Impact of pre-existing vascular disease on clinical outcomes in patients with non-ST-segment myocardial infarction: a nationwide cohort study

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Abstract

Aims: Little is known about the outcomes and processes of care of patients with non ST-segment myocardial infarction (NSTEMI) who present with 'polyvascular' disease.

Methods and results: We analysed 287,279 NSTEMI patients using the Myocardial Infarction National Audit Project (MINAP) registry. Clinical characteristics and outcomes were analysed according to history of affected vascular bed; coronary artery disease (CAD), cerebrovascular disease (CeVD) and peripheral vascular disease (PVD), with comparison to a historically disease-free control group; comprising 167,947 patients (59%). After adjusting for demographics and management, polyvascular disease was associated with increased likelihood of major adverse cardiovascular events (MACE) (CAD OR: 1.06, 95% CI: 1.01-1.12, P=0.02) (CeVD OR: 1.19, 95% CI: 1.12-1.27, P<0.001) (PVD OR: 1.22, 95% CI: 1.13-1.33, P<0.001) and in-hospital mortality (CeVD OR: 1.24, 95% CI: 1.16-1.32, P<0.001) (PVD OR: 1.33, 95% CI: 1.21-1.46, P<0.001). Patients without vascular disease were less frequently discharged on statins (PVD 88%, CeVD 86%, CAD 90% and control 78%), and those with moderate (ejection fraction (EF) 30-49%) or severe left ventricular systolic dysfunction (LVSD) (EF<30%), were less frequently discharged on angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (CAD 82%, CeVD 77%, PVD 77%, control 74%). Patients with polyvascular disease were less likely to be discharged on dual antiplatelet therapy (DAPT) (PVD 78%, CeVD 77%, CAD 80%, control 87%).

Conclusion: Polyvascular disease patients had a higher incidence of in-hospital mortality and MACE. Patients with no history of vascular disease were less likely to receive statins or ACE inhibitors/ARBs, but more likely to receive DAPT.

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Key words: NSTEMI, polyvascular disease, mortality, revascularization

Introduction

Atherosclerosis is the most common cause of mortality and morbidity globally, increasing in prevalence within an ageing population (1). There is a growing population of patients with 'polyvascular' disease, which refers to the presence of atherosclerosis within two or more arterial beds (2). Polyvascular disease is common in those with acute myocardial infarction (AMI) and its presence has been shown to increase in-hospital adverse events and mortality following AMI in registry data from the United States (US) (3, 4).

Whilst patients with polyvascular disease have been shown to have both increased severity of coronary artery disease (CAD) and have worse outcomes overall, compared to those without, prior studies looking at these outcomes have had important limitations. Much of the data is derived from administrative datasets, having limited granular data on comprehensive medical therapy (4, 5), or risk stratification on admission (5). No previous studies have focussed on delivery of care according to quality indicators. Significant limitations and contextual differences exist where outcomes are extensively investigated but where processes of care have not been thoroughly assessed. Furthermore, the impact of polyvascular disease has focused on AMI as a whole entity and not on non-ST segment myocardial infarction (NSTEMI), where vascular status differs. Patients presenting with NSTEMI are typically older, with more vascular comorbidities than those with STEMI, and have poorer long-term outcomes (6). Additionally, there are greater disparities of care in NSTEMI, where management is less algorithmic (7, 8).

Thus, we examined whether the anatomical site of polyvascular disease and the number of affected vascular beds influenced processes of care and outcomes of NSTEMI in the United Kingdom (UK) using national registry data.

Methods

Study design:

We used the Myocardial Ischaemia National Audit Project (MINAP), a prospective national registry of patients admitted to hospitals in the UK with an acute coronary syndrome (ACS) (9). The MINAP dataset consists of 130 variables including baseline demographics and clinical characteristics, comorbid conditions, management strategies, pharmacotherapy, place of care, in-hospital clinical outcomes and diagnoses on discharge (10). Data are submitted by hospital clinical and clerical staff and approximately 90,000 pseudonymised records annually are uploaded to the National Institute for Cardiovascular Outcomes Research (NICOR).

Study population:

We included patients admitted with a diagnosis of NSTEMI in any of the 230 participating hospitals in England and Wales between 1st January 2010 to 31st March 2017. The discharge diagnosis of NSTEMI was determined by local clinicians according to presenting history, clinical examination, and the results of inpatient investigations in keeping with the consensus document of the Joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) (11). Patients were excluded if they had missing data in our key variables for investigation; a history of percutaneous coronary intervention (PCI), a history of AMI, a history of coronary artery bypass graft (CABG) surgery, a history

of peripheral vascular disease (PVD) or a history of cerebrovascular disease (CeVD). Furthermore, any individual patient's subsequent admissions were excluded from analysis (Figure 1). This constituted a final cohort of 282,279 patients with NSTEMI, who were then divided into four subgroups depending on their vascular disease status; group 1; our control group (with no history of vascular disease recorded in the MINAP dataset), group 2; with a history of CAD, group 3; with a history of CeVD and group 4; with a history of PVD.

Previous CAD was defined as the presence of previous AMI, PCI, or CABG surgery in the MINAP dataset. We elected not to include history of angina in our previous CAD group; defined in the MINAP dataset as symptoms due to cardiac ischaemia developing or already in existence in the two weeks prior to admission, as this was not a validated diagnosis, and may have included symptoms from the index presentation. We defined history of CeVD and a history of PVD as per the definitions found in the MINAP dataset dictionary. History of CeVD included both transient ischaemic episodes, and acute ischaemic events with deficits persisting >24 hours. A history of PVD was defined as the presence of symptomatic PVD, which had been treated by either interventional therapy or surgery, including those with renovascular disease and aortic aneurysms.

Subgroup Analysis:

Our subgroup analysis compared the baseline characteristics, management strategies, and outcomes of patients by number of diseased vascular beds. This involved the creation of three new groups (one vascular bed, two vascular beds and three vascular beds), alongside the previously detailed control group with no affected vascular beds. A diseased vascular bed was defined as the presence of a history of coronary artery disease (the presence of previous

AMI, previous PCI or previous CABG surgery), a history of CeVD or a history of PVD in the MINAP dataset.

Outcomes:

Primary

Primary outcomes of interest included in-hospital all-cause mortality and major adverse cardiovascular events (MACE) (composite endpoint of in-patient all-cause mortality and reinfarction).

Secondary

Secondary outcomes of interest included cardiac mortality (death attributable to myocardial ischaemia or infarction, HF and cardiac arrest of unknown cause) and non-cardiac mortality (any death not attributed to a cardiac cause) and receipt of ESC Quality Indicators (QIs) for NSTEMI.

ESC Quality indicators:

We examined the ESC Quality Indicators (QIs) for NSTEMI. Specifically; the use of invasive coronary angiography (ICA) within 72 hours of admission; the assessment of left ventricular (LV) function; the use of fondaparinux or low molecular weight heparin (LMWH); and the prescription of $P2Y_{12}$ inhibition, dual antiplatelet therapy (DAPT) and statins on discharge. For patients with moderate (defined as ejection fraction (EF) of between 30-49%) and severe (defined as EF <30%) left ventricular systolic dysfunction (LVSD), the use of angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker

(ARB) and beta blocker on discharge was also evaluated. MINAP does not record the specific type or dose of statin prescribed so 'statin prescription' was used as a surrogate for high-intensity statin. We also examined whether receipt of the ESC QIs influenced our primary outcomes (in-hospital mortality and MACE), comparing each affected vascular bed and cumulative number of affected vascular beds with our disease-free control group.

Statistical analysis:

Demographics, clinical characteristics, and crude adverse outcomes of patients by vascular bed were compared using the Pearson chi-squared test for categorical variables. Continuous variables were compared using Student's t-test if normally distributed and using Wilcoxon Rank Sum test if not. Normality of distribution was assessed using Shapiro-Wilks test. Continuous variables are presented as medians and interquartile ranges (IQR) and categorical variables by proportions. Multiple imputations with chained equations (MICE) were used to impute values for variables with missing data. MICE is considered to be best practice when dealing with missing data, and can provide unbiased estimates even when levels of missing data are significant, and also some protection when the pattern of 'missingness' is not random (12). For each binary outcome of interest, multivariable logistic regression analysis was applied on imputed datasets to estimate the risk of adverse outcomes between groups. Estimates were combined using Rubin's rules (13). Logistic regression models were fitted using maximum likelihood estimation and were adjusted for age, sex, ethnicity, creatinine, heart rate, blood pressure, history of angina, family history of CAD, co-morbid conditions (hypertension, hypercholesterolaemia, diabetes, smoking, history of asthma or COPD), pharmacotherapy (prescription of low molecular weight heparin (LMWH), unfractionated heparin (UFH), warfarin, GP 2b/3a inhibitor, IV nitrate, furosemide, aldosterone antagonist, fondaparinux, beta blockers, angiotensin converting enzyme inhibitor/angiotensin receptor blockers, aspirin, P2Y12 inhibitor statins, thiazide

diuretics), cardiac arrest and procedures including ICA during admission and revascularisation (by PCI or CABG surgery during admission).

Statistical analysis was undertaken using Stata 14.2 (College Station, Texas, USA). All statistical analyses were two-tailed, with an alpha of 5% used.

Results

Baseline characteristics for type of diseased vascular beds:

Between January 2010 to March 2017 there were 369,435 patients admitted to hospitals in England and Wales with a diagnosis of NSTEMI. Applying relevant exclusion criteria (Figure 1) produced a cohort of 282,279 patients. Of these, 92,347 patients were diagnosed with prior CAD (33%), 28,420 patients with known CeVD (10%) and 15,027 (5%) patients with known PVD.

Differences in clinical characteristics at admission between the groups based on vascular bed disease status are presented in Table 1. Patients with no vascular disease presented younger, with a median age of 69 (IQR 58-80), those with CAD; a median age of 75 (IQR 66-83), CeVD; 79 (IQR 71-85) and PVD; 75 (IQR 67-82). Patients with CAD (31%) and PVD (30%) were less frequently female than the control group (38%) (P<0.001), whereas those with CeVD were more frequently female (41%) (P<0.001). Patients with vascular bed disease more frequently had hypercholesterolaemia (CAD 45%, CeVD 40%, PVD 49%, control 29%).

Patients with vascular bed disease presented more frequently in cardiac arrest, with CAD (4%), CVA (5%), PVD (5%) than the control group (3%) (P<0.001). They more

frequently presented in pulmonary oedema (PVD 12%, CeVD 10%, CAD 7% and control 5%) (P<0.001) or cardiogenic shock (PVD 1%, CeVD 1%, CAD 0.7% and control 0.5%) (P<0.001). More patients with affected vascular beds had a high-risk GRACE score (>140) (CeVD 90%, PVD 87%, CAD 84% and control 73%).

Baseline characteristics for number of diseased vascular beds:

Our 'one vascular bed' group, had 94,544 patients, 'two vascular beds' group 18,144 patients and 'three vascular beds' group 1,674 patients. Supplementary Table 1 shows the demographic comparison between 'no vascular bed' and number of affected vascular beds. Patients with affected vascular beds were older; one bed (76, IQR 66-83), two beds (77, IQR 70-84) and three beds (76, IQR 68-82) compared with our control group (69, IQR 58-80). Those with affected vascular beds were less frequently female (three beds 26%, two beds 32%, one bed 33% and control 38%) and more frequently had hypercholesterolaemia (three beds 56%, two beds 46%, one bed 43% and control 29%).

A higher proportion of patients with polyvascular disease presented with pulmonary oedema (three beds 14%, two beds 11%, one bed 5% and control 5%). They also more frequently presented with a higher GRACE score (>140) (three beds 90%, two beds 90%, one bed 84% and control 73%).

Management strategies for type of diseased vascular bed:

Table 2 shows comparison of management strategies and clinical outcomes between our control group and cohort with a known vascular bed disease. Patients with a known vascular bed disease less frequently underwent ICA (CAD 62%, CeVD 47%, PVD 60%, control 75%)

(P<0.001) and revascularisation (by PCI or CABG surgery) (CAD 44%, CeVD 35%, PVD 47%, control 57%) (P<0.001) at index hospitalization. They were also less frequently discharged on aspirin (PVD 84%, CeVD 84%, CAD 85% and control 93%) (P<0.001). A lower proportion of patients with CeVD were admitted under a cardiologist (CeVD 42%, CAD 49%, PVD 51% and control 50%) or admitted to a cardiology ward (CeVD 46%, CAD 54%, and PVD 52% and control 55%).

Management strategies for number of diseased vascular beds:

As demonstrated in Supplementary Table 2, patients with polyvascular disease, less frequently underwent ICA (three beds 52%, two beds 51%, one bed 62% and control group 75%) or revascularisation (three beds 38%, two beds 40%, one bed 45% and control group 57%). A lower proportion of patients with polyvascular disease were discharged on aspirin (three beds 83%, two beds 84%, one bed 85% and control group 93%) or admitted to a cardiology ward (three beds 52%, two beds 50%, one bed 53% and control group 55%).

Clinical outcomes for type of diseased vascular bed:

In unadjusted data (presented in Table 2), MACE was more frequent with a history of CAD (7%), CeVD (10%) or PVD (9%) compared to our control group (5%) (P<0.001). In-hospital mortality was more frequent in patients with a history of CAD (6%), CeVD (9%) and PVD (8%) compared to our control group (5%). After adjusting for differences in demographics and management strategies (presented in Table 3), vascular bed disease was associated with increased likelihood of MACE (CAD OR: 1.06, 95% CI: 1.01-1.12, P=0.019) (CeVD OR: 1.19, 95% CI: 1.12-1.27, P<0.001) (PVD OR: 1.22, 95% CI: 1.13-1.33, P<0.001) and in-hospital cardiac mortality (CAD OR: 1.08, 95% CI: 1.02-1.15, P=0.014) (CeVD OR: 1.20, 95% CI: 1.12-1.29, P<0.001) (PVD OR: 1.30, 95% CI: 1.18-1.44, P<0.001), when compared to the control group. We also observed increased likelihood of

reinfarction with CAD (OR: 1.39, 95% CI: 1.25-1.53, P<0.001), and increased likelihood of in-hospital mortality with CeVD (OR: 1.24, 95% CI: 1.16-1.32, P<0.001) and PVD (OR: 1.33, 95% CI: 1.21-1.46, P<0.001) when compared with our control group.

Clinical outcomes for number of diseased vascular beds:

Crude in-hospital mortality increased with increasing number of diseased vascular beds (three beds 9%, two beds 8%, one bed 6% and control group 5%) (Supplementary Table 2). A similar relationship is seen for MACE (three beds 10%, two beds 9%, one bed 7% and control group 5%). After adjusting for demographics and management (presented in Table 4), the odds of MACE increased with the number of affected vascular beds; one bed (OR: 1.08, 95% CI: 1.03-1.13, P=0.002), two beds (OR: 1.18, 95% CI: 1.11-1.26, P<0.001) and three beds (OR: 1.37, 95% CI 1.11-1.68, P=0.003). Mortality increased significantly when two (OR: 1.26, 95% CI: 1.17-1.35, P<0.001) or three beds are affected (OR: 1.41, 95% CI: 1.12-1.79, P<0.003).

ESC Quality Indicators (QIs) for type of diseased vascular bed:

The ESC QIs by type of diseased vascular bed are shown in Table 5. Patients with history of CAD, CeVD or PVD less frequently underwent ICA within 72 hours of admission (PVD 58%, CeVD 55%, CAD 60% and control group 67%). Similarly, patients with diseased vascular beds were less frequently discharged on DAPT (PVD 78%, CeVD 77%, CAD 80%, control 87%). Interestingly, patients with established vascular disease were more frequently discharged on statin therapy (PVD 88%, CeVD 86%, CAD 90% and control 78%) and if found to have moderate or severe LVSD they were more likely to be discharged on ACE

inhibitors or ARBs (CAD 82%, CeVD 77%, PVD 77% and control 74%). Supplementary Tables 3 and 5 show whether the receipt of the ESC QIs influences in-hospital mortality and MACE. Patients that had their LV function recorded during admission less frequently suffered in-hospital mortality (control group 3% vs 6%, CAD 4% vs 7%, CeVD 6% vs 12%, and PVD 6% vs 11%) or MACE (control group 4% vs 7%, CAD 5% vs 8%, CeVD 8% vs 12% and PVD 7% vs 11%) when compared with those that did not have a recording of LV function.

ESC QIs for number of diseased vascular beds:

The ESC QIs by number of diseased vascular beds are shown in Table 6. Patients with polyvascular disease were less likely to undergo ICA within 72 hours of admission (three beds 56%, two beds 56%, one bed 60% and control group 67%). They were less frequently discharged on DAPT (and three beds 78%, two beds 77%, one bed 80% and control group 87%), but more frequently discharged on statins (three beds 90%, two beds 89%, one bed 88% and control group 78%). They were also more frequently discharged with ACE inhibitors or ARBs in the presence of moderate or severe LVSD (three beds 81%, two beds 80%, one bed 81% and control 74%). Supplementary Tables 4 and 6 show whether receipt of the ESC QIs influences in-hospital mortality or MACE. Patients that had their LV function recorded during admission less frequently suffered in-hospital mortality (control 3% vs 6%, one bed 4% vs 8%, two beds 6% vs 11% and three beds 8% vs 11%) and MACE (control 4% vs 7%, one bed 5% vs 8%, two beds 7% vs 11% and three beds 9% vs 12%) when compared with our control group.

Our key findings are presented in Figure 2 (Central Illustration Figure)

Discussion

The results of this analysis of more than 275,000 patients hospitalised with NSTEMI reveal several important findings. First, only half of patients who presented with NSTEMI had no history of pre-existing vascular disease. Of those who had vascular disease, patients were most likely to have a history of CAD followed by CeVD and PVD respectively. Second, patients with pre-existing vascular disease had distinct phenotypes depending on the anatomical site of disease, with patients with prior CeVD presenting almost a decade older than patients without pre-existing vascular disease, were more comorbid, more likely to be female and most likely to present acutely. Our analysis suggests that patients with prior vascular disease across all vascular beds studied were least likely to receive invasive coronary angiography or PCI, with patients with PVD having the greatest odds of in-hospital mortality and MACE. Finally, as the number of vascular beds increased incrementally, we found that patients had higher mortality and MACE. There was significant variation in the quality of care as per the ESC guidelines where patients with no vascular disease were more likely to receive DAPT therapy and undergo ICA within 72 hours; whereas they were less likely to receive statins than patients with vascular disease.

Previous studies that have investigated outcomes of patients with AMI and polyvascular disease have important limitations and contextual differences. First, there is a lack of granular data on the medical management of AMI patients with polyvascular disease (4). Secondly, our study focussed on NSTEMI and not AMI as a collective. This is important as the management for NSTEMI is less algorithmic than STEMI and thus greater disparities of care are likely (14). Finally, previous studies have not compared NSTEMI management against established quality indicators of care, whereas our analysis has investigated adherence to the ESC QIs for AMI (15). Prior studies utilising the 'National Inpatient Sample' (NIS) and CRUSADE registry from the US have shown outcomes of patients differ by vascular

status (3, 4). *Bhatt et al* used 95,749 NSTEMI patients from the CRUSADE registry to demonstrate the increased risk of a composite of in-hospital adverse events in patients with pre-existing vascular disease. *Kobo et al* used the NIS to investigate 2,184,614 AMI admissions from the US, and showed poorer clinical outcomes (MACE, mortality, stroke and major bleeding) with a cumulative increase in diseased vascular beds, and reduced rates of revascularisation. We demonstrate similar outcomes in our UK data, but extend these findings in several ways. Firstly, we show differences in the management of NSTEMI by reference to the ESC QIs, depending on the presence of, and degree of, vascular bed involvement. Our analysis showed that patients with polyvascular disease, particularly those with CeVD and PVD were less likely to receive optimum care as stipulated by certain ESC QIs. This was particularly evident with reduction in the use of aspirin and P2Y12 inhibitors compared to those with no vascular disease. This is consistent with smaller trials in comparable nations such as Canada, where in a trial of 10,667 NSTEMI patients, those with polyvascular disease were less likely to receive aspirin, P2Y12 inhibitors or DAPT (16). DAPT has been clearly demonstrated to reduce MACE after ACS when compared with single antiplatelet therapy, but at a cost of higher bleeding risk (17). Reduced ischaemic events, stent thrombosis and MACE have been shown in ACS patients treated with DAPT (18, 19). It is likely that the reduction in proportion of patients with polyvascular disease receiving DAPT is in part contributed to by the higher rates of oral anticoagulation with warfarin in this group, given the concerns regarding bleeding risk with combined DAPT and oral anticoagulation (20). It is also likely that the reduced rates of DAPT prescription in patients with polyvascular disease are influenced by the reduced rates of revascularisation. The proportion of patients treated with DAPT following AMI has been demonstrated previously to be lower in patients treated medically compared with those undergoing PCI (21), despite strong evidence to suggest the significant mortality benefits of DAPT in medically managed

ACS (22, 23). This is particularly relevant to our study as the benefits of dual antiplatelet therapy appear to be particularly relevant in prior AMI patients with polyvascular disease (24). Furthermore, patients with a history of CeVD or PVD, had a reduction in the use of ICA within 72 hours when compared with our control group. Interestingly, undergoing coronary angiography within 72hr did not appear to influence the frequency of in-hospital mortality or MACE in our unadjusted results.

NSTEMI patients with a history of CeVD are less likely to be admitted to a cardiology ward or under a consultant cardiologist. Our previous work has shown that NSTEMI patients admitted to a cardiology ward or under a consultant (attending) cardiologist have improved in-hospital mortality, are more likely to receive guideline directed medical therapy (GDMT) and have higher revascularisation rates than those admitted elsewhere (25, 26). There is likely an element of selection bias, with the patients most perceived as being unwell or most comorbid not being managed under cardiology services but by general medical teams or wards, which could affect their outcomes.

Whilst management with invasive therapies was lower in patients with established polyvascular disease, paradoxically the prescription of some evidence-based therapies was greater in this group. Our analysis showed that statin prescription was significantly lower in our disease-free control group compared to patients with polyvascular disease. The PROVE IT-TIMI 22 trial demonstrated how high-intensity statin therapy reduces mortality and MACE after ACS (27). Similarly, the benefits of ACE inhibition in patients post-AMI are well known in the context of LV impairment (28). We observe that patients without polyvascular disease with moderate or severe LVSD post NSTEMI are less likely to receive ACE inhibitors or ARBs identifies. This may reflect that heart failure patients with established polyvascular disease are recognised as high-risk phenotypes and are therefore more likely to be managed in line with best practice.

Our finding that rates of MACE and in-hospital mortality after NSTEMI are higher where more vascular beds are diseased is consistent with trials in comparable healthcare systems(3, 4, 16). Similar results are seen in the 'Gulf Registry of Acute Coronary Events', comprising 7,689 ACS patients (29). *Al Thani et al* showed how the presence of polyvascular disease was associated with increased in-hospital mortality, one-year mortality and reduced DAPT prescription. Similar results are shown in the MASCARA registry, a multicentre registry of 32 Spanish hospitals, where the presence of CeVD and PVD was independently associated with in-hospital and six-month mortality following ACS (30). *Ferreira-González et al* further noted the finding of more severe CAD in those with CeVD or PVD. This association has also been demonstrated elsewhere (31-33). These patients with severe CAD and polyvascular disease have been demonstrated to have particularly high rates of cardiovascular death and readmission in 544 post-AMI patients in Sweden (34).

Our analysis has several implications for practice. We showed that for patients with polyvascular disease, rates of ICA and revascularisation were lower. There is a complex interplay between balancing the risk of aggressive medical therapy and performing invasive procedures versus harm caused by their omission in the context of advanced age and multimorbidity, particularly in patients with multiple affected vascular beds. The risk of MACE increases as cumulative number of affected vascular beds increases, and within this high-risk polyvascular disease patient group, the presence of CeVD confers the poorest outcome (35, 36). It could be that our medical treatment of patients with polyvascular disease needs to change, with more of a focus on prevention. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial highlighted a significant reduction in ischaemic events in patients with stable atherosclerotic disease that were treated with a combination of aspirin and low-dose rivaroxaban, compared with aspirin alone, but at the cost of an increase in the risk of major bleeding events (37). Further analyses of the

COMPASS trial highlighted that this reduction in adverse events was greatest in the highest-risk patients, whereas the risk of major bleeding was less significant than initially reported (38). The increased mortality in AMI patients experiencing major bleeding in the thirty days post-hospitalisation is well documented, so it is clear to see why this treatment strategy is not widespread (39). Further work needs be undertaken to identify which patients are most at risk of this increased major bleeding risk, which could allow clinicians to target appropriate patients with intensive medical therapy, with a focus on the prevention of ischaemic events.

We also identify potential deficiencies in the processes of care in our control group of patients without a history of vascular disease, with reference to a reduced likelihood of being prescribed statin therapy, or ACE inhibitors/ARBs in the context of LVSD. There is growing interest in the outcomes of patients suffering AMI without 'standard modifiable cardiovascular risk factors', coined 'SMuRFs', with recent studies suggesting that their all-cause mortality following STEMI are worse than those with 'SMuRFs', and the reduced prescription of GDMT is one of the suggested reasons for this discrepancy in outcomes (40). Although not identical, our polyvascular disease groups had high proportions of the 'SMuRFs', whereas our control group is similar to the 'SMuRF-less' cohort, with low frequencies of common comorbidities. Our results give credence to the suggestion that we are undertreating this heterogenous group of minimally comorbid patients with GDMT, and that efforts should be made to improve the proportions of those receiving statin therapy and ACE inhibitors/ARBs post NSTEMI.

Strengths:

There are several significant strengths to our study. The MINAP registry records comprehensive details of every NSTEMI admission within the UK over our study period, in a publicly funded healthcare system which should limit the disparities in access to healthcare

seen in privately funded healthcare systems such as the US (41). This is one of the largest databases of NSTEMI patients in the world, with a population large enough to give sufficient power to detect differences in our clinical outcome measures between comparison groups.

Limitations:

There are several important limitations common to observational studies of this type. The MINAP data collection shares the weakness of other national registries, including self-reporting of adverse events where there is no external validation. Although the MINAP dataset included important clinical and demographic variables of interest, there are limitations to data collected. For instance, the database does not capture frailty score, severity of CAD socioeconomic or psychosocial risk factors, access to use of healthcare, rationale for specific medications or an exhaustive list of comorbid conditions. Furthermore, the database does not capture markers of inflammation, biomarkers, LDL-c levels, or less common risk factors such as malignancy, lipoprotein(a) or clonal haematopoiesis of indeterminate potential. Inherent to large registries such as MINAP is the issue of missing data. We have mitigated this using MICE, however we acknowledge that the significantly different denominators due to missing data does affect the comparison between variables such as percentage undergoing ICA and percentage undergoing PCI in our unadjusted results

The MINAP database only records in-hospital clinical outcomes and long-term follow-up data may reveal further differences in crude clinical outcomes and management of patients by polyvascular status and would allow better assessment of QIs such as cardiac rehabilitation referral. The MINAP data dictionary has strict definitions for the recorded variables, for example, the definition of PVD requires either symptoms or prior treatment by percutaneous intervention or surgery, encompassing severe PVD. This definition likely

misses many patients with mild or moderate PVD and could affect the generalizability of the results.

Likewise, the definition of hypercholesterolaemia is 'elevation of serum cholesterol requiring dietary or drug treatment', and we note for example that only 56% of patients with three affected vascular beds have a diagnosis of hypercholesterolaemia in the registry. It is likely that this is underestimating the burden of hypercholesterolaemia in this patient group, as it will be missing patients who do not volunteer a diagnosis of hypercholesterolaemia or have discontinued their statin therapy in the community prior to admission, which is relevant given the high rates of non-compliance with statin therapy in the UK (42).

Finally, some cases of NSTEMI may have been misdiagnosed or misclassified as type 2 MI, and we are unable to differentiate between type 1 and type 2 MI within the MINAP registry of NSTEMI patients. We acknowledge that this may mean that ESC QIs, such coronary angiography within 72 hours, may not be appropriate for the subgroup of patients with type 2 MI included within the NSTEMI group, and that this may be more prevalent in the polyvascular disease groups. We also acknowledge that the significant differences in the proportion affected by common comorbidities in our polyvascular disease patients when compared to our control group makes the differentiation between type 1 and type 2 MI more challenging. Of note, the proportion of patients with chronic renal failure (control group 6% vs. three vascular beds 30%) and diabetes (control group 19% vs. three vascular beds 49%) may make the polyvascular disease groups more prone to misclassification as type 1 or 2 MI, and therefore make comparisons with our control group less reliable.

Conclusion

In our study of 282,279 NSTEMI patients in the UK, we demonstrate a marked increase in MACE, cardiovascular and non-cardiovascular in-hospital mortality in patients with polyvascular disease. We also demonstrate that these patients are less likely to be discharged on DAPT, are more likely to present acutely unwell and are less likely to be investigated by ICA and receive revascularisation therapy by PCI or CABG.

Competing interests

None

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Data Availability

The data underlying this article were provided by the National Institute for Cardiovascular Outcomes Research (NICOR). Data will be shared on request to corresponding author with permission of NICOR.

Ethics

Secondary use of anonymised MINAP dataset for research purposes is authorised under NHS research governance arrangements and further supported under section 251 of NHS act 2006 (NIGB: ECC1-06(d)/ 2011), which allows researchers to use patient information collected within the dataset for medical research without patient consent. Therefore, formal ethical approval was not sought for this study.

Authors' Contributions

Nicholas Weight and Saadiq Moledina are joint 1st authors.

Nicholas Weight and Saadiq Moledina: Conception of project, data analysis, writing first draft of manuscript and making subsequent corrections.

Giuseppe Biondi Zoccai: Interpretation of data and re-drafting of manuscript.

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Muhammad Rashid: Interpretation of data and revision of draft manuscripts.

James Nolan: Interpretation of data and revision of draft manuscripts.

Mamas A Mamas: Conception and design of project, interpretation of data and revision of draft manuscripts.

All authors reviewed and approved final submitted manuscript.

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Figure 1: STROBE diagram detailing exclusion criteria

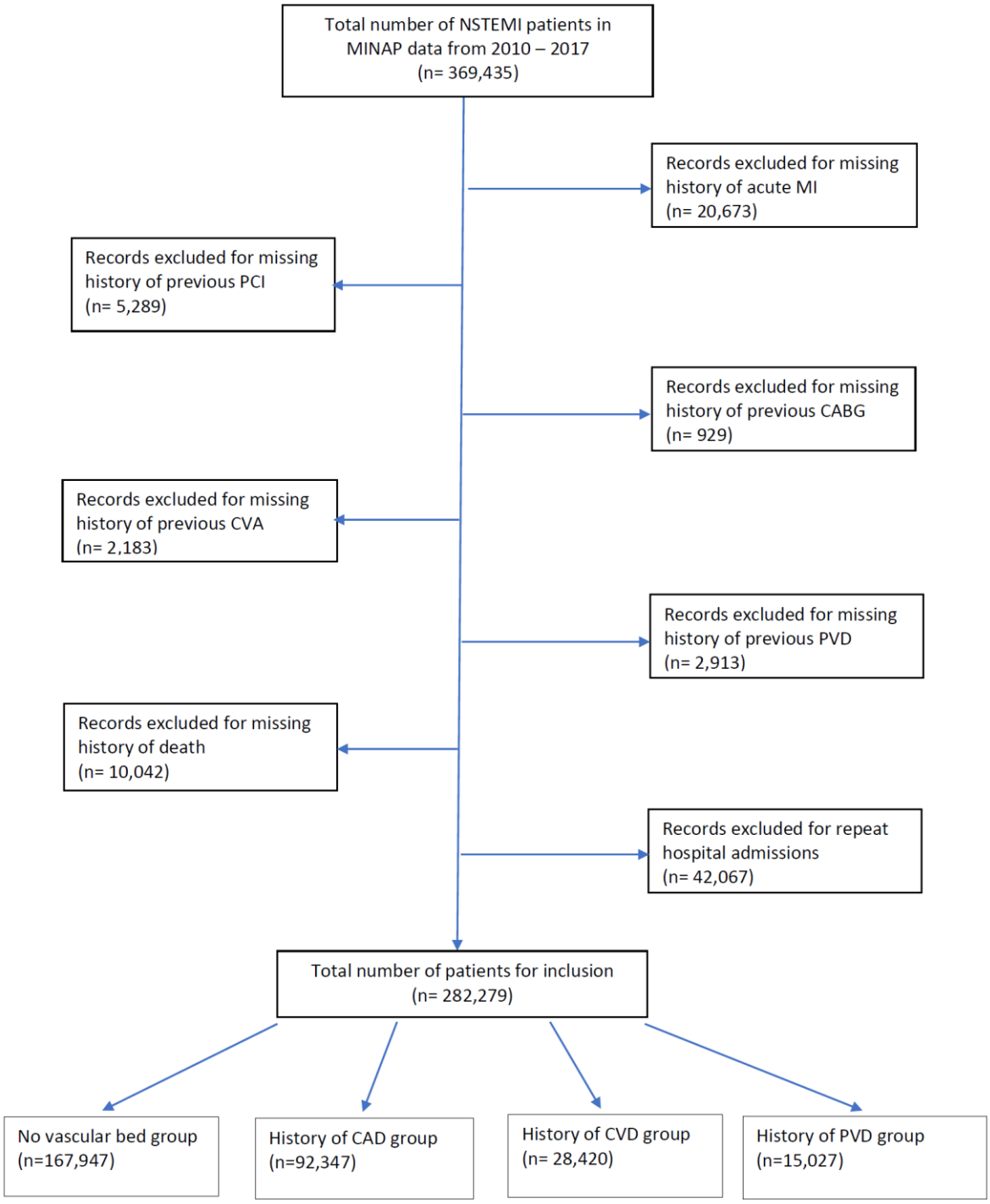

Figure 1: STROBE diagram detailing exclusion criteria

Figure 2: Graphical abstract

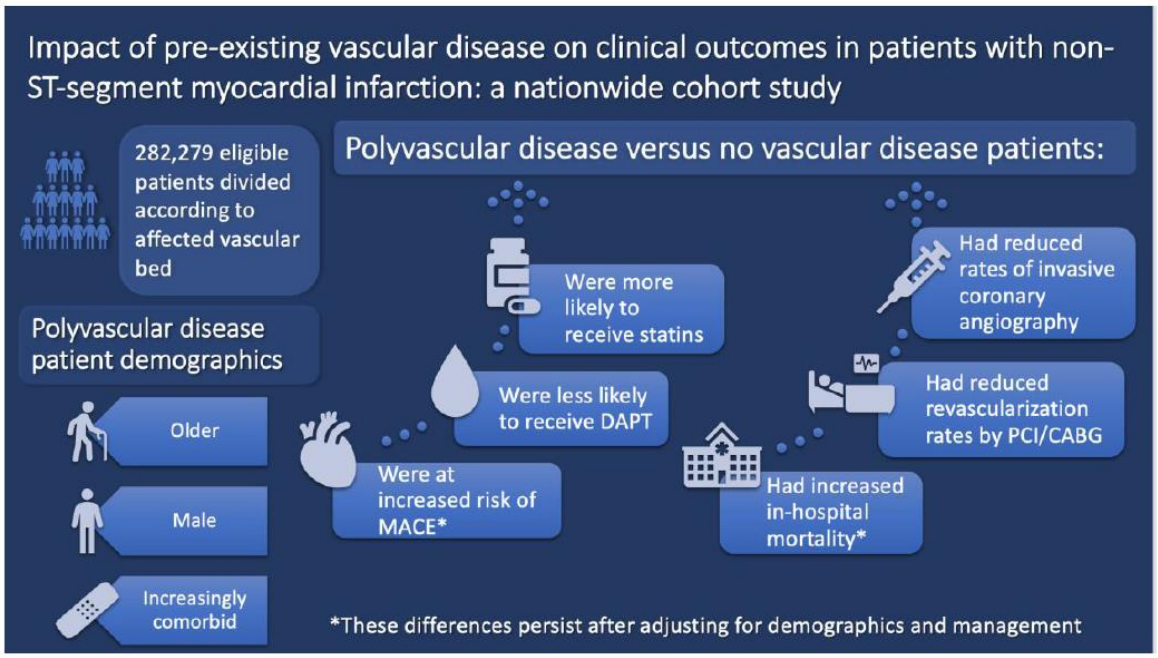

Figure 2: Graphical Abstract

Table 1: Demographic comparison between 'No vascular bed' and the major vascular beds

Variable	No vascular bed (167,947)	History of coronary artery disease (92,347)	History of cerebrovascular disease (28,420)	History of peripheral vascular disease (15,027)
Age, years, median (IQR)	69(58-80)	75 (66-83)	79 (71-85)	75 (67-82)
Women (%)	64,163/167,947 (38%)	28,424/92,347 (31%)	11,589/28,420 (41%)	4,352/15,027 (30%)
BMI, median [IQR]	27.2 (24.1-30.8)	27.3 (24.1-30.9)	26.4 (23.4-30.3)	27.0 (23.7-30.8)
Ethnicity- White	142,065/153,542 (93%)	77,063/85,494 (91%)	24,576/26,392 (93%)	13,056/13,857 (94%)
Killip Class				
Basal crepitations (%)	15,163/109,609 (14%)	11,834/59,378 (20%)	4,472/18,452 (24%)	2,368/10,147 (23%)
Pulmonary oedema (%)	5,254/109,609 (5%)	4,377/59,378 (7%)	1,786/18,452 (10%)	1,239/10,147 (12%)
Cardiogenic shock (%)	543/109,609 (0.5%)	408/59,378 (0.7%)	136/18,452 (1%)	116/10,147 (1%)
GRACE – risk score				
High risk GRACE score >140 (%)	77,225/105,210 (73%)	48,023/57,395 (84%)	16,061/17,842 (90%)	8,604/9,845 (87%)
Intermediate risk GRACE score 109-140 (%)	21,947/105,210 (21%)	7,747/57,395 (14%)	1,500/17,842 (8%)	1,032/9,845 (11%)
Low risk GRACE score <109 (%)	6,038/105,210 (6%)	1,625/57,395 (3%)	281/17,842 (2%)	209/9,845 (2%)
ECG ST changes (%)	127,077/163,769 (78%)	69,765/90,194 (77%)	22,263/27,809 (80%)	11,888/14,705 (81%)
Smoking				
Previous smoker (%)	52,409/160,884 (33%)	38,923/87,879 (44%)	10,887/26,494 (41%)	6,949/14,341 (49%)
Current smoker (%)	40,833/160,884 (25%)	14,626/87,879 (17%)	3,965/26,494 (15%)	3,442/14,341 (24%)
Chronic renal failure (%)	9,339/167,335 (6%)	12,095/91,859 (13%)	4,358/28,420 (15%)	3,134/14,914 (21%)
Prior percutaneous coronary intervention (%)	N/A (167,947) (0)	36,616/92,347 (40%)	3,886/28,420 (14%)	3,020/15,027 (20%)
Diabetes (%)	32,065 /166,746 (19%)	32,587/91,638 (36%)	9,475/28,210 (34%)	6,387/14,923 (43%)
CCF (%)	6,914/167,313 (4%)	12,483/91,760 (14%)	3,684/28,221 (13%)	2,287/14,906 (15%)

Hypercholesterolemia (%)	48,080/165,801 (29%)	40,785/90,763 (45%)	11,150/27,896 (40%)	7,252/14,698 (49%)
Previous MI (%)	N/A (0) (167,947)	76,865/92,347 (83%)	10,851/28,420 (38%)	6,267/15,027 (42%)
Cerebrovascular disease (%)	N/A (0) 167,947	12,555/92,347 (14%)	N/A (100%)	2,971/15,027 (20%)
Peripheral vascular disease (%)	N/A (0) (167,947)	7,610/92,347 (8%)	2,971/28,420 (11%)	N/A (100%)
Hypertension (%)	82,035/167,472 (49%)	57,521/91,906 (63%)	18,560/28,303 (66%)	10,137/14,952 (68%)
Asthma / COPD (%)	26,518/167,603 (16%)	18,059/92,100 (20%)	5,873/28,329 (21%)	3,705/14,948 (25%)
Family history of CAD (%)	43,174/144,285 (30%)	18,827/75,243 (25%)	4,263/22,200 (19%)	2,995/11,940 (25%)
Heart rate, bpm, median (IQR)	78 (67-92)	76 (65-90)	80 (68-95)	80 (68-95)
Systolic blood pressure, median (IQR)	141 (124-160)	136 (120-155)	138 (120-158)	138 (120-157)
LVSD				
Good LV function	57,991/87,014 (67%)	21,908/44,708 (49%)	6,952/13,537 (51%)	3,779/8,104 (47%)
Moderate LVSD (%)	21,469/87,014 (16%)	15,230/44,708 (21%)	4,362/13,537 (20%)	2,847/8,104 (24%)
Severe LVSD (%)	7,554/87,014 (6%)	7,570/44,708 (10%)	2,223/13,537 (10%)	1,478/8,104 (12%)
Cardiac arrest (%)	5,070/164,468 (3%)	3,265/90,446 (4%)	1,245/27,929 (5%)	715/14,636 (5%)
Previous CABG surgery (%)	N/A (0%) (167,947)	24,232/92,347 (26%)	3,354/27,929 (12%)	2,616/15,027 (17%)
Admission under cardiologist (%)	81,281/161,143 (50%)	43,720/88,736 (49%)	11,309/27,060 (42%)	7,157/14,107 (51%)
Admission to cardiology ward (%)	92,148/ 167,214 (55%)	49,508/91,982 (54%)	12,997/28,334 (46%)	7,807/14,978 (52%)

CABG; coronary artery bypass graft, LVSD; left ventricular systolic dysfunction, CAD; coronary artery disease, COPD; chronic obstructive pulmonary disease, MI; myocardial infarction, CCF; congestive cardiac failure, BMI; body mass index, GRACE; global registry of acute coronary events, IQR; interquartile range. Admission to cardiology ward is a composite of admission to coronary care unit (CCU) and general cardiology ward.

*Chronic renal failure is defined within the MINAP data dictionary as a serum creatinine chronically >200 micromol/L

Table 2: Management strategy and clinical outcome comparison between 'No vascular bed' and the major vascular beds

Variables	No vascular bed (167,947)	History of coronary artery disease (92,347)	History of cerebrovascular disease (28,420)	History of peripheral vascular disease (15,027)
Low molecular weight heparin (%)	78,798/151866 (48%)	43,772/83897 (52%)	13,983/26,035 (54%)	7,212/13,560 (53%)
Fondaparinux (%)	73,818/152,606 (48%)	37,427/84,150 (45%)	11,044/26,091 (42%)	5,855/13,545 (43%)
Warfarin (%)	6,891/151,150 (5%)	7,513/83,611 (9%)	3,042/26,023 (12%)	1,387/13,493 (10%)
Unfractionated heparin (%)	22,157/150,739 (15%)	11,014/83,374 (13%)	2,859/25,959 (11%)	2,284/13,467 (17%)
Glycoprotein 2b/3a inhibitor (%)	5,279/153,249 (3%)	2,355/84,674 (3%)	479/26,338 (2%)	390/13,699 (3%)
IV Nitrate (%)	18,992/151,139 (13%)	11,081/83,590 (13%)	3,078/25,975 (12%)	2,074/13,498 (15%)
Furosemide (%)	32,686/151,378 (22%)	32,545/83,918 (39%)	11,125/26,087 (43%)	6,218/13,568 (46%)
Calcium channel blockers (%)	24,457/151,196 (16%)	4,576/20,015 (24%)	6,198/26,031 (24%)	3,915/13,524 (29%)
IV beta blockers (%)	1,801/151,874 (1%)	912/83,935 (1%)	274/26,080 (1%)	161/13,555 (1%)
MRA (%)	7,330/150,196 (5%)	8,834/83,044 (11%)	2,388/25,800 (9%)	1,487/13,421 (11%)
Thiazide diuretics (%)	7,025/150,960 (5%)	3,937/83,444 (5%)	1,474/25,971 (6%)	800/13,479 (6%)
Aspirin (%)	154,910/166,934 (93%)	77,596/91,271 (85%)	23,686/28,136 (84%)	12,510/14,877 (84%)
P2Y12 inhibitor (%)	153,947/167,322 (92%)	84,263/92,014 (92%)	25,125/28,296 (89%)	13,516/14,977 (90%)
Statins (%)	130,774/167,774 (78%)	82,469/91,978 (90%)	24,212/28,309 (86%)	13,112/14,924 (88%)
ACE inhibitors/ARB (%)	117,742/166,902 (71%)	73,096/91,862 (80%)	20,392/28,271 (72%)	11,018/14,891 (74%)
Beta-Blockers (%)	137,143/166,389 (82%)	75,240/91,669 (82%)	21,736/28,207 (77%)	11,435/14,876 (77%)
Radionuclide Study (%)	3,583/151,174 (2%)	2,340/83,569 (3%)	615/25,729 (2.4%)	443/13,435 (3%)
Exercise test (%)	6423/153,785	2,707/84,835	575/26,133 (2.2%)	356/13,543 (3%)

	(4%)	(3%)		
Coronary angiogram (during admission) (%)	120,512/160,678 (75%)	54,615/88,280 (62%)	12,919/27,235 (47%)	8,618/14,299 (60%)
Percutaneous coronary intervention (%)	64,301/131,386 (49%)	27,320/70,544 (39%)	5,990/20,826 (29%)	4,352/11,516 (38%)
CABG surgery (%)	11,110/131,386 (9%)	3,887/70,544 (6%)	1,198/20,826 (6%)	1,001/11,516 (9%)
Revascularization (CABG surgery/PCI) (%)	75,411/131,386 (57%)	31,207/70,544 (44%)	7,188/20,826 (35%)	5,353/11,516 (47%)
Death (%)	7,618/167,947 (5%)	5,296/92,347 (6%)	2,670/28,420 (9%)	1,253/15,027 (8%)
Cardiac mortality (%)	5,832/167,947 (4%)	4,250/92,347 (5%)	2,048/28,420 (7%)	984/15,027 (7%)
Reinfarction (%)	1,170/160,915 (0.7%)	1,072/88,443 (1%)	295/27,322 (1%)	152/14,336 (1%)
Major bleeding (%)	2,468/165,139 (1.5%)	1,460/90,862 (1.6%)	578/28,022 (2%)	339/14,682 (2%)
MACE* (%)	8,534/167,947 (5%)	6,113/92,347 (7%)	2,873/28,420 (10%)	1,356/15,027 (9%)

IV; intravenous, MRA; mineralocorticoid receptor antagonist, ACE: angiotensin-converting-enzyme, ARB; angiotensin receptor blockers, CABG; coronary artery bypass graft, PCI; percutaneous coronary intervention and MACE; major adverse cardiovascular events. MACE is defined as composite endpoint of in-hospital death and reinfarction.

Table 3: Adjusted Outcomes of individual vascular beds vs no vascular bed

Outcome variables	History of coronary artery disease (control group of no vascular bed) (92,347)		History of cerebrovascular disease (control group of no vascular bed) (28,420)		History of peripheral vascular disease (control group of no vascular bed) (15,027)	
	OR	P-value	OR	P-value	OR	P-value
Primary Outcomes						
MACE (In-hospital)	1.06 (1.01-1.12)	0.019	1.19 (1.12-1.27)	<0.001	1.22 (1.13-1.33)	<0.001
Mortality (In-hospital)	1.03 (0.97-1.09)	0.376	1.24 (1.16 1.32)	<0.001	1.33 (1.21-1.46)	<0.001
Secondary Outcomes						
Cardiac mortality (In-hospital)	1.08 (1.02-1.15)	0.014	1.20 (1.12-1.29)	<0.001	1.30 (1.18-1.44)	<0.001
Reinfarction (In-hospital)	1.39 (1.25-1.53)	<0.001	1.14 (0.99-1.31)	0.067	1.09 (0.91-1.31)	0.351

Each vascular bed compared against our reference group of 'No vascular bed'.

Adjusted for: age, sex, ethnicity, creatinine, heart rate, blood pressure, history of angina, family history of coronary artery disease, co-morbid conditions (hypertension, hypercholesterolaemia, diabetes, smoking, history of asthma or COPD), pharmacotherapy (prescription of low molecular weight heparin (LMWH), unfractionated heparin (UFH), warfarin, GP 2b/3a inhibitor, IV nitrate, furosemide, aldosterone antagonist, fondaparinux, beta blockers, angiotensin converting enzyme inhibitor/angiotensin receptor blockers, aspirin, P2Y12 inhibitor statins, thiazide diuretics), cardiac arrest and procedures including coronary angiography during admission and revascularisation (by PCI or CABG during admission). MACE is defined as composite endpoint of in-hospital death and reinfarction.

Table 4: Adjusted Outcomes by number of vascular beds vs no vascular bed

Outcome variables	One vascular bed affected (control group of no vascular bed) (94,544)		Two vascular beds affected (control group of no vascular bed) (18,114)		Three vascular beds affected (control group of no vascular bed) (1,674)	
	OR	**P-value**	**OR**	**P-value**	**OR**	**P-value**
Primary Outcomes						
MACE (In-hospital)	1.08 (1.03-1.13)	0.002	1.18 (1.11-1.26)	<0.001	1.37 (1.11-1.68)	0.003
Mortality (In-hospital)	1.05 (0.99-1.11)	0.051	1.26 (1.17-1.35)	<0.001	1.41 (1.12-1.79)	0.003
Secondary Outcomes						
Cardiac mortality (In-hospital)	1.10 (1.04-1.16)	0.002	1.24 (1.15-1.35)	<0.001	1.22 (0.94-1.58)	0.129
Reinfarction (In-hospital)	1.28 (1.16-1.40)	<0.001	1.14 (0.99-1.32)	0.076	1.54 (1.03-2.29)	0.035

Each vascular bed compared against our reference group of 'No vascular bed'. Adjusted for: age, sex, ethnicity, creatinine, heart rate, blood pressure, history of angina, family history of coronary artery disease, co-morbid conditions (hypertension, hypercholesterolaemia, diabetes, smoking, history of asthma or COPD), pharmacotherapy (prescription of low molecular weight heparin (LMWH), unfractionated heparin (UFH), warfarin, GP 2b/3a inhibitor, IV nitrate, furosemide, aldosterone antagonist, fondaparinux, beta blockers, angiotensin converting enzyme inhibitor/angiotensin receptor blockers, aspirin, P2Y12 inhibitor statins, thiazide diuretics), cardiac arrest and procedures including coronary angiography during admission and revascularisation (by PCI or CABG during admission). MACE is defined as composite endpoint of in-hospital death and reinfarction.

Table 5: ESC ACVC Quality indicators for each affected vascular bed

	No vascular bed (control group) (167,947)	**History of coronary artery disease (92,347)**	**History of cerebrovascular disease (28,420)**	**History of peripheral vascular disease (15,027)**
Coronary Angiography received within 72 hours * (%)	52,458/78,338 (67%)	21,610/35,951 (60%)	4,712/8,528 (55%)	3,533/6,067 (58%)
GRACE Risk score recorded in notes	N/A	N/A	N/A	N/A
CRUSADE risk score recorded in notes	N/A	N/A	N/A	N/A
LV Function recorded in notes (%)	87,014/167,947 (52%)	44,708/92,347 (48%)	13,537/28,420 (48%)	8,104/15,027 (54%)
Adequate $P2Y_{12}$ Inhibition on discharge (%)	153,947/167,322 (92%)	84,263/92,014 (92%)	25,125/28,296 (89%)	13,516/14,977 (90%)
Fondaparinux or LMWH received (%)	130,746/148,557 (88%)	69,578/78,949 (88%)	21,302/23,906 (89%)	11,048/12,687 (87%)
DAPT received on discharge (%)	144,889/166,711 (87%)	72,697/91,260 (80%)	21,666/28,118 (77%)	11,599/14,866 (78%)
High intensity statin on discharge** (%)	130,774/167,105 (78%)	82,469/91,978 (90%)	24,212/28,309 (86%)	13,112/14,924 (88%)
ACEi or ARB on discharge for those with moderate and severe LVSD (%)	21,364/28,812 (74%)	18,624/22,674 (82%)	5,021/6,549 (77%)	3,311/4,284 (77%)
Beta Blocker on discharge for those for those with moderate and severe LVSD (%)	24,471/28,769 (85%)	19,334/22,640 (85%)	5,407/6,547 (83%)	3,479/4,282 (81%)
Composite All/None score*** (%)	118,780/167,120 (71%)	66,960/91,377 (73%)	19,264/28,160 (68%)	10,519/14,884 (71%)
Composite All/None score for those with moderate and severe LVSD**** (%)	20,455/28,898 (71%)	16,641/22,615 (74%)	4,627/6,541 (71%)	3,092/4,294 (72%)

ESC; European Society of Cardiology, ACVC; Association for Acute Cardiovascular Care, GRACE; global registry of acute coronary events, CRUSADE; can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines, LV; left ventricle, EF; ejection fraction, LMWH; low molecular weight heparin, DAPT; dual antiplatelet therapy, ACEi/ARB; angiotensin converting enzyme inhibitor/angiotensin receptor blockers, LVSD; left ventricular systolic dysfunction, N/A; Not Available

* Coronary angiography received within 72 hours is expressed as a percentage of patients that underwent coronary angiography during the index admission, for which the time to angiography was able to be calculated from registry data

** MINAP does not record the specific type of statins, so 'statin prescription' was used as a surrogate for high intensity statin.

*** Composite score of receipt of low dose aspirin, $P2Y_{12}$ inhibition and statin.

**** Patients with moderate and severe LVSD (LVEF<50%), receipt of beta-blockers and ACEi/ARB were included in addition making five variables in total.

Table 6: ESC ACVC Quality indicators for each number of affected vascular beds

	No vascular bed (control group) (167,947)	**One vascular bed (94,544)**	**Two vascular beds (18,114)**	**Three vascular beds (1,674)**
Coronary Angiography received within 72 hours* (%)	52,458/78,338 (67%)	22,159/36,755 (60%)	3,338/5,982 (56%)	340/609 (56%)
GRACE Risk score recorded in notes	N/A	N/A	N/A	N/A
CRUSADE risk score recorded in notes	N/A	N/A	N/A	N/A
LV Function recorded in notes (%)	87,014/167,947 (52%)	46,132/94,544 (49%)	8,796/18,114 (49%)	875/1674 (52%)
Adequate $P2Y_{12}$ Inhibition on discharge (%)	153,947/167,322 (92%)	85,880/94,209 (91%)	16,229/18,040 (90%)	1,522/1,666 (91%)
Fondaparinux or LMWH received (%)	130,746/148,557 (88%)	71,447/81,012 (88%)	13,448/15,210 (88%)	1,195/1,370 (87%)
DAPT received on discharge (%)	144,889/166,711 (87%)	74,393/93,446 (80%)	13,857/17,918 (77%)	1,285/1,654 (78%)
High intensity statin on discharge** (%)	130,774/167,105 (78%)	83,096/94,173 (88%)	16,088/18,020 (89%)	1,507/1,666 (90%)
ACEi or ARB on discharge for those with moderate and severe LVSD (%)	21,364/28,812 (74%)	17,856/22,093 (81%)	3,926/4,936 (80%)	416/514 (81%)
Beta Blocker on discharge for those for those with moderate and severe LVSD (%)	24,471/28,769 (85%)	18,707/22,058 (85%)	4,119/4,936 (83%)	425/513 (83%)
Composite All/None score*** (%)	118,780/167,120 (71%)	67,794/93,597 (72%)	12,697/17,928 (71%)	1,185/1,656 (72%)
Composite All/None score for those with moderate and severe LVSD**** (%)	20,455/28,898 (71%)	16,118/22,057 (73%)	3,557/4,927 (72%)	376/513 (73%)

ESC; European Society of Cardiology, ACVC; Association for Acute Cardiovascular Care, GRACE; global registry of acute coronary events, CRUSADE; can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines, LV; left ventricle, EF; ejection fraction, LMWH; low molecular weight heparin, DAPT; dual antiplatelet therapy, ACEi/ARB; angiotensin converting enzyme inhibitor/angiotensin receptor blockers, LVSD; left ventricular systolic dysfunction, N/A; Not Available

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**** Patients with moderate and severe LVSD (LVEF<50%), receipt of beta-blockers and ACEi/ARB were included in addition making five variables in total.