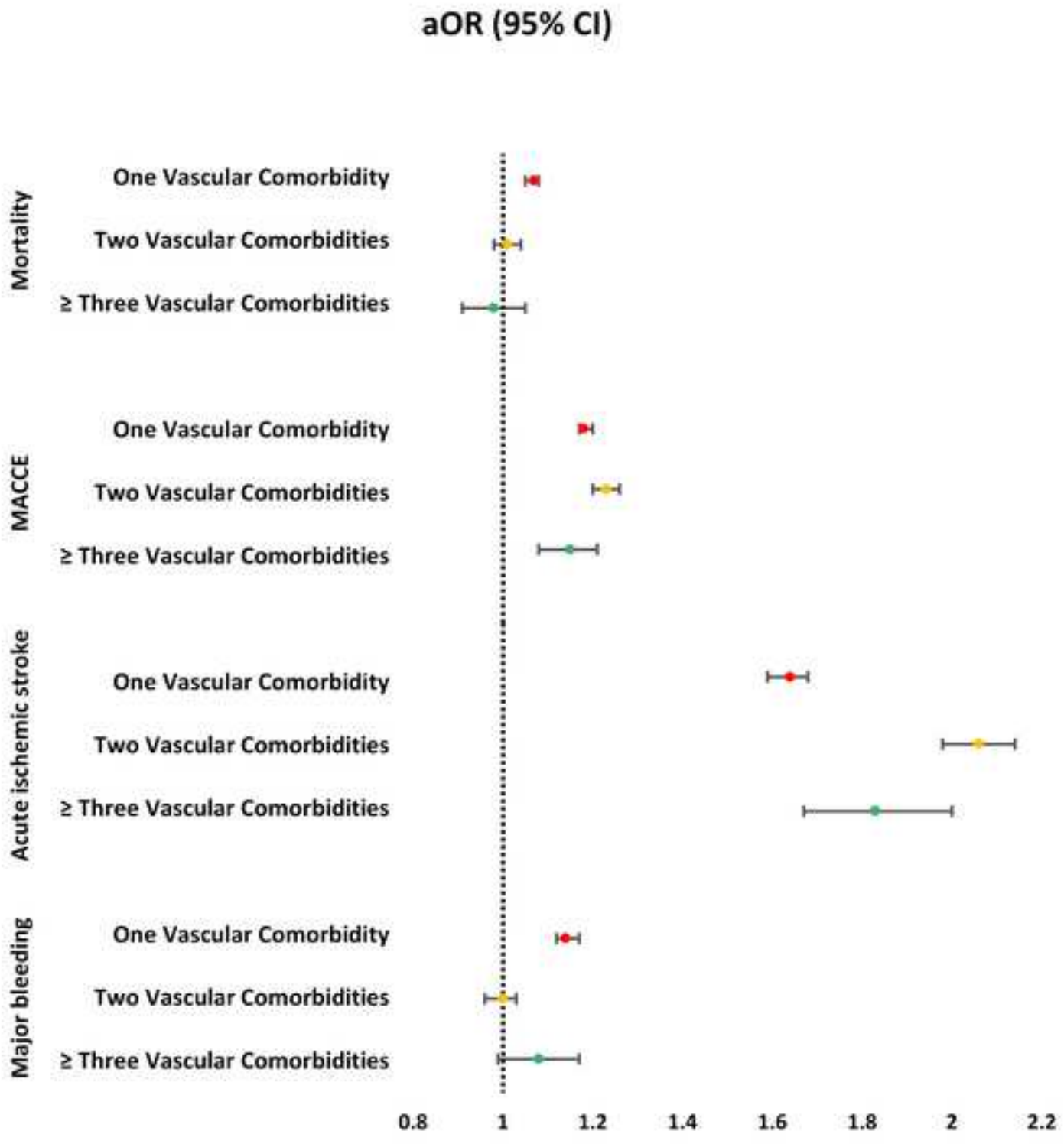


Figure 2

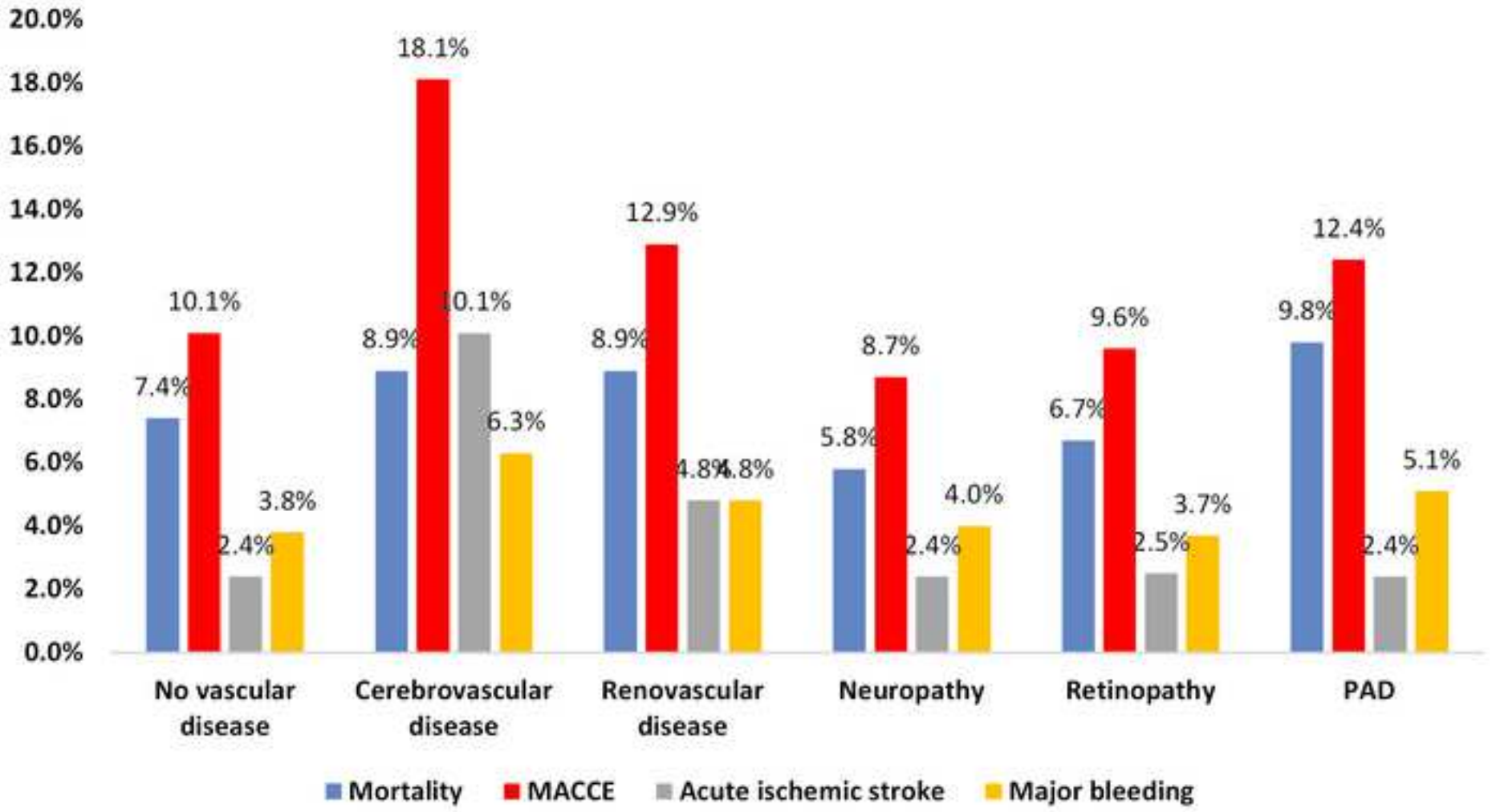
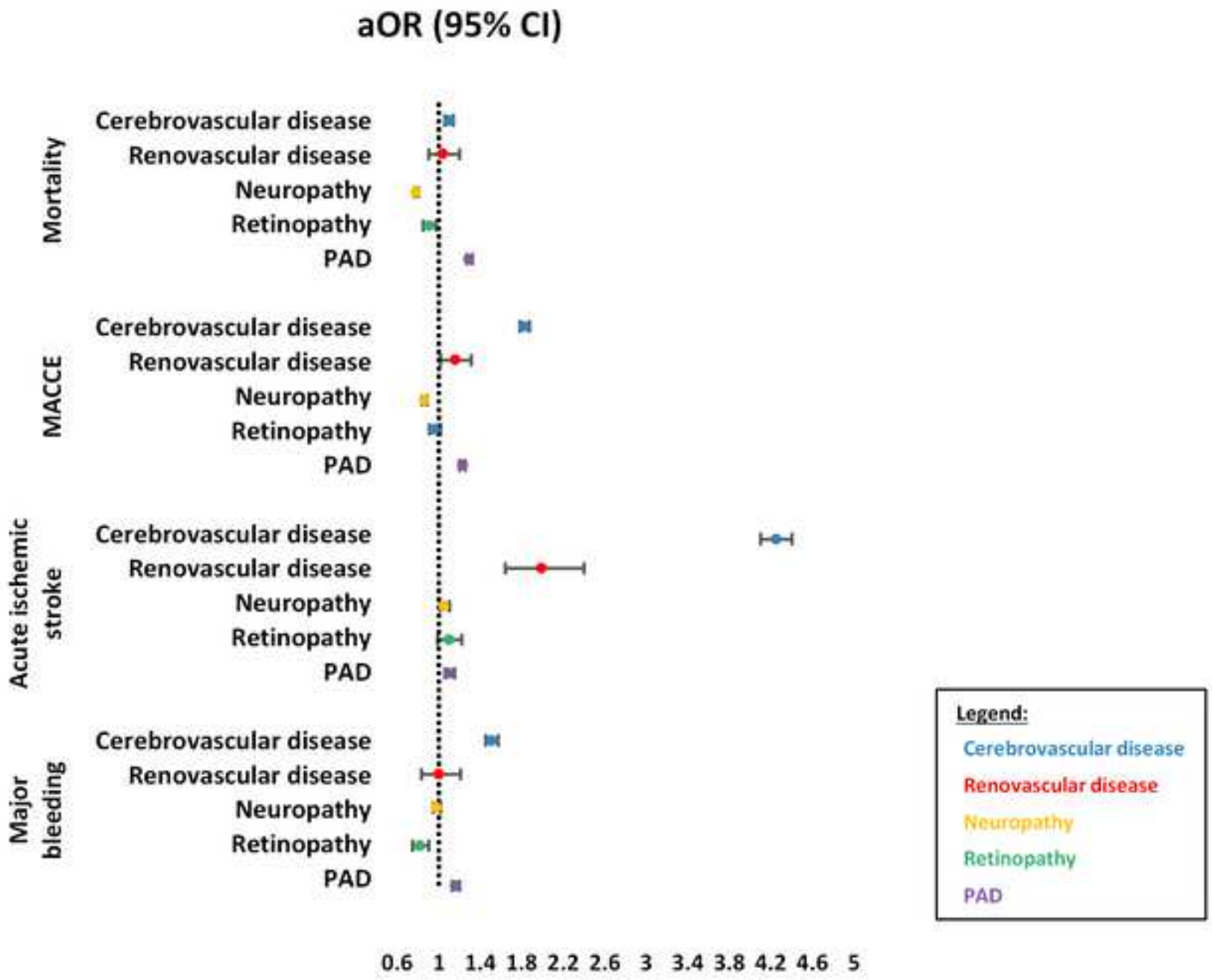


Figure 3



Graphical Abstract

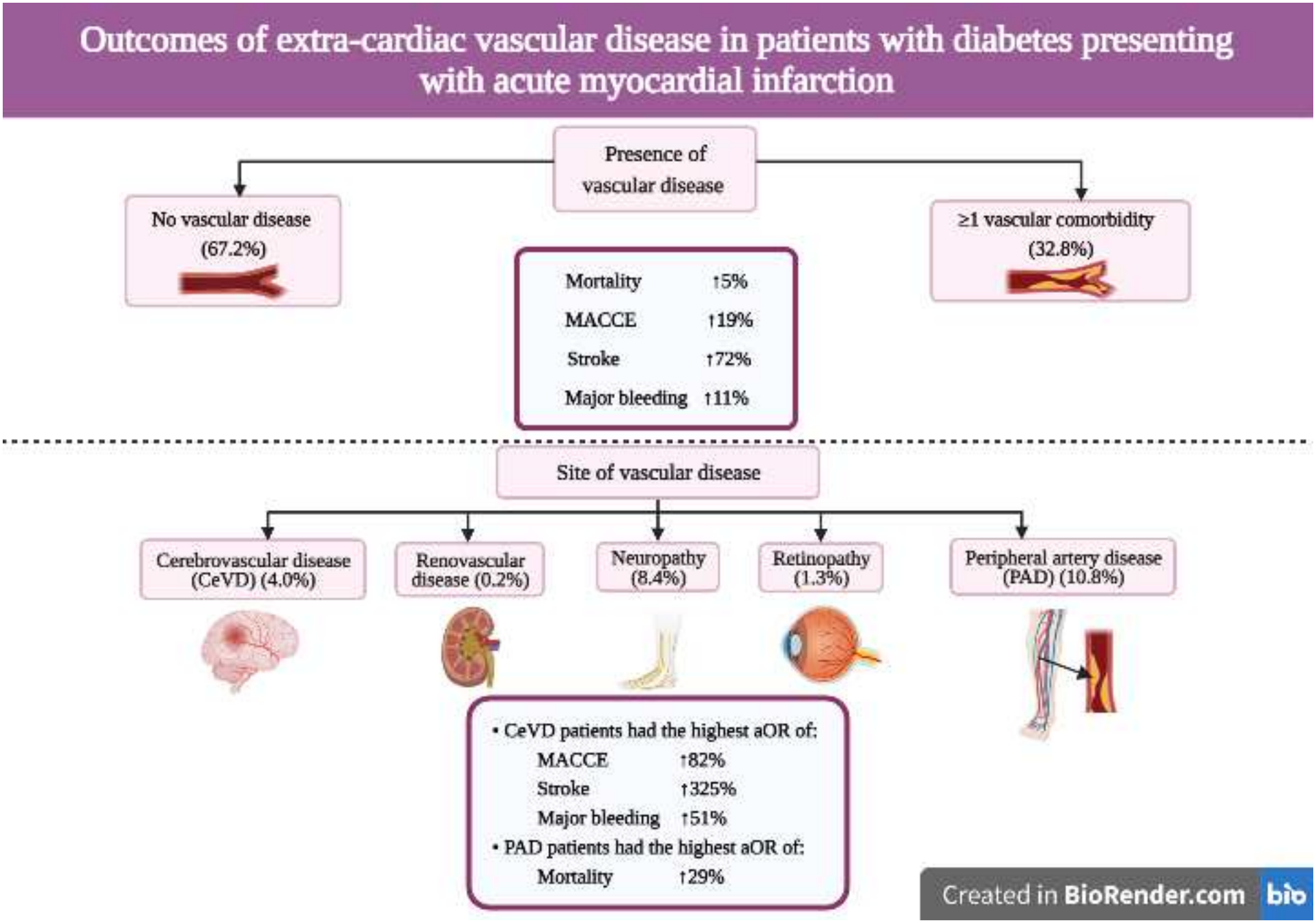


Figure S1

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: