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 and secondary analyses of randomized controlled trials 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%, and current clinical guidelines fail to offer firm recommendations for its concurrent management in the ACS setting.

Patients with anemia are older with a significantly greater burden of comorbidities such as chronic kidney disease, diabetes, heart failure, and more extensive coronary artery disease and are less likely to
undergo cardiac catheterization. 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, heart failure, and risk of major bleeding and of reinfarction. 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 or cardiovascular mortality, although other studies report that the relationship persists. Other studies have reported different relationships between anemia and cardiovascular 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.

Data derived from secondary analyses from randomized controlled trials (RCT) have suggested adverse mortality outcomes associated with anemia in patients with ACS, but such RCTs often exclude older patients with the most severe comorbid conditions and may therefore underestimate 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 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 an ACS admission from all 230 NHS trusts in England and Wales and is part of the NHS data dictionary. The data are collected by nurses and clinical audit staff and contain 123 fields. The details of development and initial findings are reported elsewhere.

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.

### 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.

### 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. The data are collected by nurses and clinical audit staff and contain 123 fields. The details of development and initial findings are reported elsewhere.

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 | | | |
| 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 | 7,286/177,567 (4%) | 7,870/68,411 (12%) | <0.001 |
| Stroke | 12,320/177,656 (7%) | 9,337/68,366 (14%) | <0.001 |
| PVD | 58,52/171,572 (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 |
| 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%) | 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 | | | |
| NSTEMI or unstable angina | 104,928/170,135 (62%) | 41,049/65,285 (63%) | <0.001 |
| STEMI | 65,207/170,135 (38%) | 24,235/65,285 (37%) | <0.001 |
| 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%) | 12,056/16,098 (75%) | <0.001 |
| Angiography performed | | | |
| Angiography | 70,914/185,521 (38%) | 27,034/71,223 (38%) | 0.319 |

Continued
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).

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.

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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 myocardic 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  |

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).

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.
Our observed prevalence of anemia of 28% is greater than that reported in data derived from RCTs reporting rates of between 10% and 25%, although registry data reveal significantly higher prevalences. 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%. 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.

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. 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, 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. 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, which might contribute to increased cardiovascular events. Analysis of the

![Figure 1](http://jaha.ahajournals.org/)

**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.
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 trial36 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 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              | 254 999| 2.905 (2.770-3.045) | <0.001  |
| Unadjusted                        | 34 861| 1.472 (1.197-1.810) | <0.001  |
| Fully adjusted                    | 34 731| 1.588 (1.430-1.763) | <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 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) |

NSTEMI indicates non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
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) | <0.001  |
| Median troponin T (IQR), μg/L | 0.8 (0.1–5.6) | 1.3 (0.2–9.4) | <0.001  |
| Mean troponin I (SD), μg/L | 7 (±20)          | 10 (±23)         |         |
| Mean troponin T (SD), μg/L | 7 (±18)          | 10 (±22)         |         |

Comorbidities

| Variable                          | Female (n=132 621) | Male (n=247 578) | P Value† |
|----------------------------------|--------------------|------------------|---------|
| 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 (37%) | 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

| Variable         | Female (n=130 128) | Male (n=234 196) | P Value† |
|------------------|--------------------|------------------|---------|
| 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

| Variable         | Female (n=134 524) | Male (n=252 401) | P Value† |
|------------------|--------------------|------------------|---------|
| 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

| Variable         | Female (n=134 064) | Male (n=252 401) | P Value† |
|------------------|--------------------|------------------|---------|
| 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

| Variable         | Female (n=147 064) | Male (n=275 791) | P Value† |
|------------------|--------------------|------------------|---------|
| Angiography      | 55 049/147 064 (37%) | 103 267/275 791 (37%) | 0.939   |

Mortality outcomes

| Variable         | Female (n=275 888) | Male (n=251 888) | P Value† |
|------------------|--------------------|------------------|---------|
| 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).
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,

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.

[Graph showing adjusted odds of mortality at 30 days for men and women across different hemoglobin groups.]
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

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 |

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                 | 27,912/249,078 (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%) | 2,521/6,622 (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%) | 445/7,006 (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%) | 1,061/7,683 (15%) | 0.82 |
| Diabetes | 74,123/368,835 (20%) | 1,479/7,326 (20%) | 0.85 |
| Renal failure | 25,446/350,922 (7%) | 551/7,015 (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), Chi² 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 (1.385-1.536) | <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

Total sample size 424,848 of MINAP cohort.
- 257,999 participants with hemoglobin
- 422,591 participants with mortality at 30 days
- 420,430 participants with mortality at 1 year

Total sample size 422,855 for each imputed dataset after imputations for all variables.

Total sample size in anemia and relation to outcomes were:
- 412,396 participants for mortality at 30 days
- 410,301 participants with mortality at 1 year
**Figure S2.** Adjusted odds of mortality at 30 days according to hemoglobin levels and sex with exclusion of participants with bleed outcome

3A) Men only

3B) Women only
Relationship Between Anemia and Mortality Outcomes in a National Acute Coronary Syndrome Cohort: Insights From the UK Myocardial Ischemia National Audit Project Registry

Mamas A. Mamas, Chun Shing Kwok, Evangelos Kontopantelis, Anthony A. Fryer, Iain Buchan, Max O. Bachmann, M. Justin Zaman and Phyo K. Myint

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