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Original Investigation

Prognosis of patients with chronic and hospital-acquired anaemia after acute coronary syndromes

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ABBREVIATIONS

ACS = acute coronary syndrome

CA = chronic anaemia

CI = confidence interval

GRACE score = Global Registry of Acute Coronary Events

HAA = hospital-acquired anaemia

HR = hazard ratio

LVEF = left ventricular ejection fraction

MACE = major adverse cardiovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

PPI = proton pump inhibitor

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ABSTRACT

Discharge anaemia is common following acute coronary syndromes (ACS). However, it is unknown if chronic anaemia (CA) and hospital-acquired anaemia (HAA) are associated with similar outcomes.

In this retrospective analysis of 4083 ACS admissions treated with percutaneous coronary intervention in Switzerland (SPUM-ACS registry), 1896 patients (46.4%) had discharge anaemia (CA: n=643[15.7%] vs. HAA: n=1253[30.7%]). Landmark analysis that matched patients with CA (n=504) and HAA (n=866) with non-anaemic patients found increased one-year major adverse cardiovascular events (cardiovascular mortality, myocardial infarction, stroke) among patients with CA (6.9% vs. 3.0%, HR 2.073, 95% CI 1.039- 4.134, p=0.039) and HAA (3.8% vs. 2.3%, HR 1.772, 95% CI 1.002-3.232, p=0.049). Only CA was associated with increased one-year all-cause mortality (7.9% vs. 1.6%, HR 4.255, 95% CI 1.950-9.284, p<0.001).

CA and HAA were associated with poor one-year cardiovascular outcomes. Only CA was associated with increased all-cause mortality suggesting that HAA and CA represent distinct subclinical entities.

Keywords

Acute coronary syndrome, invasive coronary angiography, anaemia

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INTRODUCTION

Baseline anaemia is prevalent among patients presenting with acute coronary syndromes (ACS) and is strongly associated with increased mortality [1,2]. It is typically a chronic anaemia associated with older age and comorbidities such as diabetes mellitus, chronic heart failure, chronic kidney disease and cerebrovascular disease [1]. However, patients can also develop hospital-acquired anaemia (HAA) during admission with ACS through bleeding that complicates pharmacological and invasive therapies, as well as through haemodilution [3]. It has been shown to develop in over 50% of ACS patients and is associated with increased mortality [4–6] .

There is limited data available on the cardiovascular outcomes of patients with discharge anaemia following ACS. Furthermore, CA and HAA likely represent distinct pathophysiological groups, and it is unknown if these groups experience similar outcomes following ACS.

We aimed to determine the relationship between discharge anaemia (CA and HAA) and one-year clinical outcomes among patients with ACS treated with percutaneous intervention (PCI). We performed a retrospective analysis of patients admitted with ACS to four university hospitals in Switzerland and compared the one-year outcomes of patients discharged with CA and HAA with those of patients discharged without anaemia.

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METHODS

Patients

Data was obtained from the SPUM-ACS (Special Program University Medicine - Acute Coronary Syndromes) registry, a cohort of consecutive patients admitted with ACS to four university hospitals in Switzerland. All patients were aged 18 years or over. The only exclusion criteria were: severe physical disability, inability to comprehend the study or life expectancy of less than 1 year (for non-cardiac reasons). Further details of this registry have been reported previously [7]. For the present study, patients hospitalised between 2009 and 2017 who received PCI were selected. The World Health Organisation thresholds were used to define anaemia as a haemoglobin <130 g/l in men and <120 g/l in women. Patients were defined as having CA if they were anaemic on both admission and discharge. Patients without anaemia on admission who were discharged with anaemia were defined as having HAA.

Primary and secondary endpoints

To eliminate the direct impact of bleeding on the endpoints, a landmark analysis was performed with a starting point of 7 days post-angiography. Events before this timepoint were not counted. The primary endpoint was defined as one-year major adverse cardiovascular events (MACE), a composite of cardiovascular mortality, recurrent MI (using the universal definition of MI) and stroke. The secondary endpoint was defined as one-year all-cause mortality. The incidence of events during follow-up was ascertained by telephone consultation 30 days post discharge, and in a clinical face-to-face visit at one year. When patients could not be reached for the one-year follow-up visit, medical information was obtained from primary care physicians, family members, hospital records or a registry office. Three certified cardiologists adjudicated all events.

Statistical analysis

Normally distributed, continuous variables are expressed as mean ± SD and compared using the 2-tailed Student *t*-test. Non-normally distributed continuous variables are expressed as a median with interquartile range and analysed using the Mann-Whitney *U* test. Comparisons between categorical variables were performed using the Pearson $\chi 2$ test. Missing values in baseline clinical characteristics were treated with multiple imputation in order to create five imputed datasets. Baseline and treatment characteristics as well as clinical endpoint rates are

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presented for a single imputed dataset. Logistic and Cox regression analyses were performed on each imputed dataset before pooling of estimates as per Rubin's Rules [8]. Multiple logistic regression was used to identify independent factors associated with HAA and CA. These models included the following covariates: age, sex, hypertension, diabetes, previous cardiovascular disease, valvular disease, chronic lung disease, active or previous malignancy, previous gastrointestinal bleeding, smoking status, body mass index (BMI), baseline use of anticoagulation/$P2Y_{12}$ agent, heart rate, systolic blood pressure, ECG ischaemia, Killip class, type of ACS, stenting vs. balloon angioplasty only, presence of thrombus, $P2Y_{12}$ agent prescribed. A 1:1 propensity score-matched analysis with a nearest-neighbour matching algorithm was used to manage intergroup differences in baseline and treatment variables prior to the sampling of the discharge haemoglobin level. Univariate Cox proportional hazards models and Kaplan-Meier analysis evaluated the impact of discharge anaemia on the clinical endpoints. Cubic spline functions were derived from multivariate Cox models of the unmatched populations and were plotted with four degrees of freedom. Among patients with a CRP value at the time of admission, a subgroup analysis was performed. A p-value <0.05 was defined as statistically significant. Statistical analysis was performed using R version 3.5.1.

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RESULTS

Study population

Among 4,083 patients, anaemia was present in 643 (16.0%) on admission and 1896 (46.4%) at discharge. Among those with discharge anaemia, 1253 patients (66.1%) had HAA compared with 643 patients (33.9%) with CA **(Table 1)**. Only 9 patients with baseline anaemia were discharged with a normal haemoglobin value.

Baseline clinical characteristics

Missing values in baseline clinical characteristics were managed with multiple imputation (**Online Table 1**). The median discharge haemoglobin level was 139 g/l (IQR 133.00-146.00) in the non-anaemic (NA) group compared with 118.00 g/l (IQR 108.00-124.00) in the HAA group and 107.00 g/l (IQR 92.00-116.00) in the CA group (**Table 2**). Although all three groups (NA, CA, HAA) experienced a decrease in median haemoglobin level between admission and discharge, this was largest among HAA patients (NA: 9.00 g/l vs. HAA: 22.00 g/l vs. CA: 8.00 g/l, $p<0.001$). Both HAA and CA groups differed significantly from the NA group for the majority of baseline factors (**Table 1**). Compared with the NA group, patients with discharge anaemia (HAA and CA) were significantly older, more often female, and had a higher prevalence of the majority of comorbidities including hypertension, diabetes mellitus, previous cardiovascular disease, valvular disease, chronic lung disease, previous/active malignancy, and previous gastrointestinal bleeding. With regards to clinical features, they also had higher GRACE scores, lower left ventricular ejection fractions (LVEF) and lower estimated glomerular filtration rates (eGFR). Conversely, the discharge anaemia groups had a significantly lower body mass index (BMI) and lower rates of smoking.

Treatment factors

In the unmatched population, the NA and discharge anaemia groups differed significantly with regards to a number of treatment factors (Table 2). In general, patients with discharge anaemia were more likely to have three or more stents implanted,TIMI grade flow <3 following PCI and be prescribed clopidogrel over prasugrel or ticagrelor. Although there was a high degree of compliance with ACS prescription guidelines, both discharge anaemia groups had fewer patients prescribed a statin. There was a higher rate of proton pump inhibitor (PPI) prescriptions in the discharge anaemia groups, and this was highest in the CA group. The HAA group had the highest occurrence of coronary thrombosis identified during angiography, with the CA group having the lowest.

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The CA group also had a significantly lower proportion of patients with a percentage coronary stenosis of ≥95% at the site of the culprit lesion.

Factors associated with the CA and HAA

Multiple logistic regression applied to the unmatched population demonstrated that diabetes, chronic lung disease, chronic kidney disease, history of malignancy, and history of gastrointestinal bleeding were independently associated with CA. Additionally, low BMI and baseline use of oral anticoagulation and clopidogrel were independently correlated with CA. A history of malignancy was the only comorbidity independently associated with the development of HAA. However, HAA was also associated with baseline use of oral anticoagulation, raised GRACE score, elevated heart rate on admission, and the presence of thrombus during coronary angiography.

Propensity-score matched analyses

Chronic anaemia

After 1:1 propensity score matching, 504 patients without discharge anaemia and 504 patients with CA were deemed equivalent in terms of all baseline and treatment factors, with the exception of baseline haemoglobin levels which were 147.00 g/l and 119.00 g/l, respectively (p<0.001) (**Table 1 + 2)**. The median discharge haemoglobin level was 137 g/l in the NA group and 109 g/l in the CA group (p<0.001). Patients in the NA and CA groups experienced a similar decrease in haemoglobin level between admission and discharge (NA: 8.00 g/l (IQR 3.00-15.00) vs. CA 8.00 g/l (IQR 3.00-15.00), p=0.949). Baseline haemoglobin demonstrated a positive correlation with baseline eGFR in the CA group but not in the NA group **(Online Figure 1)**.

At one-year, the primary endpoint (MACE) occurred in 3.0% of patients in the NA group and 6.9% of patients in the CA group (HR 2.073, 95% CI 1.039- 4.134, p=0.039) (**Figure 1**). The CA group was also noted to have markedly higher rates of the secondary endpoint (all-cause mortality) compared with the NA group (7.9% vs. 1.6%, HR 4.255, 95% CI 1.950-9.284, p<0.001). These findings were corroborated with Kaplan-Meier analyses (**Figure 2A**).

Cubic spline functions demonstrated an exposure-response relationship, with rates of MACE and all-cause mortality increasing significantly with decreases in haemoglobin level below 120 g/l (**Figure 3A**).

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Hospital-acquired anaemia

After 1:1 propensity score matching, 866 patients with HAA and 866 patients without discharge anaemia presented no significant differences in baseline or treatment factors (**Table 1 + 2)**. The median baseline haemoglobin value was 143.00 g/l in the NA group and 142.00 g/l in the HAA group (p=0.088). The median discharge haemoglobin value was 135 g/l in the NA group and 119 g/l in the HAA group (p<0.001). This corresponded to a median decrease in haemoglobin level between admission and discharge of 7.00 g/l (IQR 2.00-12.00) in the NA group compared with 23.00 g/l (IQR 15.00-34.00) in the HAA group (p<0.001).

At one-year, the primary endpoint occurred in 2.3% of patients in the NA group compared with 3.8% of patients in the HAA group (HR 1.772, 95% CI 1.002-3.232, p=0.049) (**Figure 1**). With regards to the secondary endpoint, similar rates were noted in the NA and HAA groups (1.3% vs. 1.8%, HR 1.452, 95% CI 0.647-3.628, p=0.363). These findings were confirmed with Kaplan-Meier analyses (**Figure 2B)**.

Cubic spline functions suggested an exposure-response relationship between discharge haemoglobin and MACE, with rates of MACE increasing with decreases in haemoglobin below 120 g/l (**Figure 3B**). However, there was no clear association between discharge haemoglobin and all-cause mortality.

Medication compliance at one-year

At one-year, compliance with ACS prescription guidelines was similar among surviving NA and discharge anaemia patients, including similar rates of aspirin and $P2Y_{12}$ agent use (**Online Table 2**).

C-reactive protein (CRP) in CA and HAA

In a separate analysis, CRP values on admission were available for 1208 patients from the unmatched population. After propensity score matching, median CRP was slightly higher in the HAA group (NA: 2.10 mg/l (IQR 0.90-5.50) vs. HAA: 2.80 mg/l (IQR 1.10-6.93), p=0.021) and even higher in the CA group (NA: 2.10 mg/l (IQR 0.93-6.62) vs. CA: 3.80 mg/l (IQR 1.30-16.80), p=0.004).

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DISCUSSION

The key findings of this retrospective analysis were:

1) Discharge anaemia among ACS patients treated with PCI was common (46.4%).
2) Both CA and HAA were independently associated with poorer one-year cardiovascular outcomes.
3) Only CA was associated with increased one-year all-cause mortality.

CA vs. HAA: different entities?

Our results demonstrate that patients with CA are a vulnerable group with more comorbidities and significantly worse outcomes following ACS. They also suggest that patients who develop HAA represent a distinct subclinical group with a different risk profile.

CA is often considered a marker of increasing age or the accumulation of comorbidities. However, this matched analysis demonstrates that CA is independently associated with significantly worse outcomes following ACS. A number of pathophysiological processes are responsible for the development of CA. Among patients ≥ 65 years old in the National Health and Nutrition Examination Survey (NHANES) III cohort, anaemia was explained by nutrient deficiency in one third, anaemia of chronic disease or chronic renal disease in another third, with the remaining third having unexplained anaemia [9]. CRP levels were also significantly higher among patients with anaemia of chronic disease. In the present study, CRP levels too were found to be significantly higher among patients with CA. Additionally, baseline haemoglobin correlated positively with baseline eGFR among CA patients. One could therefore postulate that anaemia of chronic disease and chronic renal disease may in part underlie the anaemia in the CA group.

Two important mechanisms that lead to the development of HAA are bleeding and haemodilution [3]. Bleeding can arise from antiplatelet and anti-thrombotic treatments prescribed following ACS, as well as from the catheterisation site used for PCI. Combined with a pre-existing bleeding tendency from underlying medical conditions or medications these patients may be at a particularly high risk of bleeding, leading to anaemia. In this study, the identification of malignancy and baseline oral anticoagulation as independent factors associated with the development of HAA provide support for this hypothesis. Additionally, the higher incidence of coronary thrombus in patients that went on to develop HAA may indicate that these were patients who were more likely to

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have received adjunctive glycoprotein IIB/IIIA inhibitors, thus increasing their bleeding tendency further [10]. With regards to PPI usage, prescription rates at discharge in this study were similar to those in previously reported studies [11,12]. There was a higher rate of PPI prescriptions at discharge among patients who developed HAA, which could suggest a higher rate of gastrointestinal bleeding events in this group. Unfortunately, data on bleeding events was not available for analysis. Therefore, we can only speculate about the contribution of bleeding events to the development of HAA in this study. Interestingly, Salisbury *et al.* reported that in a cohort of ACS patients, of which over 70% underwent PCI, only 13.5% of those who developed HAA had any reported bleeding, emphasising that causes other than bleeding need to be considered in the development of HAA [6]. With regards to gastrointestinal bleeding, the latest guidance from the European Society of Cardiology now recommend the routine use of a PPI in combination with dual antiplatelet therapy [13]. Thus, it is likely that an increasing rate of PPI prescriptions in the future could reduce the contribution of gastrointestinal bleeding to the development of both HAA and CA [13].

Another important mechanism to consider is haemodilution, which can arise through the administration of IV fluids/medications during hospitalisation, as well as through fluid retention in acute heart failure following ACS [14,15]. While bleeding and haemodilution are likely to contribute to the development of HAA, further studies are needed to elucidate the exact mechanisms behind HAA following ACS.

Why is anaemia associated with poor outcomes?

Patients with anaemia are known to receive fewer evidence-based treatments following ACS [16]. This could, in part, explain their worse outcomes. However, in this analysis there were no significant differences in prescriptions between anaemic and non-anaemic, both at time of discharge and at one-year follow-up. This suggested that differences in pharmacological therapy did not explain the worse outcomes in discharge anaemia patients in this study,

One mechanism that may drive poorer outcomes among anaemic patients is a worsening of the imbalance between myocardial oxygen supply and demand that is seen in coronary artery disease. This can be exacerbated by systemic vasodilatation and increased sympathetic tone seen in anaemic patients which in turn drive increased stroke volume and heart rate [17]. In the long-term, these haemodynamic changes can drive adverse myocardial remodelling [18,19]. In addition, two non-haemodynamic mechanisms may include impaired vascular healing and

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chronic inflammation among anaemic patients. Anaemic patients have been shown to have reduced circulating endothelial progenitor cells following an ACS which could impair vascular healing [20]. Another consideration is anaemia of chronic inflammation, a chronic inflammatory condition driven by an underlying inflammatory disease [9]. Anaemia of chronic inflammation is independently associated with increased rates of hospitalisation and mortality [9,21]. In the setting of ischaemic heart disease, inflammation is known to play an important role in all stages of atherothrombosis [22]. Furthermore, CRP has been shown to be an potent predictor of future vascular events, even when it lies in the high-normal range [23]. The present study noted raised CRP levels among the CA group, suggesting anaemia of chronic disease may have been present in at least some of these patients.

Why do HAA and CA have different outcomes?

One possible explanation is that patients with HAA were only affected by the haemodynamic changes associated with anaemia, whereas CA patients were also susceptible to non-haemodynamic complications such as chronic inflammation. Another consideration is the duration of anaemia following discharge. Patients with CA were more likely to have persistent anaemia during the follow-up period. Conversely, HAA may have resolved in some patients during follow-up as these patients were more likely to have normal haematopoietic function. Interestingly, Hasin *et al.* reported that among ACS patients discharged with anaemia, the outcomes of patients with resolving anaemia were similar to those without discharge anaemia [5]. Thus, it is plausible that the better outcomes in this group relate to recovery of haemoglobin levels in some of these patients.

Time for intervention studies?

There is sufficient evidence of the prognostic importance of anaemia following ACS to justify intervention studies. These could explore the impact of standardised testing of haematinics in all ACS patients with baseline anaemia in order to diagnose and treat deficiencies during the index admission. They could also evaluate the benefits of a lower blood transfusion threshold, particularly in the context of HAA.

Limitations

This study is limited by its retrospective, observational design and thus these findings can only be considered as hypothesis generating. However, the SPUM-ACS registry represents a multicentre cohort of consecutive patients hospitalised with ACS. Given the very few exclusion criteria, we feel that the risk of bias is limited and that patients included in this study are likely representative of those encountered in routine clinical practice. The

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prevalence of anaemia in this cohort was similar to previously reported figures, further suggesting that this population was representative [4]. Another limitation was the absence of data on bleeding events, blood transfusions and administration of IV fluids, all of which would have given better context to the discharge haemoglobin values. To tackle the absence of bleeding data, we performed a landmark analysis from day 7 post-angiography in order to exclude events directly attributable to severe angiography-related bleeding rather than the longer-term effects of anaemia. Finally, there was no data available on haemoglobin levels following discharge, or whether patients received blood transfusions or other treatments for anaemia, thus it was not possible to evaluate the outcomes of patients who possibly had resolution of anaemia during the follow-up period.

Conclusions

In an observational cohort of patients treated with PCI for ACS, both HAA and CA were associated with poorer one-year cardiovascular outcomes. However, CA and HAA likely represent distinct subclinical entities as only CA was associated with all-cause mortality.

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DISCLOSURES

None.

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HUMAN SUBJECTS/INFORMED CONSENT STATEMENT

This project did not require approval by an ethics committee. Data collection for SPUM-ACS study was approved by Swiss ethics (Swiss Ethics Committees on research involving humans) involving the ethics committees of each local centre (Lausanne, Geneva, Bern and Zurich) and complies with all laws and international ethics guidelines outlined in the Declaration of Helsinki. All human patients provided written, informed consent.

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ANIMAL STUDIES

No animal studies were carried out by the authors of this study.

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FIGURE LEGENDS

Figure 1: Forest plot of one-year endpoints in patients without discharge anaemia compared with patients with: (A) chronic anaemia, and (B) hospital-acquired anaemia. For each propensity-matched analysis, event rates for each one-year clinical endpoint are presented for the non-anaemic and discharge anaemia groups along with the hazard ratio and p-value from the corresponding Cox proportional hazards model. MACE represents a composite of cardiovascular mortality, recurrent MI and stroke. CI = confidence interval; GRACE = Global Registry of Acute Coronary Events; MACE = major adverse cardiovascular events; MI = myocardial infarction.

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Figure 2: Kaplan-Meier plots for propensity-score matched analyses of: (A) chronic anaemia, and (B) hospital-acquired anaemia. Landmark timepoint from which events were recorded was set at 7 days post-angiography (dotted line). For each endpoint, the p-value from the corresponding log-rank test is presented. MACE = major adverse cardiovascular events

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Figure 3: Cubic spline functions demonstrating the impact of discharge haemoglobin value on one-year clinical endpoints for: (A) chronic anaemia, and (B) hospital-acquired anaemia. MACE = major adverse cardiovascular events

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Online Figure 1: Association between baseline eGFR and baseline haemoglobin among patients with chronic anaemia. eGFR = estimated glomerular filtration rate.

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TABLES

Table 1: Baseline characteristics of unmatched and matched population. The unmatched population is stratified by type of discharge anaemia. For the matched analysis, patients with hospital-acquired anaemia (HAA) and chronic anaemia (CA) were matched to patients without discharge anaemia. Propensity-score matching (1:1) used a nearest-neighbour algorithm and a caliper setting of 0.1.

BASELINE CHARACTERISTICS	**UNMATCHED**				**MATCHED***					
	ALL DISCHARGE ANAEMIA				**HOSPITAL-ACQUIRED ANAEMIA**			**CHRONIC ANAEMIA**		
	No discharge anaemia (n=2178)	**HAA (n=1253)**	**CA (n=643)**	**p-value**	**No discharge anaemia (n=866)**	**HAA (n=866)**	**p-value**	**No discharge anaemia (n=504)**	**CA (n=504)**	**p-value**
Age, median (IQR)	59.20 [51.60, 68.50]	65.50 [56.30, 74.60]	72.00 [61.85, 79.70]	**<0.001**	62.85 [54.62, 72.28]	63.25 [54.90, 71.15]	0.888	68.45 [58.50, 76.43]	68.65 [59.63, 77.80]	0.330
Female (%)	346 (15.9)	341 (27.2)	158 (24.6)	**<0.001**	193 (22.3)	192 (22.2)	1.000	111 (22.0)	119 (23.6)	0.599
Hypertension (%)	1058 (48.6)	715 (57.1)	450 (70.0)	**<0.001**	455 (52.5)	466 (53.8)	0.630	327 (64.9)	333 (66.1)	0.740
Diabetes (%)	288 (13.2)	213 (17.0)	181 (28.1)	**<0.001**	144 (16.6)	127 (14.7)	0.290	115 (22.8)	120 (23.8)	0.766
Hypercholesterolemia (%)	1387 (63.7)	794 (63.4)	375 (58.3)	**0.041**	543 (62.7)	553 (63.9)	0.654	298 (59.1)	298 (59.1)	1.000
Previous MI (%)	226 (10.4)	134 (10.7)	136 (21.2)	**<0.001**	95 (11.0)	89 (10.3)	0.697	89 (17.7)	87 (17.3)	0.934
Previous PCI (%)	268 (12.3)	153 (12.2)	159 (24.7)	**<0.001**	108 (12.5)	99 (11.4)	0.553	113 (22.4)	102 (20.2)	0.442
Previous CABG (%)	55 (2.5)	41 (3.3)	54 (8.4)	**<0.001**	26 (3.0)	26 (3.0)	1.000	26 (5.2)	26 (5.2)	1.000
Previous stroke (%)	39 (1.8)	28 (2.2)	43 (6.7)	**<0.001**	20 (2.3)	17 (2.0)	0.740	22 (4.4)	17 (3.4)	0.514

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Previous CVD (%)	388 (17.8)	265 (21.1)	249 (38.7)	**<0.001**	180 (20.8)	166 (19.2)	0.435	160 (31.7)	160 (31.7)	1.000
Valvular disease (%)	12 (0.6)	17 (1.4)	19 (3.0)	**<0.001**	4 (0.5)	8 (0.9)	0.385	7 (1.4)	9 (1.8)	0.801
Chronic lung disease (%)	56 (2.6)	39 (3.1)	46 (7.2)	**<0.001**	26 (3.0)	24 (2.8)	0.886	24 (4.8)	25 (5.0)	1.000
Previous/current malignancy (%)	122 (5.6)	100 (8.0)	92 (14.3)	**<0.001**	64 (7.4)	60 (6.9)	0.780	62 (12.3)	57 (11.3)	0.696
Previous GI bleed (%)	34 (1.6)	23 (1.8)	29 (4.5)	**<0.001**	17 (2.0)	16 (1.8)	1.000	16 (3.2)	17 (3.4)	1.000
Family history of CAD (%)	591 (27.1)	299 (23.9)	135 (21.0)	**0.003**	229 (26.4)	215 (24.8)	0.474	123 (24.4)	114 (22.6)	0.552
Smoking (%)	972 (44.6)	487 (38.9)	173 (26.9)	**<0.001**	344 (39.7)	351 (40.5)	0.769	159 (31.5)	160 (31.7)	1.000
BMI (kg/m^2)	27.59 (4.29)	26.34 (4.15)	26.31 (4.50)	**<0.001**	26.76 (3.91)	26.58 (4.19)	0.381	26.42 (3.92)	26.58 (4.49)	0.546
Baseline haemoglobin (g/l), median (IQR)	150.00 [142.00, 157.00]	139.00 [132.00, 146.00]	118.00 [109.00, 124.00]	**<0.001**	143.00 [136.00, 149.00]	142.00 [135.00, 149.00]	0.088	147.00 [140.00, 155.00]	119.00 [110.00, 125.00]	**<0.001**
Baseline haematocrit (%), median (IQR)	43.90 [41.70, 46.00]	41.00 [39.00, 43.00]	35.20 [32.90, 37.00]	**<0.001**	42.00 [40.00, 43.90]	41.70 [39.73, 43.80]	0.101	43.00 [41.00, 45.12]	35.50 [33.00, 37.00]	**<0.001**
eGFR, ml/min/1.73m^2, mean (SD)	92.62 (23.58)	85.70 (26.99)	78.16 (32.08)	**<0.001**	89.47 (23.33)	90.10 (26.11)	0.596	84.82 (22.83)	82.63 (31.50)	0.207
LVEF, mean (SD)	53.02 (10.33)	49.05 (11.73)	49.12 (12.65)	**<0.001**	50.80 (10.76)	50.97 (10.92)	0.751	50.47 (11.21)	50.42 (12.10)	0.943
ECG ischemia (%)	1790 (82.2)	1092 (87.2)	503 (78.2)	**<0.001**	742 (85.7)	737 (85.1)	0.786	390 (77.4)	398 (79.0)	0.594
Heart rate, beats-per-minute, mean (SD)	76.52 (18.65)	78.25 (17.06)	77.83 (17.47)	**0.017**	76.90 (15.82)	77.15 (16.46)	0.748	76.93 (16.79)	77.27 (17.69)	0.755
Systolic blood pressure, mmHg, mean (SD)	129.43 (23.17)	128.07 (25.74)	127.28 (24.40)	0.080	128.63 (22.89)	128.53 (25.10)	0.931	127.97 (22.61)	128.58 (24.77)	0.682
GRACE score, mean (SD)	130.54 (27.73)	148.82 (35.33)	155.22 (36.79)	**<0.001**	140.13 (27.99)	140.06 (30.56)	0.965	146.10 (31.53)	147.84 (32.32)	0.387

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GRACE score >140 (%)	715 (33.8)	682 (56.1)	397 (64.1)	**<0.001**	397 (47.3)	388 (46.2)	0.679	266 (55.3)	281 (57.5)	0.539
Killip class (%)				**<0.001**			0.807			0.934
1	2014 (92.5)	1018 (81.2)	494 (76.8)		756 (87.3)	758 (87.5)		421 (83.5)	417 (82.7)	
2	124 (5.7)	126 (10.1)	86 (13.4)		78 (9.0)	70 (8.1)		52 (10.3)	56 (11.1)	
3	27 (1.2)	40 (3.2)	29 (4.5)		20 (2.3)	23 (2.7)		18 (3.6)	16 (3.2)	
4	13 (0.6)	69 (5.5)	34 (5.3)		12 (1.4)	15 (1.7)		13 (2.6)	15 (3.0)	
Unstable angina (%)	67 (3.1)	27 (2.2)	29 (4.5)	**0.017**	20 (2.3)	24 (2.8)	0.647	22 (4.4)	22 (4.4)	1.000
NSTEMI (%)	850 (39.0)	344 (27.5)	291 (45.3)	**<0.001**	280 (32.3)	268 (30.9)	0.570	221 (43.8)	215 (42.7)	0.751
STEMI (%)	1261 (57.9)	882 (70.4)	322 (50.1)	**<0.001**	566 (65.4)	574 (66.3)	0.723	261 (51.8)	267 (53.0)	0.753

Abbreviations: BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous intervention; SD = standard deviation; STEMI = ST-elevation myocardial infarction

* Patients matched for: age, sex, diabetes, hypertension, hypercholesterolemia, previous MI, previous PCI, previous CABG, previous stroke, previous CVD, valvular disease, chronic lung disease, history of malignancy, history of gastrointestinal bleeding, family history of CVD, systolic blood pressure, heart rate, BMI, anaemia, Killip class, baseline eGFR, ECG ischemia, smoking, GRACE score, LVEF, type of ACS, PCI vs. balloon angioplasty only, percentage stenosis, number of stents, TIMI grade flow post-PCI, presence of coronary thrombus.

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1 **Table 2: Treatment summary**

TREATMENT CHARACTERISTICS	UNMATCHED				MATCHED					
	ALL DISCHARGE ANAEMIA				HOSPITAL-ACQUIRED ANAEMIA			CHRONIC ANAEMIA		
	No discharge anaemia (n=2178)	HAA (n=1253)	CA (n=643)	p-value	No discharge anaemia (n=866)	HAA (n=866)	p-value	No discharge anaemia (n=504)	CA (n=504)	p-value
PCI - balloon dilatation only	94 (4.3)	69 (5.5)	42 (6.5)	0.051	43 (5.0)	43 (5.0)	1.000	27 (5.4)	27 (5.4)	1.000
Percentage stenosis (%)				**<0.001**			0.807			0.904
<50%	9 (0.4)	1 (0.1)	1 (0.2)		0 (0.0)	1 (0.1)		0 (0.0)	1 (0.2)	
50-74%	83 (3.8)	50 (4.0)	35 (5.4)		40 (4.6)	37 (4.3)		24 (4.8)	25 (5.0)	
75-94%	350 (16.1)	173 (13.8)	142 (22.1)		121 (14.0)	131 (15.1)		94 (18.7)	95 (18.8)	
95-99%	841 (38.6)	342 (27.3)	216 (33.6)		264 (30.5)	265 (30.6)		182 (36.1)	181 (35.9)	
100%	895 (41.1)	687 (54.8)	249 (38.7)		441 (50.9)	432 (49.9)		204 (40.5)	202 (40.1)	
Stent number (%)				**<0.001**			0.859			0.781
0	0 (0.0)	3 (0.2)	3 (0.5)		1 (0.1)	1 (0.1)		0 (0.0)	1 (0.2)	
1	1753 (80.5)	882 (70.4)	493 (76.7)		645 (74.5)	643 (74.2)		392 (77.8)	395 (78.4)	
2	349 (16.0)	284 (22.7)	112 (17.4)		170 (19.6)	179 (20.7)		90 (17.9)	87 (17.3)	
≥3	76 (3.5)	84 (6.7)	35 (5.4)		50 (5.8)	43 (5.0)		22 (4.4)	21 (4.2)	
TIMI flow post-PCI (%)				**<0.001**			0.992			0.267
0	10 (0.5)	23 (1.8)	6 (0.9)		7 (0.8)	6 (0.7)		6 (1.2)	1 (0.2)	
1	12 (0.6)	28 (2.2)	4 (0.6)		8 (0.9)	8 (0.9)		1 (0.2)	2 (0.4)	
2	41 (1.9)	43 (3.4)	19 (3.0)		28 (3.2)	29 (3.3)		14 (2.8)	15 (3.0)	

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3	2114 (97.1)	1159 (92.5)	614 (95.5)		823 (95.0)	823 (95.0)		483 (95.8)	486 (96.4)	
Thrombus (%)	924 (42.4)	663 (52.9)	244 (37.9)	**<0.001**	420 (48.5)	427 (49.3)	0.773	203 (40.3)	204 (40.5)	1.000
Aspirin (%)	2165 (99.5)	1222 (99.3)	616 (98.7)	0.078	861 (99.4)	859 (99.4)	1.000	500 (99.2)	491 (98.8)	0.734
ACE/ARB (%)	2000 (92.0)	1125 (91.5)	569 (91.3)	0.846	798 (92.1)	785 (91.0)	0.424	463 (91.9)	457 (92.1)	0.967
Beta-blocker (%)	1804 (83.0)	1009 (82.1)	502 (80.6)	0.355	728 (84.1)	707 (81.9)	0.262	427 (84.9)	403 (81.2)	0.147
Statin (%)	2165 (99.5)	1214 (98.8)	618 (99.0)	**0.043**	862 (99.5)	853 (98.8)	0.178	502 (99.6)	493 (99.2)	0.670
P2Y12 agent (%)				**<0.001**			0.854			0.821
Clopidogrel	829 (38.1)	564 (45.0)	355 (55.2)		360 (41.6)	365 (42.1)		246 (48.8)	252 (50.0)	
Prasugrel	868 (39.9)	481 (38.4)	154 (24.0)		345 (39.8)	349 (40.3)		148 (29.4)	139 (27.6)	
Ticagrelor	481 (22.1)	208 (16.6)	134 (20.8)		161 (18.6)	152 (17.6)		110 (21.8)	113 (22.4)	
Proton pump inhibitor	486 (22.3)	426 (34.6)	266 (42.7)	**<0.001**	226 (26.1)	268 (31.0)	**0.027**	143 (28.4)	196 (39.5)	**<0.001**
Discharge haemoglobin (g/l), median (IQR)	139.00 [133.00, 146.00]	118.00 [108.00, 124.00]	107.00 [92.00, 116.00]	**<0.001**	135.00 [131.00, 139.00]	119.00 [111.00, 125.00]	**<0.001**	137.00 [131.00, 143.25]	109.00 [96.00, 117.00]	**<0.001**
Haemoglobin drop (g/l), median (IQR)	9.00 [4.00, 15.00]	22.00 [14.00, 33.00]	8.00 [3.00, 16.00]	**<0.001**	7.00 [2.00, 12.00]	23.00 [15.00, 34.00]	**<0.001**	8.00 [3.00, 15.00]	8.00 [3.00, 15.00]	0.949

1 Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary
2 artery bypass graft; IQR = interquartile range; PCI = percutaneous intervention; SD = standard deviation; TIMI =
3 thrombolysis in myocardial infarction;