ORIGINAL RESEARCH

Relationship Between Anemia and Mortality Outcomes in a National Acute Coronary Syndrome Cohort: Insights From the UK Myocardial Ischemia National Audit Project Registry

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***Background*—**We aim to determine the prevalence of anemia in acute coronary syndrome (ACS) patients and compare 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-day and 1-year mortality for anemic compared to nonanemic 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 of 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.

***Conclusions*—**The prevalence of anemia in a contemporary national ACS cohort is clinically significant. Patients with anemia are older and multimorbid and less likely to receive evidence-based therapies shown to improve clinical outcomes, with the presence of anemia independently associated with mortality outcomes. **(*J Am Heart Assoc*. 2016;5:e003348 doi: 10.1161/JAHA.116.003348)**

Key Words: acute coronary syndrome • anemia • mortality

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 comorbidities such as chronic kidney disease,[12-14] diabetes,[6,13,14] heart failure,[13,15] and more extensive coronary artery disease[6] and are less likely to

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Accompanying Tables S1 through S4 and Figures S1, S2 are available at http://jaha.ahajournals.org/content/5/11/e003348/DC1/embed/inline-supplementary-material-1.pdf

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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] and risk of major bleeding[6] and of reinfarction.[6,8,19] Some studies have reported that, once differences in age or comorbidity burden between anemic/nonanemic ACS cohorts are adjusted for, anemia is no longer an independent predictor of adverse mortality[20] or cardiovascular mortality,[21] although 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] but such RCTs often exclude older patients with the most severe comorbid conditions and may therefore underreport the prevalence of anemia and underestimate 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 or 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, which 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 MINAP registry collects data on all patients aged 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 (ST-segment elevation myocardial infarction [STEMI], non–ST-segment elevation myocardial infarction [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 data set collects standardized data on prehospital 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 are collected by nurses and clinical audit staff and contain 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, β-blocker, statin, clopidogrel, aspirin), clinical diagnosis (unstable angina, NSTEMI, STEMI), discharge medications (ACE inhibitor, β-blocker, statin, clopidogrel, aspirin), angiography, in-hospital bleeding, and mortality outcomes in hospital and within 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 were used to impute missing values for variables where possible. We describe baseline variables according to whether they were missing or nonmissing in tables, and details of participant inclusion are 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 1-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 to ≥18 g/dL for men and from <9 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 nonanemic groups 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 that 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 nonanemic 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 2 comparator groups (anemia vs no anemia 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 (ie, 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.

Ethical Considerations

The current study obtained the ethical approval from the Faculty of Medicine & Health Sciences Research Ethics Committee, University of East Anglia. Informed consent from participants was waived as data were routinely collected, and only anonymized data were used in the study.

Results

There were a total of 424 848 participants in the MINAP cohort between January 2006 and December 2010 who were followed up until August 2011. Of them, hemoglobin values were recorded in 257 999 patients. Figure S1 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 (Table S1).

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

The descriptive statistics of baseline variables in the included cohort, sorted by anemia status, are 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, to be on aspirin before admission and on discharge (30% vs 28%, $P<0.001$), to have STEMI diagnosis (52% vs 38%, $P<0.001$), to be less likely to receive angiography (26% vs 38%, $P<0.001$) and more likely to die at 30 days (6% versus 3%, $P<0.001$) and 1 year (12% vs 8%, $P<0.001$) (Table S2). Similar rates of angiography were performed in the anemic versus nonanemic cohort, but patients with anemia were significantly less likely to be prescribed secondary prevention medications postdischarge. The difference in crude mortality rates between the anemic and nonanemic groups increased with longer follow-up.

Multiple logistic regression was 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 are shown in Figure 1. Lower hemoglobin values were associated with significantly higher mortality with a nonsignificant trend toward higher mortality in those patients with elevated hemoglobin values.

The odds of mortality associated with the presence of anemia following adjustment for baseline covariates are 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 OR 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

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, y	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	86 052/1 802 044 (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	7286/177 567 (4%)	7870/68 411 (12%)	<0.001
Stroke	12 320/177 656 (7%)	9337/68 636 (14%)	<0.001
PVD	5852/171 572 (3%)	5019/66 849 (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	7025/177 840 (4%)	13 283/68 831 (19%)	<0.001
Prior PCI	18 865/179 306 (11%)	8354/68 560 (12%)	<0.001
Prior CABG	10 522/179 580 (6%)	6858/68 799 (10%)	<0.001
Medications prior to admission			
ACE inhibitor	59 891/171 542 (35%)	31 984/66 325 (48%)	<0.001
β-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%)	6782/29 402 (23%)	<0.001
Aspirin	46 856/167 055 (28%)	18 593/64 237 (29%)	<0.001
Aspirin and clopidogrel	3490/72 682 (5%)	1814/26 198 (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
β-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

Continued

Table 1. Continued

Variable*†	No Anemia (n=185 521)	Anemia (n=71 223)	*P* Value†
Mortality outcomes			
Mortality at 30 days	3425/184 228 (2%)	3691/70 771 (5%)	<0.001
Mortality at 1 year	8520/183 041 (5%)	9173/70 339 (13%)	<0.001
Bleeding outcomes			
In-hospital bleeding	3475/174 183 (2%)	1337/67 023 (2%)	0.998

BMI indicates body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; MINAP, Myocardial Ischemia National Audit Project; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST-segment elevation myocardial infarction.
*Results reported as mean (SD) for continuous variables and n (%) for categorical variables.
†Logistic regression (continuous variables), Chi-squared test (categorical variables).

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 (Table S3) and mortality outcomes associated with anemia (Table S4) 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).

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
PVD	1.427 (1.362-1.496)	<0.001
COPD	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 PCI	0.967 (0.935-1.000)	0.05
Previous CABG	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

CABG indicates coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
*All covariates in the table were included in the multiple logistic regression.

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 patients 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 associated with higher mortality only in men and not in women. Similar results were observed if patients with bleeding were excluded (Figure S2).

In terms of severity of anemia there was an increase in mortality at both 30 days and 1 year with reduced hemoglobin, which ranged from ~1.2- to 1.3-fold increase in odds of mortality for Hb 12 to 13 g/dL to a ~1.4- to 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 1 in 4 patients presenting with ACS are anemic and that these patients are older, have a greater prevalence of comorbid 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.

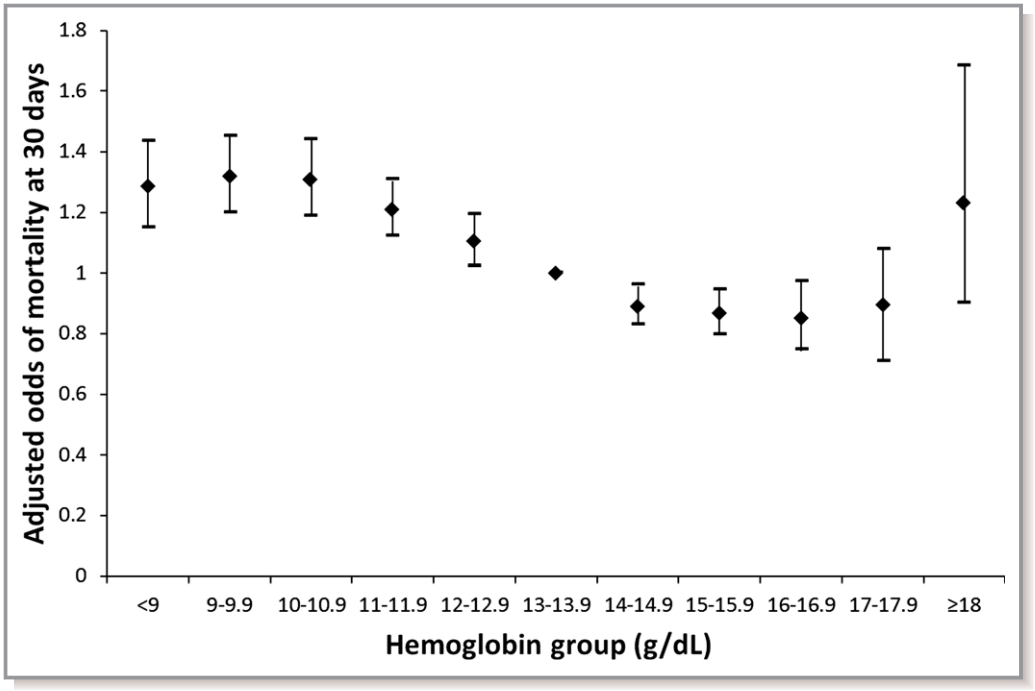

Figure 1. Adjusted odds of mortality at 30 days according to hemoglobin levels for men and women. Adjusted for age, sex, current or ex-smokers, troponin, hyperlipidemia, hypertension, prior angina, prior myocardial infarction, prior heart failure, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, renal failure, prior percutaneous coronary intervention, prior coronary artery bypass graft, medications prior to admission, diagnosis, medications at discharge and angiography.

Our observed prevalence of anemia of 28% is greater than that reported in data derived from RCTs reporting rates of between 10% and 25%,[5-7,23] although registry data reveal 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 comorbid 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 ~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 are seen between Hb levels and CV death and the composite endpoint of CV death, myocardial infarction, or recurrent ischemic events in some studies,[21] although 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, but 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 ischemia 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 underprescribed 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 ($P<0.001$), whereas 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

Table 3. Multivariate Association Between Anemia and Mortality: Logistic Regression Models

Mortality Outcome	N	Odds Ratio (95% CI)	*P* Value
Total cohort			
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 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 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

NSTEMI indicates non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Table 4. Propensity Score Matching Analysis on 10 Imputed Data Sets, 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 to 0.0114	<0.001
1-year mortality	121 276	0.0173	0.0128 to 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)

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 vs 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]

Table 5. Baseline Characteristic of the MINAP Cohort in a Single Imputed Data Set According to Sex

Variable*†	Female (n=147 064)	Male (n=275 791)	*P* Value†
Mean age, y	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	5448/130 925 (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	9795/134 079 (7%)	17 931/249 319 (7%)	0.196
Prior PCI	10 595/134 947 (8%)	30 254/251 990 (12%)	<0.001
Prior CABG	5706/135 286 (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
β-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
β-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	5711/146 336 (4%)	7474/274 278 (3%)	<0.001
Mortality at 1 year	14 149/145 659 (10%)	18 481/272 812 (7%)	<0.001
In-hospital bleeding	2766/137 132 (2%)	4932/257 591 (2%)	0.027

BMI indicates body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; MINAP, Myocardial Ischemia National Audit Project; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STEMI, ST-segment elevation myocardial infarction.

*Results reported as mean (SD) for continuous variables and n (%) for categorical variables.

†Logistic regression (continuous variables), Chi-squared test (categorical variables).

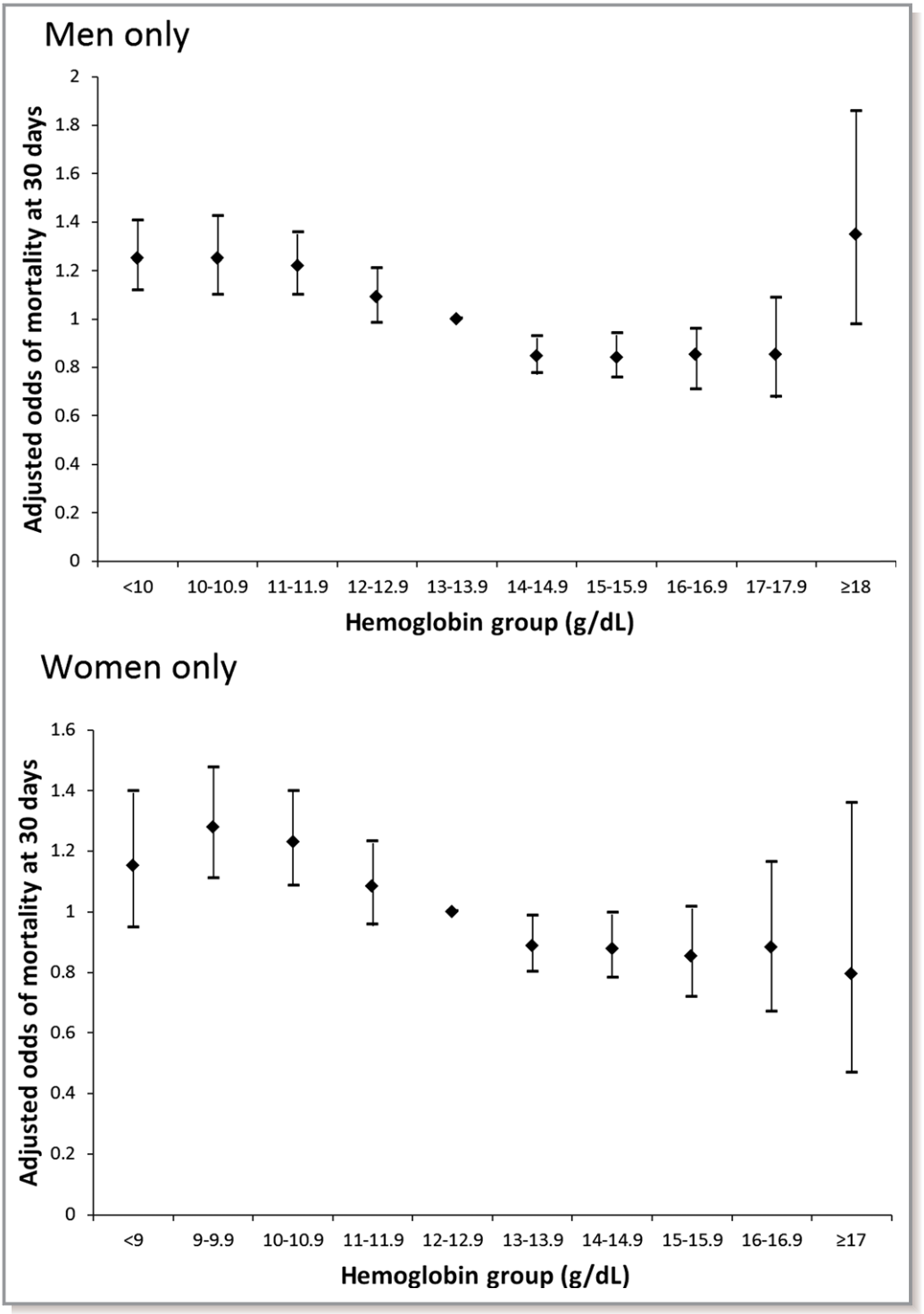

Figure 2. Adjusted odds of mortality at 30 days according to hemoglobin levels and sex. Adjusted for age, current or ex-smokers, troponin, hyperlipidemia, hypertension, prior angina, prior myocardial infarction, prior heart failure, stroke, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, renal failure, prior percutaneous coronary intervention, prior coronary artery bypass graft, medications prior to admission, diagnosis, medications at discharge, and angiography.

Our study has some limitations. The MINAP data set 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 PCI, may be post-PCI and may reflect the influence of acute bleeding complications and not reflect chronic anemia. Nevertheless,

Table 6. Evaluation of the Severity of Anemia by Sex Using Multiple Logistic Regression

Outcome for Men	Hemoglobin ≥13	Hemoglobin 12 to 13	Hemoglobin 11 to 12	Hemoglobin 10 to 11	Hemoglobin <10
Crude rate of mortality at 30 days	5270/230 540 (2%)	666/18 252 (4%)	589/10 918 (5%)	458/7318 (6%)	491/7250 (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%)	1703/18 135 (9%)	1440/10 844 (13%)	1129/7276 (16%)	1242/7210 (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 to 12	Hemoglobin 10 to 11	Hemoglobin 9 to 10	Hemoglobin <9
Crude rate of mortality at 30 days	4224/119 303 (4%)	550/12 595 (4%)	481/7882 (6%)	282/3869 (7%)	174/2687 (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%)	1387/12 522 (11%)	1140/7842 (15%)	672/3839 (18%)	460/2671 (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), $P<0.001$

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, but we cannot infer causality. Although 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 and nonanemic cohorts, but 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 in extent depending on the study variable, and we tried to approximate these values using multiple imputations to impute the missing values. Finally, the MINAP data set 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 study of 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 1 in 4 patients presenting with ACS being anemic, and that these patients are older, have a greater prevalence of comorbid 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, and there is considerable uncertainty in the value of such an approach. Targeted intervention strategies in this patient population should be explored.

Author Contributions

Mamas, Zaman, and Myint conceived and planned the study. Kwok and Kontopantelis analyzed the data. Mamas and Kwok wrote the first draft of the paper. All authors contributed to the interpretation of the findings and reporting of the work.

Myint is the guarantor. Myint and Zaman are co-PIs of the MINAP-older age project.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

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

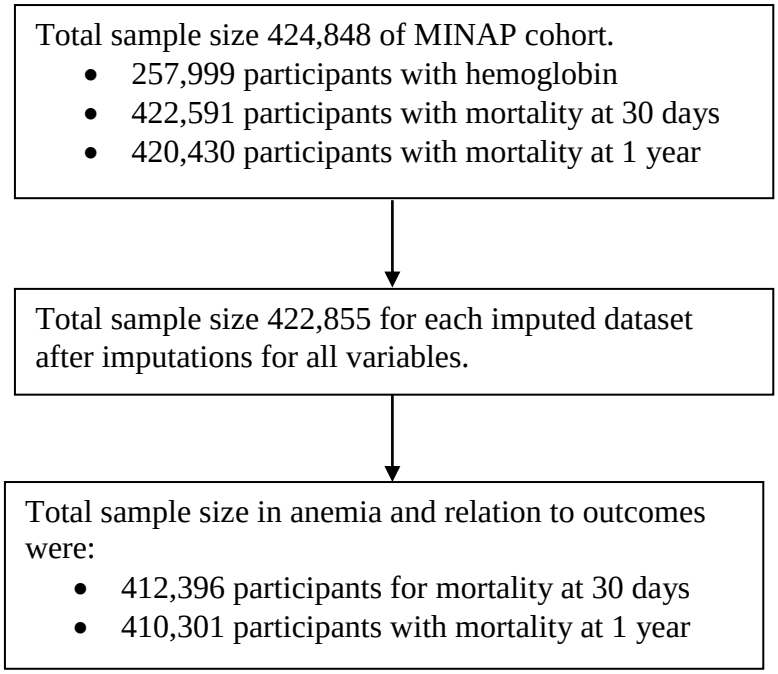
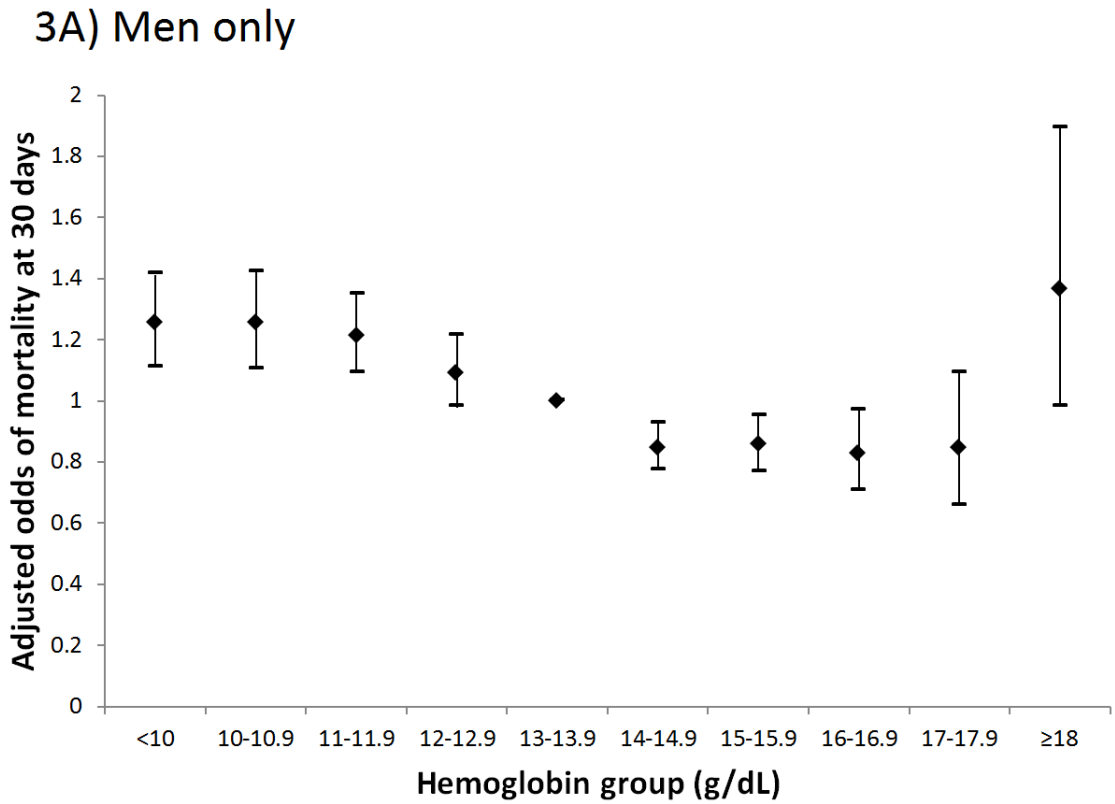
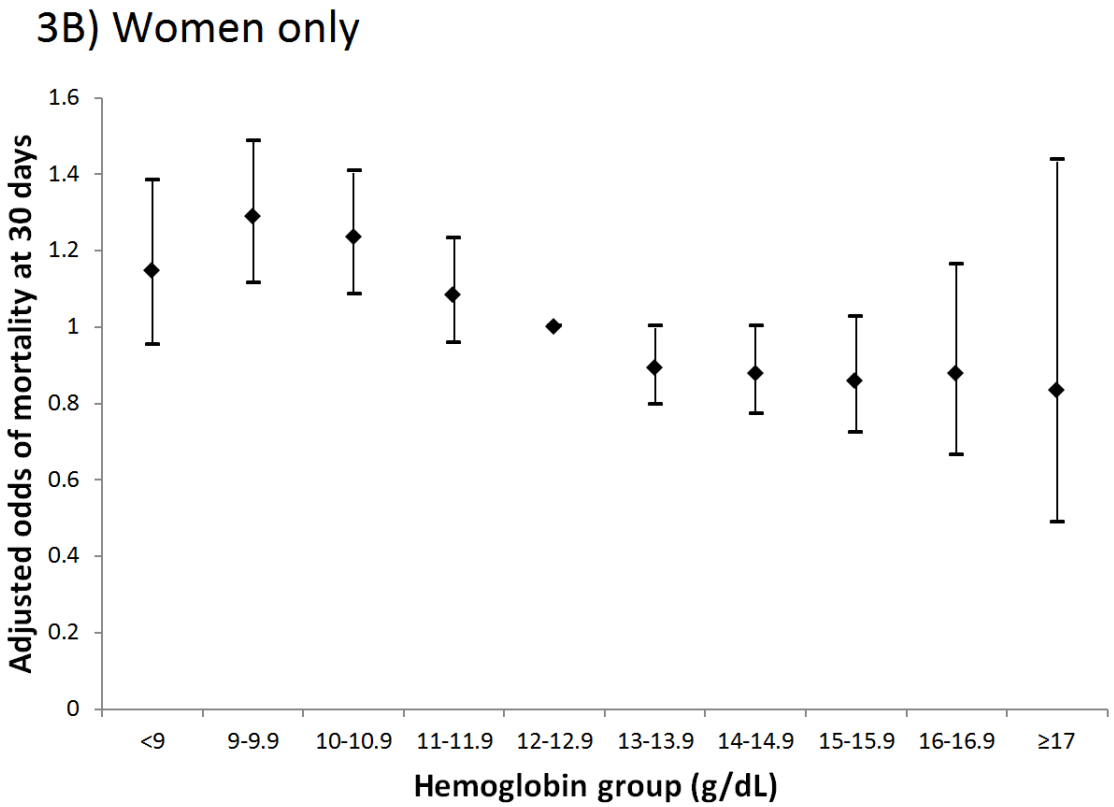


Figure S2. Adjusted odds of mortality at 30 days according to hemoglobin levels and sex with exclusion of participants with bleed outcome





Relationship Between Anemia and Mortality Outcomes in a National Acute Coronary Syndrome Cohort: Insights From the UK Myocardial Ischemia National Audit Project Registry

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