Relationship between anemia and mortality outcomes in a national ACS cohort: insights from the UK MINAP registry

Short title: Anemia and mortality in acute coronary syndrome

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Abstract

Background: We aim to determine the prevalence of anemia in ACS patients and compared their clinical characteristics, management and clinical outcomes to those without anemia in an unselected national ACS cohort.

Methods and Results: The Myocardial Ischemia National Audit Project (MINAP) registry collects data on all adults admitted to hospital trusts in England and Wales with diagnosis of an ACS. We conducted a retrospective cohort study by analyzing patients in this registry between January 2006 and December 2010 and followed them up until August 2011. Multiple logistic regressions were used to determine factors associated with anemia and the adjusted odds of 30-day mortality with 1 g/dl incremental hemoglobin increase and the 30-days and 1-year mortality for anemic compared to non-anemic groups. Analyses were adjusted for covariates. Our analysis of 422,855 patients with ACS showed that 27.7% of patients presenting with ACS are anemic, and that these patients are older, have a greater prevalence renal disease, peripheral vascular disease, diabetes mellitus and previous acute myocardial infarction and are less likely to receive evidence based therapies shown to improve clinical outcomes. Finally our analysis suggests that anemia is independently associated with 30-day (OR 1.28, 95%CI 1.22-1.35) and 1-year mortality (OR 1.31, 95%CI 1.27-1.35) and we observed a reverse J-shaped relationship between hemoglobin levels and mortality outcomes.

Conclusion: The prevalence of anemia in a contemporary national ACS cohort is clinically significant. Patients with anemia are older and multi-morbid, and less likely to receive evidence-based therapies shown to improve clinical outcomes with the presence of anemia independently associated mortality outcomes.

Keywords: Acute coronary syndrome; anemia; mortality

List of abbreviations

ACS=acute coronary syndrome

CV=cardiovascular

RCT=randomized controlled trials

NHS=National Health Service

STEMI=ST segment elevation myocardial infarction

NSTEMI=non-ST segment elevation myocardial infarction

ACE=angiotensin converting enzyme

WHO=World Health Organization

ATE=average treatment effects

COPD=chronic obstructive pulmonary disease

PCI=percutaneous coronary intervention

Introduction

Both registry data[1-4] and secondary analyses of randomized controlled trials[5-7] have suggested that the burden of anemia in patients presenting with acute coronary syndromes (ACS) is significant. A recent meta-analysis of 27 studies including 233,144 patients has reported a prevalence of anemia in ACS patients close to 20%[8] and current clinical guidelines fail to offer firm recommendations for its concurrent management in the ACS setting.[9,10]

Patients with anemia are older[3,6,7,11] with a significantly greater burden of co-morbidities such as chronic kidney disease,[12-14] diabetes,[6,13,14] heart failure,[13,15] more extensive coronary artery disease[6] and are less likely to undergo cardiac catheterization.[4,6,11] These adverse clinical characteristics are well known to contribute to adverse outcomes in patients with ACS. Previous reports have suggested that ACS patients with anemia have significantly worse in-hospital and longer-term total and cardiac mortality outcomes,[5-7,16,17] heart failure,[18] risk of major bleeding[6] and of re-infarction.[6,8,19] Some studies have reported that once differences in age or co-morbidity burden between anemic/non-anemic ACS cohorts are adjusted for; anemia is no longer an independent predictor of adverse mortality[20] or cardiovascular mortality[21] whilst other studies report that the relationship persists.[6,7,19,22] Other studies have reported different relationships between anemia and cardiovascular (CV) outcomes according to sex, with baseline anemia independently associated with higher rates of all cause and cardiac mortality at 30-days and 1-year in men but not in women.[7]

Data derived from secondary analyses from randomized controlled trials (RCT) have suggested adverse mortality outcomes associated with anemia in patients with ACS,[5,6,23] such RCTs often exclude older patients with the most severe co-morbid conditions and may therefore under-report the prevalence of anemia and under-estimate its prognostic impact. Many of the studies that have reported relationships between anemia and adverse outcomes in the setting of ACS, have not adjusted for/excluded patients with major bleeding events[3,5,24] that may further confound the relationships reported.

We have estimated the prevalence of anemia in ACS patients and compared their clinical characteristics, management and clinical outcomes to those without anemia in an unselected national ACS cohort derived from the Myocardial Ischaemia National Audit Project (MINAP) registry that collects data on all patients in the UK admitted with a confirmed diagnosis of ACS. We also examined the relationship between anemia and short

(30-day) and longer-term (1-year) mortality outcomes in this setting and assessed whether the prognostic impact of anemia relates to its severity.

Methods

Study design and population

The Myocardial Ischemia National Audit Project (MINAP) registry collects data on all patients age 18 or over in the United Kingdom who are admitted to all 230 NHS hospital trusts in England and Wales with a confirmed diagnosis of an ACS. We analyzed data from the registry for patients admitted between January 2006 and December 2010 on this registry and followed them up until August 2011. Participants were included in the current study if they had a diagnosis of any ACS (STEMI, NSTEMI or unstable angina) determined by the medical team at time of discharge. Mortality outcome was ascertained by linkage through the Office of National Statistics.[25]

Data collection

The MINAP dataset collects standardized data on pre-hospital and in-hospital care for all ACS admissions from all 230 NHS trusts in England and Wales and is part of the NHS data dictionary.[http://www.hqip.org.uk/minap-2013-report/] The data is collected by nurses and clinical audit staff and contains 123 fields. The details of development and initial findings are reported elsewhere.[26]

In the current study variables included in the analyses were hemoglobin at the time of admission with an ACS, age, sex, smoking status, peak troponin levels, hyperlipidemia, hypertension, prior angina, prior myocardial infarction, prior heart failure, prior stroke, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, renal failure, prior percutaneous coronary intervention, prior coronary artery bypass graft, prior medications (angiotensin converting enzyme (ACE) inhibitor, beta-blocker, statin, clopidogrel, aspirin), clinical diagnosis (unstable angina, NSTEMI, STEMI), discharge medications (ACE inhibitor, beta-blocker, statin, clopidogrel, aspirin), angiography, in-hospital bleeding and mortality outcomes in-hospital, 30-days and 1-year. World Health Organization (WHO) hemoglobin thresholds were used to define anemia as <13 g/dl for men and <12 g/dl for women.

Statistical analysis

Multiple imputations by chained equations in STATA version 13.0 was used to impute missing values for variables where possible. We describe baseline variables according to whether they were missing or non-missing in tables and details of participant inclusion is shown graphically. Descriptive statistics are presented for baseline variables and outcome according to anemia status and sex. Associations between anemia status and individual variables were tested using one-way analysis of variance for continuous variables and Chi-squared test for categorical variables. We used multiple logistic regression with adjustments for baseline variables to determine factors associated with anemia. The same regression methods were used to determine the adjusted odds of 30-day mortality with 1 g/dl incremental hemoglobin increase from <10 g/dl to ≥18 g/dl for men and from <9 g/dl to ≥17 g/dl for women. These results were presented graphically. Additional analyses were performed to determine the adjusted odds ratio of mortality at 30-days and 1-year for anemic compared to non-anemic group for the whole cohort, the male only cohort, female only cohort, NSTEMI cohort, STEMI cohort and subgroups where bleeding was excluded. The baseline variables of the group of participants who bled and did not bleed were also compared. Further analysis was performed restricting the cohort which had no imputations. Severity of anemia was examined by stratifying the cohort by sex specific hemoglobin cutoffs (Hb <10 g/dl, Hb 10-11 g/dl, Hb 11-12 g/dl, Hb 12-13 g/dl, Hb ≥13 g/dl for men and Hb <9 g/dl, Hb 9-10 g/dl, Hb 10-11 g/dl, Hb 11-12 g/dl, Hb ≥12 g/dl for women. To better control for baseline differences across the anemic and non-anemic groups, further analysis was performed using propensity score matching (*mi estimate:teffects psmatch*) to estimate average treatment effects (ATE). Although multiple regression is the most widely used method to control for measured confounders, it can be inadequate when the two comparator groups (anaemia vs no anaemia in our analyses) are very different across key confounders. Propensity score matching can be a better approach in such extreme scenarios and can thus serve as a useful sensitivity analysis. Propensity scores were calculated using multiple logistic regression and then 1:1 matching with replacement (i.e. including all cases and controls) was performed prior to simple logistic regression models to obtain the ATE. Statistics to demonstrate the success of the matching are also reported.

Ethics approval

The current study obtained the ethical approval from the Faculty of Medicine & Health Sciences Research Ethics Committee, University of East Anglia.

Results

There were a total of 424,848 participants in the MINAP cohort between January 2006 to December 2010 who were followed up till August 2011. Of them, hemoglobin values were recorded in 257,999 patients. Supplementary Figure 1 shows the flow diagram of participant inclusion and comparison of characteristics between those with and without available data on Hb did not show any material differences (Supplementary Table 1)

The prevalence of anemia in this cohort was 71,223/256,744 (27.7%). After multiple imputations the sample size of the complete dataset with all imputed variables was 256,744.

The descriptive statistics of baseline variables the included cohort by anemia status is shown in Table 1. The anemic cohort was significantly older with a higher proportion of smokers (85% vs 68%, p<0.001), prior hypertension (59% vs 48%, p<0.001), angina (43% vs 27%, p<0.001), myocardial infarction (38% vs 23%, p<0.001), prior heart failure (12% vs 4%, p<0.001), stroke (14% vs 7%, p<0.001), peripheral vascular disease (8% vs 3%, p<0.001), COPD (18% vs 14%, p<0.001), diabetes (31% vs 16%, p<0.001) and renal failure (19% vs 4%, p<0.001). Participants who were anemic were more likely to have aspirin and clopidogrel prior to admission (7% vs 5%, p<0.001) and less likely to be prescribed dual-antiplatelet therapy on discharge (75% vs 79%, p<0.001). Participants whose anemia occurred in the context of a bleeding complication were more likely to be female, be on aspirin before admission and on discharge (30% vs 28%, p<0.001), have STEMI diagnosis (52% vs 38%, p<0.001), less likely to receive angiography (26% vs 38%, p<0.001) and more likely die at 30 days (6% vs 3%, p<0.001) and 1 year (12% vs 8%, p<0.001) (Supplementary Table 2).Similar rates of angiography were performed in the anemic vs. non-anemic cohort but patients with anemia were significantly less likely to be prescribed secondary prevention medications post discharge. The difference in crude mortality rates between the anemic and non-anemic groups increased with longer follow up.

Multiple logistic regression where used to determine the independent factors associated with the presence of anemia at baseline (Table 2). The most significant associations were observed with presence of peripheral vascular disease (OR 1.427 95% CI 1.362-1.496, p<0.001), diabetes mellitus (OR 1.786 95% CI 1.742-1.832, p<0.001) and renal disease (OR 3.058 95% CI 2.962-3.158, p<0.001).

The adjusted odds of mortality by incremental (1 g/dl) increase in hemoglobin is shown in Figure 1. Lower hemoglobin values were associated with significantly higher mortality with a non-significant trend towards higher mortality in those patients with elevated hemoglobin values.

The odds of mortality associated with the presence of anemia following adjustment for baseline co-variates is shown in Table 3. We observed that there was a ~1.3 fold increase in odds of 30-day mortality (OR 1.281 95% CI 1.217-1.350, p<0.001) and 1-year (OR 1.311 95% CI 1.274-1.348, p<0.001) mortality respectively with anemia after adjustment for potential confounders. Similar significant increases in mortality with anemia were observed for men (30 day mortality OR 1.298 95% CI 1.217-1.384, p<0.001. 1 year mortality OR 1.354 95%CI 1.299-1.411, p<0.001) and women (30 day mortality OR 1.255 95% CI 1.146-1.374, p<0.001, 1 year mortality OR 1.252 95% CI 1.198-1.309, p<0.001) as well as diagnosis of NSTEMI (30 day mortality OR 1.291 95% CI 1.213-1.374, p<0.001, 1 year mortality OR 1.326 95% CI 1.281-1.374, p<0.001) and STEMI (30 day mortality 1.269 95% CI 1.163-1.384, p<0.001, 1 year mortality OR 1.284 95% CI 1.284-1.352, p<0.001). In order to eliminate the potential confounding influence of major bleeding complications on the relationship between anemia and mortality, we repeated the analysis following exclusion of patients with major bleeding complications and similar results were recorded (30 day mortality OR 1.279 95% CI 1.213-1.348, p<0.001, 1 year mortality OR 1.309 95% CI 1.271-1.347, p<0.001). Furthermore, a sensitivity analysis was undertaken in patients in whom Hb values were recorded at baseline (257,999 patients) and similar independent factors associated with anemia (Supplementary Table 3) and mortality outcomes associated with anemia (Supplementary Table 4) were observed.

Propensity score matched analysis is shown in Table 4 and anemia is associated with significant increase in mortality at both 30 days and 1 year after adjustments for propensity score (30 day mortality coefficient 0.0080 95% CI 0.0045-0.0114, p<0.001, 1 year mortality coefficient 0.0173 95% CI 0.0128-0.0218, p<0.001).

There were also differences in baseline characteristics according to sex (Table 5). Most notably, females were younger (mean age 74 vs 67 years, p<0.001) but more were smokers (79% vs 70%, p<0.001) and hypertensive (56% vs 47%, p<0.001). However

medication at discharge was higher in men and women had a higher proportion of patient with adverse outcomes.

The sex specific adjusted odds of mortality by incremental (1 g/dl) increase in hemoglobin is shown in Figure 2. For both sexes, lower hemoglobin values were associated with significantly higher mortality but high values of hemoglobin were only associated with higher mortality in men but not women. Similar results were observed if patients with bleeding were excluded (Supplementary Figure 2).

In terms of severity of anemia there was a increase in mortality at both 30 days and 1 year with reduced hemoglobin which ranged from ~1.2-1.3 fold increase in odds of mortality for Hb 12-13 g/dl to ~1.4-1.5 fold increase for Hb <10 g/dl for men (Table 6). For women, similar results were recorded.

Discussion

Our analysis is the largest analysis to study the prevalence, clinical characteristics and outcomes associated with anemia in an unselected national cohort of ACS patients in the United Kingdom. We have observed that more than to one in four patients presenting with ACS are anemic, and that these patients are older, have a greater prevalence of co-morbid conditions and are less likely to receive evidence based therapies shown to improve clinical outcomes. Finally our analysis suggests that anemia is independently associated with adverse in-hospital and longer-term mortality outcomes, with a reverse J-shaped relationship between Hb levels and both short and longer mortality outcomes observed.

Our observed prevalence of anemia of 28% is greater than that reported in data derived from RCTs reporting rates of between 10-25%[5-7,23] although registry data reveals significantly higher prevalences.[4,12,27] For example, an analysis of 78,974 Medicare beneficiaries aged 65 years or older hospitalized with acute myocardial infarction revealed a prevalence of anemia of 43%.[12] We have observed that ACS patients with anemia are older, have a greater prevalence of co-morbid conditions and are less likely to receive evidence based therapies for the treatment of ACS in agreement with previous literature.[5-7,19,21]

In the current analysis, we report that the presence of anemia is independently associated with an approximately 50% increased risk of mortality in the short and long-term, and that this prognostic impact is observed in both men and women, in contrast to the findings of a secondary analysis of the HORIZONS-AMI trial that failed to demonstrate an association between anemia and increased risk of mortality in women.[7] We have observed a reverse J-shaped relationship between decreasing Hb values and 30-day mortality, with a dose-response effect with progressively lower odds of survival with more profound degrees of anemia in both men and women. Similar reverse j-shaped relationships between Hb levels and CV death and CV death, myocardial infarction or recurrent ischemic events in some studies,[21] whilst other studies have not revealed such statistically significant relationships in either in-hospital cardiac mortality[16] or longer term mortality.[1]

Previous studies have reported that anemia is independently associated with adverse clinical outcomes, many of these studies did not report whether patients with bleeding events were excluded from their analyses as it is well documented that major bleeding is independently associated with mortality in the ACS setting[28-30] which might have confounded

any reported relationships between the presence of anemia and mortality. In the current analysis, we report anemia independently predicts adverse mortality outcomes and that the J-shaped relationship between Hb level and mortality persists even after exclusion of patients with bleeding events.

There are several biological and clinical reasons why anemia may lead to worse clinical outcomes in patients with ACS. In the setting of ACS, anemia might worsen ischaemia by decreasing the oxygen delivery to the jeopardized myocardium and increase myocardial oxygen demand due to greater cardiac output to maintain adequate systemic oxygen delivery.[31,32] Clinically, patients with anemia are often under-prescribed antiplatelet therapy due to bleeding concerns, for example in our current analysis clopidogrel was prescribed in 73% of patients without anemia and 66% with anemia (P<0.001) whilst in the CADILLAC trial 18% of patients with anemia at the time of their ACS were no longer receiving aspirin at 1 year,[23] which might contribute to increased cardiovascular events. Analysis of the ACUITY trial suggests that patients with anemia were less likely to undergo percutaneous coronary intervention (PCI) and more likely to be medically managed which may further contribute to worse cardiovascular outcomes in this group.[6] Finally anemia may be a manifestation of numerous chronic disease states and the presence of anemia is merely a marker of poorer outcomes in patients with chronic diseases.

Our analysis suggests that anemia is independently associated with adverse clinical outcomes in patients presenting with ACS, there is a lack of clarity in contemporary guideline recommendations as to whether such patients with anemia should be transfused and the optimal transfusion strategy.[33] The American Association of Blood Banks recommendation for patients presenting with ACS is "No recommendation for or against a liberal or restrictive transfusion threshold for hospitalized, hemodynamically stable patients with acute coronary syndrome."[33] Furthermore, the CRIT (conservative versus liberal red cell transfusion in acute myocardial infarction) randomized pilot trial[34] demonstrated that patients with ACS and a hematocrit level <30% who were randomized to a liberal transfusion arm had a significantly higher composite endpoint of in-hospital death, recurrent myocardial infarction, or congestive heart failure than those who underwent more restrictive transfusion practice (38% vs. 13%; p = 0.046). In contrast, in the MINT (A Multicenter, Randomized Study of Argatroban Versus heparin as Adjunct to Tissue Plasminogen Activator [TPA] in Acute Myocardial Infarction: Myocardial Infarction With Novastan and TPA) pilot study undertaken in 110 patients presenting with an ACS or stable angina with anemia undergoing cardiac catheterization,

patients randomized to a liberal blood transfusion strategy had 50% lower primary outcome rates of death, myocardial infarction, and unscheduled revascularization compared to those patients randomized to a restrictive transfusion strategy, with lower 30-day mortality too. A recent meta-analysis of 10 studies consisting mainly of registry studies including 203,665 patients has shown a close to 3-fold independent increase in the risk of mortality associated with a liberal blood transfusion strategy in the AMI setting with meta-regression adjusting for a history of bleeding or baseline hemoglobin level revealing a similar increased risk, indicating a significant risk for blood transfusion over and above that associated with bleeding or anemia[35] with similar findings reported in the PCI setting.[36]

Our study has some limitations. The MINAP dataset requires the recording of Hb within 24 hours of admission, many of these Hb values particularly in the setting of hemodynamically unstable NSTEMI or STEMI treated with primary PCImay be post PCI and may reflect the influence of acute bleeding complications and not reflect chronic anemia. Nevertheless, even following exclusion of patients who sustained bleeding complications during their in-hospital course, the relationships that we examined remained unchanged. We report an association between anemia and in-hospital and longer-term mortality, we cannot infer causality. While it would be interesting to know whether anemia was associated with cardiac mortality, we were unable to determine the cause of death for participants. We have adjusted for differences in baseline characteristics between the anemic/non-anemic cohorts, other unmeasured confounders may be contributing to the adverse clinical outcomes associated with anemia that we report. Another limitation was the missing data, which varied extent depending on the study variable, and we tried to approximate these values using multiple imputations to impute the missing values. Finally, the MINAP dataset does not record the receipt of blood transfusions which may contribute to the adverse clinical outcomes reported.[35]

Conclusions

In conclusion, this is the largest to study the prevalence, clinical characteristics and outcomes associated with anemia in an unselected national cohort of ACS patients in the United Kingdom. We report a significant prevalence of anemia in a contemporary ACS cohort, with approximately one in four patients presenting with ACS being anemic, and that these patients are older, have a greater prevalence of co-morbid conditions and are less likely

to receive evidence based therapies shown to improve clinical outcomes. Finally our findings suggest that anemia is independently associated with adverse 30-day and longer-term mortality outcomes, with a reverse J-shaped relationship between Hb levels and mortality outcomes observed in both men and women. The clinical effectiveness of correcting anemia routinely in ACS has not been widely explored, there is considerable uncertainty in the value of such an approach. Targeted intervention strategies in this patient population should be explored.

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Contributorship statement:

MAM, MJSZ and PKM conceived and planned the study. CSK and EK analyzed the data. MAM and CSK wrote the first draft of the paper. All authors contributed to the interpretation of the findings and reporting of the work. PKM is the guarantor. PKM and MJSZ are co-PIs of the MINAP-older age project.

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Disclosures:

None.

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List of Tables and Figures

Table 1: Baseline characteristic of the MINAP cohort according to anemia status

Table 2: Significant factors associated with anemia: logistic regression model

Table 3: Multivariate association between anemia and mortality: logistic regression models

Table 4: Propensity score matching analysis on 10 imputed datasets, reporting average treatment effects (ATE).

Table 5: Baseline characteristic of the MINAP cohort in a single imputed dataset according to sex

Table 6: Evaluation of the severity of anemia by sex

Figure 1: Adjusted odds of mortality at 30 days according to hemoglobin levels for men and women

Figure 2A & 2B: Adjusted odds of mortality at 30 days according to hemoglobin levels and sex

List of Supplementary Tables and Figures

Supplementary Table 1: Comparison of patients with missing and no missing hemoglobin values

Supplementary Table 2: Baseline characteristic of the MINAP cohort according to bleeding status

Supplementary Table 2: Baseline characteristic of the MINAP cohort according to bleeding status

Supplementary Table 3: Significant multivariate predictors of anemia in patients in whom baseline hemoglobin values were recorded (n=256,744)

Supplementary Table 4: Sensitivity analysis of multivariate association between anemia and mortality in patients in whom baseline hemoglobin values were recorded

Supplementary Figure 1: Flow chart of patient inclusion

Supplementary Figure 2: Adjusted odds of mortality at 30 days according to hemoglobin levels and sex with exclusion of participants with bleed outcome

Table 1: Baseline characteristic of the MINAP cohort according to anemia status

Variable[†‡]	**No anemia (n=185,521)**	**Anemia (n=71,223)**	**p-value**[‡]
Mean age (years)	66 (±14)	76 (±12)	<0.001
Male (%)	124,143/185,521 (67%)	44,027/71,223 (62%)	<0.001
Current or ex-smokers	118,634/174,003 (68%)	54,361/64,210 (85%)	<0.001
Peak troponin			NA
Median Troponin I (IQR) (µg/L)	1.1 (0.2-7.1)	1.0 (0.2-5.3)	
Median Troponin T (IQR) (µg/L)	1.2 (0.2-7.4)	1.0 (0.2-5.6)	
Mean Troponin I (SD) (µg/L)	10 (±24)	9 (±22)	
Mean Troponin T (SD) (µg/L)	10 (±22)	8 (±20)	
Comorbidities			
Hyperlipidemia	62,060/113,535 (35%)	24,442/67,499 (36%)	<0.001
Hypertension	86,052/180,2044 (48%)	40,573/69,230 (59%)	<0.001
Prior angina	47,915/179,636 (27%)	29,629/68,890 (43%)	<0.001
Prior myocardial infarction	41,215/180,166 (23%)	26,028/69,119 (38%)	<0.001
Prior heart failure	7,286/177,567 (4%)	7,870/68,411 (12%)	<0.001
Stroke	12,320/177,656 (7%)	9,337/68,636 (14%)	<0.001
PVD	5,852/171,572 (3%)	5,019/66,849 (8%)	<0.001
COPD	24,625/173,811 (14%)	12,489/67,813 (18%)	<0.001
Diabetes	29,016/180,989 (16%)	21,915/69,594 (31%)	<0.001
Renal failure	7,025/177,840 (4%)	13,283/68,831 (19%)	<0.001
Prior PCI	18,865/179,306 (11%)	8,354/68,560 (12%)	<0.001
Prior CABG	10,522/179,580 (6%)	6,858/68,799 (10%)	<0.001
Medications prior to admission			
ACE inhibitor	59,891/171,542 (35%)	31,984/66,325 (48%)	<0.001
Beta blocker	49,387/171,865 (29%)	25,446/66,413 (38%)	<0.001
Statin	71,339/173,840 (41%)	37,842/66,978 (57%)	<0.001
Clopidogrel	13,506/81,575 (17%)	6,782/29,402 (23%)	<0.001
Aspirin	46,856/167,055 (28%)	18,593/64,237 (29%)	<0.001
Aspirin and clopidogrel	3,490/72,682 (5%)	1,814/26,198 (7%)	<0.001
Diagnosis at current admission			<0.001
NSTEMI or unstable angina	104,928/170,135 (62%)	41,049/65,285 (63%)	
STEMI	65,207/170,135 (38%)	24,235/65,285 (37%)	
Medications at discharge			
ACE inhibitor	121,885/185,521 (66%)	39,458/71,223 (55%)	<0.001
Beta blocker	117,353/185,521 (63%)	38,709/71,223 (54%)	<0.001
Statin	136,696/185,521 (74%)	47,976/71,223 (67%)	<0.001
Clopidogrel	56,980/64,186 (89%)	17,381/20,595 (84%)	<0.001
Aspirin	129,872/145,076 (90%)	49,657/55,517 (89%)	0.623
Aspirin and clopidogrel	39,445/50,208 (79%)	12,065/16,098 (75%)	<0.001
Angiography performed			
Angiography	70,914/185,521 (38%)	27,034/71,223 (38%)	0.319
Mortality outcomes			
Mortality at 30 days	3,425/184,228 (2%)	3,691/70,771 (5%)	<0.001
Mortality at 1 year	8,520/183,041 (5%)	9,173/70,339 (13%)	<0.001
Bleeding Outcomes			
In-hospital bleeding	3,475/174,183 (2%)	1,337/67,023 (2%)	0.998

† Results reported as mean (SD) for continuous variables and n (%) for categorical variables.
‡ Logistic regression (continuous variables), Chi^2 square test (categorical variables).
BMI=body mass index, COPD=chronic obstructive pulmonary disease, PVD=peripheral vascular disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Table 2: Significant factors associated with anemia (n=422,855): logistic regression model*

Variable[†]	**Odds Ratio (95% CI)**	**p-value**[‡]
Age	1.046 (1.045-1.046)	<0.001
Male sex	1.108 (1.088-1.128)	<0.001
Smoker	1.243 (1.216-1.271)	<0.001
Hypercholesterolemia	0.896 (0.876-0.916)	<0.001
Angina	1.208 (1.182-1.235)	<0.001
Previous myocardial infarction	1.208 (1.182-1.235)	<0.001
Previous heart failure	1.242 (1.192-1.293)	<0.001
Previous stroke	1.191 (1.153-1.230)	<0.001
Peripheral vascular disease	1.427 (1.362-1.496)	<0.001
Chronic obstructive pulmonary disease	1.109 (1.083-1.136)	<0.001
Diabetes mellitus	1.786 (1.742-1.832)	<0.001
Renal disease	3.058 (2.962-3.158)	<0.001
Previous percutaneous coronary intervention	0.967 (0.935-1.000)	0.05
Previous coronary artery bypass graft	1.074 (1.040-1.110)	<0.001
Admission medication		
Clopidogrel	1.223 (1.186-1.262)	<0.001
Aspirin	1.024 (1.004-1.045)	<0.001

*All covariates in the table were included in the multiple logistic regression.

Table 3: Multivariate association between anemia and mortality: logistic regression models

Total cohort

Mortality outcome	N	Odds ratio (95% CI)	p-value
Mortality at 30 days	420,614	1.281 (1.217-1.350)	<0.001
Mortality at 1 year	418,471	1.311 (1.274-1.348)	<0.001
Men only			
Mortality at 30 days	274,278	1.298 (1.217-1.384)	<0.001
Mortality at 1 year	272,812	1.354 (1.299-1.411)	<0.001
Women only			
Mortality at 30 days	146,336	1.255 (1.146-1.374)	<0.001
Mortality at 1 year	145,659	1.252 (1.198-1.309)	<0.001
NSTEMI			
Mortality at 30 days	260,446	1.291 (1.213-1.374)	<0.001
Mortality at 1 year	259,003	1.326 (1.281-1.374)	<0.001
STEMI			
Mortality at 30 days	159,962	1.269 (1.163-1.384)	<0.001
Mortality at 1 year	159,265	1.284 (1.220-1.352)	<0.001

Bleeding excluded

Mortality outcome	N	Odds ratio (95% CI)	p-value
Mortality at 30 days	412,396	1.279 (1.213-1.348)	<0.001
Mortality at 1 year	410,301	1.309 (1.271-1.347)	<0.001
Men only			
Mortality at 30 days	268,985	1.293 (1.209-1.381)	<0.001
Mortality at 1 year	267,547	1.348 (1.294-1.405)	<0.001
Women only			
Mortality at 30 days	143,378	1.255 (1.150-1.371)	<0.001
Mortality at 1 year	142,720	1.253 (1.198-1.310)	<0.001

Total cohort without imputations

Mortality outcome	N	Odds ratio (95% CI)	p-value
Mortality at 30 days			
Unadjusted	254,999	2.905 (2.770-3.045)	<0.001
Fully adjusted	34,861	1.472 (1.197-1.810)	<0.001
Mortality at 1 year			
Unadjusted	253,380	3.072 (2.978-3.168)	<0.001
Fully adjusted	34,731	1.588 (1.430-1.763)	<0.001

Table 4: Propensity score matching analysis on 10 imputed datasets, reporting average treatment effects (ATE).

Analysis of propensity score matching with ATE

Outcome	N	Coefficient	95% CI		p-value
30 day mortality	121,979	0.0080	0.0045	0.0114	<0.001
1 year mortality	121.276	0.0173	0.0128	0.0218	<0.001

Propensity score matching statistics

Group	Mean (SD)	Median (IQR)
Case (anemia)	0.739 (0.174)	0.782 (0.642, 0.875)
Control (no anemia)	0.739 (0.174)	0.782 (0.642, 0.875)
Abs (Case-Control)	0.00001 (0.00011)	$7*10^{-6}$ ($2*10^{-6}$, 0.00002)

Table 5: Baseline characteristic of the MINAP cohort in a single imputed dataset according to sex

Variable[†‡]	**Female (n=147,064)**	**Male (n=275,791)**	**p-value**[‡]
Mean age (years)	74 (±13)	67 (±14)	<0.001
Current or ex-smokers	103,049/131,067 (79%)	175,401/251,888 (70%)	<0.001
Peak troponin			NA
Median Troponin I (IQR) (µg/L)	0.8 (0.2-4.4)	1.1 (0.2-7.0)	
Median Troponin T (IQR) (µg/L)	0.8 (0.1-5.6)	1.3 (0.2-9.4)	
Mean Troponin I (SD) (µg/L)	7 (±20)	10 (±23)	
Mean Troponin T (SD) (µg/L)	7 (±18)	10 (±22)	
Comorbidities			
Hyperlipidemia	45,444/132,621 (34%)	88,884/247,578 (36%)	<0.001
Hypertension	77,462/137,388 (56%)	120,727/255,434 (47%)	<0.001
Prior angina	45,397/136,047 (33%)	79,718/253,809 (31%)	<0.001
Prior myocardial infarction	35,001/137,514 (25%)	72,795/256,934 (28%)	<0.001
Prior heart failure	10,623/133,845 (8%)	13,559/248,960 (5%)	<0.001
Stroke	13,854/133,862 (10%)	20,079/248,892 (8%)	<0.001
PVD	5,448/130,925 (4%)	12,219/243,539 (5%)	<0.001
COPD	23,962/131,774 (18%)	34,462/244,671 (14%)	<0.001
Diabetes	29,493/140,481 (21%)	51,424/262,468 (20%)	<0.001
Renal failure	9,795/134,079 (7%)	17,931/249,319 (7%)	0.196
Prior PCI	10,595/134,947 (8%)	30,254/251,990 (12%)	<0.001
Prior CABG	5,706/135,286 (4%)	20,933/252,728 (8%)	<0.001
Medications prior to admission			
ACE inhibitor	49,929/126,128 (40%)	88,256/234,196 (38%)	<0.001
Beta blocker	41,213/126,289 (33%)	73,726/234,423 (31%)	<0.001
Statin	58,420/129,601 (45%)	110,898/241,129 (46%)	<0.001
Clopidogrel	15,230/77,245 (20%)	28,564/142,840 (20%)	0.115
Aspirin	37,535/131,780 (28%)	71,002/247,098 (29%)	0.103
Diagnosis at current admission			0.143
NSTEMI or unstable angina	83,404/134,524 (62%)	155,880/252,401 (62%)	
STEMI	51,120/134,524 (38%)	96,521/252,401 (38%)	
Medications at discharge			
ACE inhibitor	83,277/147,064 (57%)	171,311/275,791 (62%)	<0.001
Beta blocker	80,221/147,064 (55%)	165,753/275,791 (60%)	<0.001
Statin	99,246/147,064 (67%)	196,756/275,791 (71%)	<0.001
Clopidogrel	48,406/60,264 (80%)	98,181/115,628 (85%)	<0.001
Aspirin	102,340/114,611 (89%)	192,059/215,135 (89%)	0.862
Angiography performed			
Angiography	55,049/147,064 (37%)	103,267/275,791 (37%)	0.939
Mortality outcomes			
Mortality at 30 days	5,711/146,336 (4%)	7,474/274,278 (3%)	<0.001
Mortality at 1 year	14,149/145,659 (10%)	18,481/272,812 (7%)	<0.001
In-hospital bleeding	2,766/137,132 (2%)	4,932/257,591 (2%)	0.027

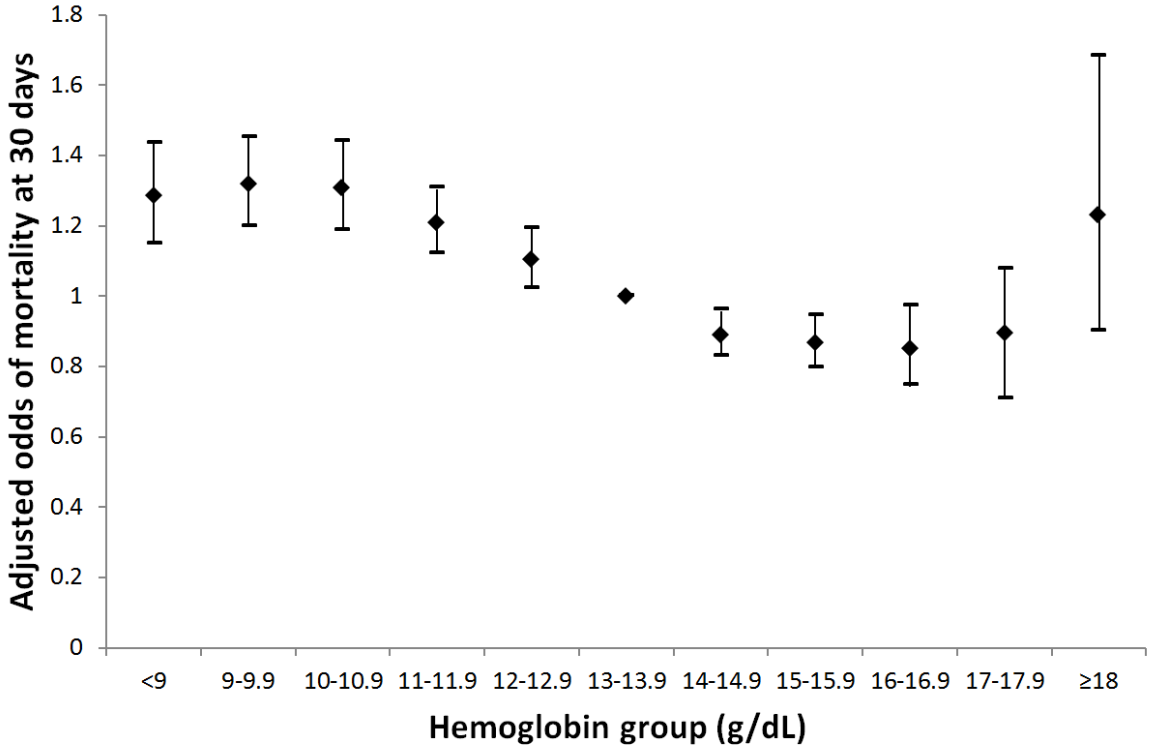
† Results reported as mean (SD) for continuous variables and n (%) for categorical variables.
‡ Logistic regression (continuous variables), Chi^2 square test (categorical variables).

BMI=body mass index, COPD=chronic obstructive pulmonary disease, PVD=peripheral vascular disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Table 6: Evaluation of the severity of anemia by sex using multiple logistic regression

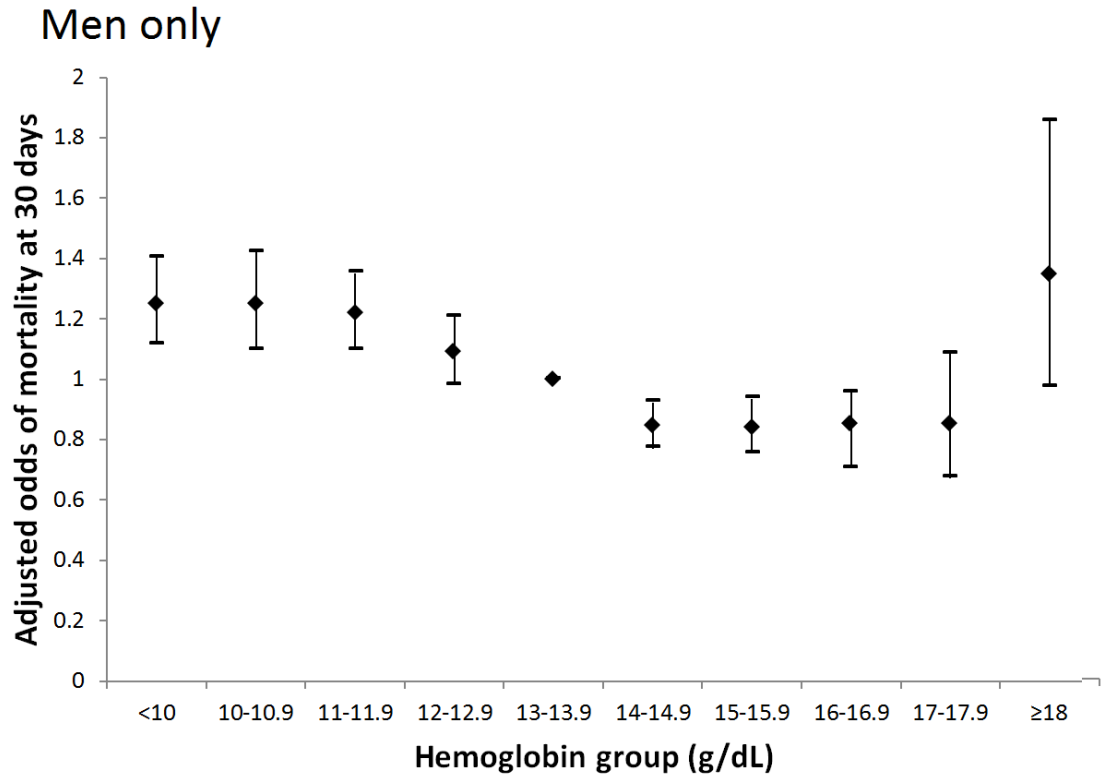
Outcome for men	Hemoglobin ≥13	Hemoglobin 12-13	Hemoglobin 11-12	Hemoglobin 10-11	Hemoglobin <10
Crude rate of mortality at 30 days	5,270/230,540 (2%)	666/18,252 (4%)	589/10,918 (5%)	458/7,318 (6%)	491/7,250 (7%)
Adjusted odds of mortality at 30 days	1.00 (reference)	1.21 (1.10-1.32), p<0.001	1.35 (1.23-1.48) , p<0.001	1.38 (1.23-1.54) , p<0.001	1.38 (1.24-1.54) , p<0.001
Crude rate of mortality at 1 year	12,967/229,347 (6%)	1,703/18,135 (9%)	1,440/10,844 (13%)	1,129/7,276 (16%)	1,242/7,210 (17%)
Adjusted odds of mortality at 1 year	1.00 (reference)	1.25 (1.18-1.33) , p<0.001	1.39 (1.31-1.48) , p<0.001	1.42 (1.32-1.53) , p<0.001	1.52 (1.42-1.63) , p<0.001
Outcome for women	Hemoglobin ≥12	Hemoglobin 11-12	Hemoglobin 10-11	Hemoglobin 9-10	Hemoglobin <9
Crude rate of mortality at 30 days	4,224/119,303 (4%)	550/12,595 (4%)	481/7,882 (6%)	282/3,869 (7%)	174/2,687 (6%)
Adjusted odds of mortality at 30 days	1.00 (reference)	1.17 (1.05-1.30), p=0.006	1.33 (1.19-1.48) , p<0.001	1.38 (1.22-1.56) , p<0.001	1.24 (1.04-1.47), p=0.015
Crude rate of mortality at 1 year	10,490/118,785 (9%)	1,387/12,522 (11%)	1,140/7,842 (15%)	672/3,839 (18%)	460/2,671 (17%)
Adjusted odds of mortality at 1 year	1.00 (reference)	1.17 (1.11-1.24) , p<0.001	1.29 (1.20-1.38) , p<0.001	1.37 (1.26-1.50) , p<0.001	1.34 (1.20-1.50) , p<0.001

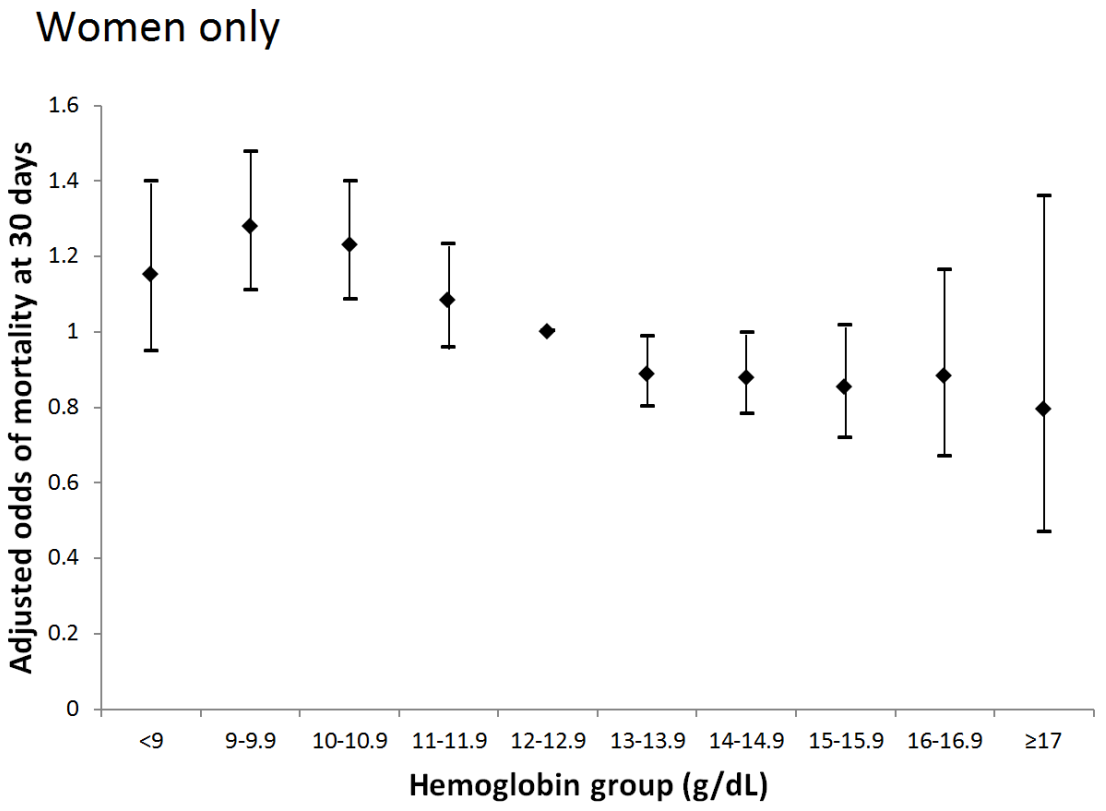
Figure 1: Adjusted odds of mortality at 30 days according to hemoglobin levels for men and women



Adjusted for age, sex, current or ex-smokers, troponin, hyperlipidemia, hypertension, prior angina, prior myocardial infarction, prior heart failure, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, renal failure, prior percutaneous coronary intervention, prior coronary artery bypass graft, medications prior to admission, diagnosis, medications at discharge and angiography.

Figure 2A & 2B: Adjusted odds of mortality at 30 days according to hemoglobin levels and sex





Adjusted for age, current or ex-smokers, troponin, hyperlipidemia, hypertension, prior angina, prior myocardial infarction, prior heart failure, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, renal failure, prior percutaneous coronary intervention, prior coronary artery bypass graft, medications prior to admission, diagnosis, medications at discharge and angiography.

Table S1. Comparison of patients with missing and no missing hemoglobin values

Variable[†‡]	**No missing hemoglobin**	**Missing hemoglobin**
Mean age (years)	69 (±14)	69 (±14)
Male (%)	168,740/257,729 (65%)	107,805/166,421 (65%)
Current or ex-smokers	173,966/239,409 (73%)	105,886/145,331 (73%)
Peak troponin		
Median Troponin I (IQR) (µg/L)	1.0 (0.2-6.5)	0.8 (0.1-4.6)
Median Troponin T (IQR) (µg/L)	1.1 (0.2-6.8)	0.8 (0.1-4.6)
Mean Troponin I (SD) (µg/L)	9.8 (±23.1)	7.7 (±19.3)
Mean Troponin T (SD) (µg/L)	9.5 (±21.6)	7.4 (±18.0)
Comorbidities		
Hyperlipidemia	87,055/244,307 (36%)	48,030/137,680 (35%)
Hypertension	127,321/250,699 (51%)	71,853/143,951 (50%)
Prior angina	78,124/249,745 (31%)	47,790/141,926 (34%)
Prior myocardial infarction	67,678/250,509 (27%)	40,725/145,773 (28%)
Prior heart failure	15,263/247,189 (6%)	9,062/137,413 (7%)
Stroke	21,784/247,508 (9%)	12,319/137,040 (9%)
PVD	10,930/239,608 (5%)	6,821/136,614 (5%)
COPD	37,359/242,828 (15%)	21,415/135,394 (16%)
Renal failure	20,415/247,885 (8%)	7,453/137,312 (5%)
Diabetes	51,220/251,808 (20%)	30,126/153,004 (20%)
Prior PCI	27,391/249,078 (11%)	13,690/139,651 (10%)
Prior CABG	17,520/249,593 (7%)	9,294/140,217 (7%)
Medications prior to admission		
ACE inhibitor	92,430/239,043 (39%)	46,515/122,997 (38%)
Beta blocker	75,333/239,462 (31%)	40,288/122,972 (33%)
Statin	109,882/242,011 (45%)	60,424/130,487 (46%)
Clopidogrel	20,493/111,931 (18%)	23,615/109,612 (22%)
Aspirin	65,746/232,428 (28%)	43,268/148,246 (29%)
Diagnosis at current admission		
NSTEMI or unstable angina	146,689 (62%)	93,749 (62%)
STEMI	89,881 (38%)	58,441 (38%)
Medications at discharge		
ACE inhibitor	162,012/257,999 (63%)	93,586/166,849 (56%)
Beta blocker	156,807/257,999 (61%)	90,242/166,849 (54%)
Statin	185,606/257,999 (72%)	111,758/166,849 (67%)
Clopidogrel	74,777/85,595 (87%)	72,487/91,533 (79%)
Aspirin	180,410/201,559 (90%)	115,392/129,727 (89%)
Angiography performed		
Angiography	98,344/257,999 (38%)	60,770/166,849 (36%)
Adverse outcomes		
Mortality at 30 days	7,147/256,244 (3%)	6,089/166,347 (4%)
Mortality at 1 year	17,777/254,614 (7%)	15,004/165,816 (9%)
In-hospital bleeding	4,833/242,369 (2%)	2,899/154,200 (2%)

† Results reported as mean (SD) for continuous variables and n (%) for categorical variables.
BMI=body mass index, COPD=chronic obstructive pulmonary disease, PVD=peripheral

vascular disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Table S2. Baseline characteristic of the MINAP cohort according to bleeding status

Variable[†‡]	**No bleed (n=387,025)**	**Bleed (n=7,698)**	**p-value**[‡]
Mean age (years)	69 (±14)	69 (±14)	0.49
Male (%)	252,659/387,025 (65%)	4,932/7,698 (64%)	0.027
Current or ex-smokers	255,007/350,600 (73%)	5,070/6,967 (73%)	0.95
Peak troponin			NA
Median Troponin I (IQR) (µg/L)	0.9 (0.2-5.7)	0.9 (0.2-6.2)	
Median Troponin T (IQR) (µg/L)	1.0 (0.2-6.0)	1.1 (0.2-6.7)	
Mean Troponin I (SD) (µg/L)	9 (±22)	9 (±22)	
Mean Troponin T (SD) (µg/L)	9 (±20)	9 (±22)	
Comorbidities			
Hyperlipidemia	122,875/348,013 (35%)	2,521/6,929 (36%)	0.064
Hypertension	181,448/359,503 (50%)	3,678/7,140 (52%)	0.082
Prior angina	114,293/356,737 (32%)	2,261/7,111 (32%)	0.66
Prior myocardial infarction	98,633/360,908 (27%)	1,930/7,172 (27%)	0.43
Prior heart failure	22,106/350,347 (6%)	445/7,015 (6%)	0.91
Stroke	31,051/350,336 (9%)	616/7,008 (9%)	0.83
PVD	16,155/342,771 (5%)	327/6,849 (5%)	0.81
COPD	53,567/344,689 (16%)	1,061/6,873 (15%)	0.82
Diabetes	74,123/368,835 (20%)	1,479/7,326 (20%)	0.85
Renal failure	25,446/350,922 (7%)	551/7,006 (8%)	0.050
Prior PCI	37,473/354,160 (11%)	777/7,032 (11%)	0.21
Prior CABG	24,400/355,121 (7%)	525/7,063 (7%)	0.065
Medications prior to admission			
ACE inhibitor	126,548/329,866 (38%)	2,569/6,622 (39%)	0.48
Beta blocker	105,134/330,237 (32%)	2,147/6,623 (32%)	0.32
Statin	154,984/339,574 (46%)	3,123/6,813 (46%)	0.75
Clopidogrel	39,264/198,190 (20%)	736/3,896 (19%)	0.11
Aspirin	99,895/351,685 (28%)	2,166/7,166 (30%)	0.001
Diagnosis at current admission			<0.001
NSTEMI or unstable angina	223,184/358,532 (62%)	3,536/7,302 (48%)	
STEMI	135,348/358,532 (38%)	3,766/7,302 (52%)	
Medications at discharge			
ACE inhibitor	223,296/387,025 (60%)	4,645/7,698 (60%)	0.91
Beta blocker	225,456/387,025 (58%)	4,445/7,698 (58%)	0.37
Statin	271,095/387,025 (70%)	5,405/7,698 (70%)	0.75
Clopidogrel	132,016/158,384 (83%)	2,562/3,104 (83%)	0.23
Aspirin	274,090/305,303 (90%)	4,230/5,631 (75%)	<0.001
Angiography performed			
Angiography	148,882/387,025 (38%)	2,039/7,698 (26%)	<0.001
Mortality outcomes			
Mortality at 30 days	11,711/384,955 (3%)	473/7,625 (6%)	<0.001
Mortality at 1 year	29,829/382,920 (8%)	889/7,578 (12%)	<0.001

† Results reported as mean (SD) for continuous variables and n (%) for categorical variables.
‡ Logistic regression (continuous variables), Chi^2 square test (categorical variables).
BMI=body mass index, COPD=chronic obstructive pulmonary disease, PVD=peripheral vascular disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

Table S3. Significant multivariate predictors of anemia in patients in whom baseline hemoglobin values were recorded (n=256,744)

Variable[†]	**Odds Ratio (95% CI)**	**p-value**[‡]
Age	1.053 (1.052-1.054)	<0.001
Male sex	1.153 (1.129-1.176)	<0.001
Smoker	1.229 (1.196-1.263)	<0.001
Hypercholesterolemia	0.880 (0.861-0.991)	<0.001
Angina	1.048 (1.026-1.070)	<0.001
Previous myocardial infarction	1.214 (1.184-1.244)	<0.001
Previous heart failure	1.257 (1.211-1.304)	<0.001
Previous stroke	1.209 (1.171-1.247)	<0.001
Peripheral vascular disease	1.430 (1.367-1.496)	<0.001
Chronic obstructive pulmonary disease	1.151 (1.121-1.181)	<0.001
Diabetes mellitus	1.942 (1.898-1.987)	<0.001
Renal disease	3.213 (3.107-3.323)	<0.001
Previous coronary artery bypass graft	1.100 (1.060-1.141)	<0.001
Admission medication		
Clopidogrel	1.208 (1.159-1.259)	<0.001
Aspirin	1.029 (1.007-1.052)	0.011

Table S4. Sensitivity analysis of multivariate association between anemia and mortality in patients in whom baseline hemoglobin values were recorded

Total cohort

Mortality outcome	N	Odds ratio (95% CI)	p-value
Mortality at 30 days	254,999	1.530 (1.452-1.612)	<0.001
Mortality at 1 year	253,380	1.589 (1.535-1.645)	<0.001
Men only			
Mortality at 30 days	166,996	1.566 (1.458-1.681)	<0.001
Mortality at 1 year	165,901	1.698 (1.620-1.780)	<0.001
Women only			
Mortality at 30 days	88,003	1.479 (1.369-1.599)	<0.001
Mortality at 1 year	87,479	1.459 (1.38501.536)	<0.001

Bleeding excluded

Mortality outcome	N	Odds ratio (95% CI)	p-value
Mortality at 30 days	249,901	1.524 (1.445-1.608)	<0.001
Mortality at 1 year	248,317	1.584 (1.529-1.641)	<0.001
Men only			
Mortality at 30 days	163,723	1.553 (1.444-1.671)	<0.001
Mortality at 1 year	162,648	1.684 (1.605-1.766)	<0.001
Women only			
Mortality at 30 days	86,170	1.481 (1.368-1.603)	<0.001
Mortality at 1 year	85,660	1.464 (1.389-1.542)	<0.001

Total cohort without imputations

Mortality outcome	N	Odds ratio (95% CI)	p-value
Mortality at 30 days			
Unadjusted	254,999	2.905 (2.770-3.045)	<0.001
Fully adjusted	34,861	1.472 (1.197-1.810)	<0.001
Mortality at 1 year			
Unadjusted	253,380	3.072 (2.978-3.168)	<0.001
Fully adjusted	34,731	1.588 (1.430-1.763)	<0.001

Figure S1. Flow chart of patient inclusion

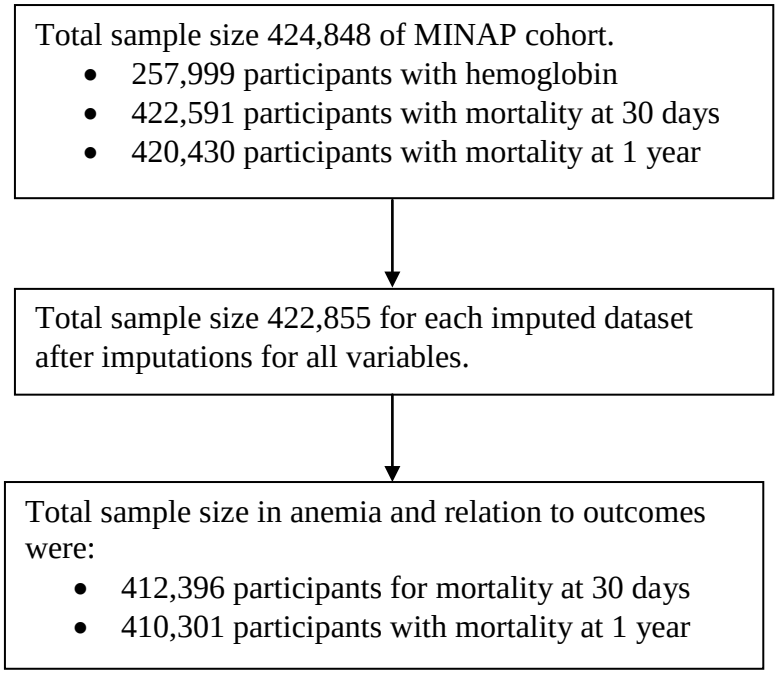


Figure S2. Adjusted odds of mortality at 30 days according to hemoglobin levels and sex with exclusion of participants with bleed outcome