Overcoming mass and photon transfer limitations in a scalable reactor: Oxidation in an aerosol photoreactor

KAYAHAN, Emine; Urbani, D; Dambruoso, P; Massi, A; BRAEKEN, Leen; Van Gerven , T & Leblebici, ME (2021) Overcoming mass and photon transfer limitations in a scalable reactor: Oxidation in an aerosol photoreactor. In: Chemical engineering journal (1996. Print), 408 (Art N° 127357).

DOI: 10.1016/j.cej.2020.127357
Handle: http://hdl.handle.net/1942/37701

Prognostic Implications of In-Hospital Hemoglobin Drop With and Without Overt Bleeding in Acute Coronary Syndromes

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Relationships with Industry and Other Entities
The trial was sponsored by the Società Italiana di Cardiologia Invasiva (GISE, a non-profit organization), which received grant support from The Medicines Company and TERUMO. This substudy did not receive any direct or indirect funding.
Dr. Leonardi reports grants and personal fees from AstraZeneca, BMS/Pfizer, Chiesi, personal fees from Bayer, outside the submitted work.
Dr. Gragnano reports research grant support from the European Society of Cardiology (ESC Research grant).
Dr. Vranckx reports personal fees from Astra Zeneca, Terumo, CLS Bhering, Daiichi Sankyo, and from Bayer Health Care outside the submitted work.
Dr. Frigoli is affiliated with CTU Bern, University of Bern, which has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html.
Dr. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, Sinomed, outside the submitted work.
Dr. Valgimigli reports grants and personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from Astrazeneca, personal fees from Biosensors, personal fees from Idorsia, outside the submitted work.
All other Authors reported no relationships relevant to the contents of this paper to disclose.
Word count (including text, references, and figure legends): 4,331

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Abbreviations List

ACE, angiotensin-converting-enzyme
ACS, Acute Coronary Syndromes
BARC, Bleeding Academic Research Consortium
CEC, Clinical Event Committee
CI, Confidence Intervals
eGFR, estimated glomerular filtration rate
HB, Hemoglobin
HR, Hazard Ratio
MATRIX, Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
NSTEACS, non-ST-segment elevation acute coronary syndrome
OR, Odss Ratio
PCI, Percutaneous Coronary Intervention
STEACS, ST-segment elevation acute coronary syndrome
TIMI, Thrombolysis in Myocardial Infarction

ABSTRACT

Background Contemporary definitions of bleeding endpoints are restricted to clinically overt events. Whether hemoglobin drop *per se*, with or without overt bleeding, adversely affects the prognosis of acute coronary syndrome (ACS) patients remains unclear.
Objectives To examine incidence, predictors and prognostic implications of in-hospital hemoglobin drop in patients with ACS managed invasively stratified by the presence of adjudicated in-hospital bleeding.
Methods Patients were categorized by the presence and amount of in-hospital hemoglobin drop based on baseline and nadir hemoglobin values and further stratified by the occurrence of adjudicated in-hospital bleeding. Hemoglobin drop was defined as minimal if <3 g/dL, minor ≥3 g/dL and <5 gr/d, and major ≥5 g/dL. Using multivariable Cox-regression, we modeled the association between hemoglobin drop and mortality in patients with and without overt bleeding.
Results Among 7,806 patients included in the MATRIX trial with available hemoglobin values, 6,522 patients (83.6%) had hemoglobin drop, of whom 5,766 (88.4%) without and 756 (11.6%) with overt bleeding. In patients without overt bleeding, minor (hazard ratio [HR]:1.88; 95% confidence interval [CI]:1.06-3.34; p=0.030) and major (HR:2.47; 95% CI:1.02-5.99; p=0.046) hemoglobin drop were independently associated with increased 1-year mortality. In patients with overt bleeding, the association of minor and major hemoglobin drop with 1-year mortality was directionally similar but had wider confidence intervals (minor: HR:2.17, 95% CI:0.77-6.08; major: HR:7.97, 95% CI:2.08-30.54).
Conclusions Among patients with ACS managed invasively, in-hospital hemoglobin drop of 3 g/dL or more, even in the absence of overt bleeding, is common and independently associates with increased risk of 1-year mortality.

Trial registration ClinicalTrials.gov number NCT01433627.

Condensed abstract

Using data from the MATRIX trial, we investigated incidence, predictors and prognostic implications of in-hospital hemoglobin drop in patients with ACS managed invasively with and without in-hospital overt bleeding. In those without overt bleeding, an hemoglobin reduction ≥ 3 gr/dL was common and independently associated with a 2-fold higher risk of 1-year mortality. A similar association was shown in patients with overt bleeding, but with wider confidence intervals. These results may have implications for the use of hemoglobin reductions in clinical trials and clinical practice.

Keywords: Hemoglobin; Bleeding; Acute coronary syndromes; Percutaneous coronary intervention.

INTRODUCTION

Bleeding events have been extensively associated with higher mortality rates in patients with cardiovascular diseases, including patients with acute coronary syndromes (ACS) and those receiving coronary revascularization (1,2); therefore, their accurate definition and quantification as endpoint are essential. In the context of cardiovascular randomized controlled trials, contemporary classifications of bleeding endpoints have been restricted to clinically evident (i.e., overt) bleeding, using thresholds of 3 and 5 g/dL of hemoglobin reductions to grade their severity (1–4).

It is unclear, however, whether an hemoglobin reduction *per se*, in patients without overt bleeding, independently associates with mortality and, if so, if this association is quantitatively similar to that observed in patients with overt bleeding. Using data from the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial of patients with ACS managed invasively (5,6), we examined the incidence, predictors, effects on randomized treatments, and prognostic implications of in-hospital hemoglobin drop in patients with and without adjudicated overt bleeding.

METHODS

MATRIX programme design

The MATRIX (NCT01433627) was a programme of three independent randomized controlled trials enrolling an all-comers population of ACS patients, with or without ST-segment elevation, receiving invasive management (7). Detailed study design, methods, and enrollment criteria have been previously published (7). In brief, the first trial, MATRIX Access, randomized 8,404 ACS patients to radial access or femoral access (5). The second trial, MATRIX Antithrombin, randomized 7,213 patients

comparing an antithrombotic strategy of bivalirudin versus unfractionated heparin (with optional glycoprotein IIb/IIIa inhibitors) (8). The third trial, MATRIX Treatment Duration, randomized patients assigned to bivalirudin to receive extended bivalirudin administration after percutaneous coronary intervention (PCI) or short-term administration during PCI (8). Patients with ST-segment elevation ACS were eligible if they presented within 12 hours of symptom onset or between 12-24 hours with evidence of continuing ischemia or previous fibrinolytic treatment, and if they had ST-segment elevation of ≥1 mm in 2 or more contiguous ECG leads, or a new left bundle-branch block or true posterior myocardial infarction. Patients with non-ST-segment elevation ACS were eligible if they had a history consistent with new or worsening cardiac ischemia, occurring at rest or with minimal activity within 7 days before randomization and fulfilled at least two high-risk criteria among the following: age ≥60 years, elevation of cardiac biomarkers, or ECG changes consistent with cardiac ischemia, consideration as possible candidates for PCI after completion of coronary angiography (7).

Study patients and definitions

For this analysis, the study population included all patients enrolled in the MATRIX programme who had qualifying in-hospital hemoglobin information available, including values at baseline and at nadir, which were prospectively collected in the electronic care report form. Baseline hemoglobin was the first hemoglobin value obtained at admission and prior to randomization. Nadir hemoglobin was the lowest value collected during hospitalization. All laboratory values, including in-hospital hemoglobin, were entered by the site and then locally monitored and centrally verified for quality using consistency checks. We defined patients as *with hemoglobin drop*

those with a positive difference between baseline and nadir hemoglobin values (i.e., the baseline was higher than the nadir). If this difference was 0 or negative (i.e., the baseline was equal or lower than the nadir), patients were categorized into the *no hemoglobin drop* group. Patients with in-hospital hemoglobin drop were then further stratified based upon the presence or absence of an adjudicated overt bleeding during hospitalization. According to contemporary definitions of bleeding (3,4), thresholds of 3 and 5 g/dL were used to classify hemoglobin drop severity. A reduction was considered *minimal* if the difference between baseline and nadir hemoglobin concentrations was >0 and <3 g/dL, *minor* if this difference was ≥3 g/dL and <5 g/dL, and *major* if ≥5 g/dL.

Study endpoints

The primary endpoint for this analysis was all-cause mortality at 1-year. As secondary endpoint, all-cause mortality at 30 days was also evaluated. An independent clinical events committee (CEC) blinded to randomized treatment allocation adjudicated all suspected primary or secondary outcomes, including death and bleeding, by reviewing relevant medical records after site monitoring, and systematically identified potential bleeding events, either reported or not by the investigators, in patients with and without hemoglobin reduction. Specifically, all patients with in-hospital hemoglobin drop of at least 3 g/dL were centrally triggered and source documentation submitted to the CEC for potential unreported bleeding events.

Statistical Analysis

Differences across groups were assessed using Student t-test or Wilcoxon-Mann-Whitney test in case of continuous variables and chi-square or Fisher exact test in case of categorical data. The incidence, distribution, and degree of hemoglobin reduction in

the study population were assessed. Potential predictors of hemoglobin drop and Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding were identified at univariate analysis ($p<0.10$), and independent predictors selected with multivariate backward selection ($p<0.10$). We applied a multivariable Cox Proportional-Hazard model to evaluate the association of hemoglobin drops during index hospitalization (as a categorical and continuous variable) with all-cause mortality in patients with and without overt bleeding. Covariates tested in the model were chosen among previously validated predictors of death in ACS populations, including those reported in the Global Registry of Acute Coronary Events (GRACE) risk score (9). The final multivariable model included the following covariates: age, heart rate, systolic blood pressure, estimated glomerular filtration rate, and baseline hemoglobin values as continuous variables; sex, diabetes, cardiac arrest on admission, Killip class, prior myocardial infarction, ST-segment elevation at presentation, and number of diseased coronary vessels (1-, 2-, or ≥3) as categorical variables. Continuous relation between hemoglobin drop and mortality was assessed using restricted cubic splines. Kaplan-Meier method was used to estimate cumulative rates of events at 30-day and 1-year follow-up. Waterfall plots were used to graphically illustrate the distribution of hemoglobin drop in patients with and without overt bleeding. We performed an additional analysis according to the pre-specified randomization subgroups to estimate possible effects of radial access versus femoral access and bivalirudin versus heparin on (i) in-hospital bleeding and (ii) minor or major hemoglobin drop. We also evaluated the association of in-hospital hemoglobin drops with and without overt bleeding with blood transfusions as endpoint. The analyses were done using Stata release 14.1 (StataCorp LLC, College Station, Texas) and R statistical Software (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 8,404 patients enrolled in the MATRIX trial, 598 (7.1 %) were excluded because of incomplete hemoglobin values (baseline, nadir, or both). Of the 7,806 patients with complete hemoglobin information, 83.6% or 6,522 experienced a hemoglobin drop during the index hospitalization, and 16.4% or 1,284 did not. Baseline characteristics, procedural data, and medications of patients with and without hemoglobin drop, as well as of those with missing hemoglobin values, are reported in **eTables 1-3.** Unadjusted mortality rates of patients with or without qualifying hemoglobin values are shown in **eFigure 1**, indicating a high, upfront in-hospital mortality for patients with incomplete as compared with those with complete hemoglobin information.

Of the 6,522 patients with in-hospital hemoglobin drop, 756 (11.6%) had at least one adjudicated overt bleeding event. Baseline characteristics, procedural data, and medications at discharge of these patients are shown in **Table 1, eTable 4 and eTable 5.** As compared with patients without overt bleeding, patients with both hemoglobin drop and bleeding were older, had more comorbidities and cardiovascular risk factors at presentation (i.e., higher risk profile), and received more often clopidogrel at discharge. The distribution of hemoglobin drop in patients with and without overt bleeding is presented in **eFigure 2**. The proportion of patients with minor or major hemoglobin drop was higher among those with overt bleeding (17.1% and 4%, respectively) as compared with those without overt bleeding (5.6% and 1.3%, respectively; p-value <0.001 for both comparisons) **(Figure 1 and Table 2)**. On the other hand, a minor or major hemoglobin drop without overt bleeding was observed in 400 patients as compared to 159 patients with the same level of hemoglobin drop

and concomitant overt bleeding. Among patients with overt bleeding, 36.5% had a Bleeding Academic Research Consortium BARC type 2 bleeding, while 16.9% had a BARC type 3 or 5 **(eTable 6)**. The percent change of hemoglobin levels in patients with overt bleeding stratified by BARC type severity (1,2 versus 3,4,5) is reported in **eFigure 3**.

Predictors of major or minor hemoglobin drop and BARC 3 or 5 bleeding

Multivariate predictors of major or minor hemoglobin drop – in the overall population and separately in patients without overt bleeding – and of BARC 3 or 5 type bleeding are listed in **Table 3**. Female sex, chronic obstructive pulmonary disease, ejection fraction, non-ST-segment elevation ACS presentation, PCI not attempted after coronary angiography, SYNTAX score, and total contrast volume emerged as independent predictors of hemoglobin drop ≥3 g/dL in the absence of overt bleeding, whereas they did not predict the risk of BARC 3 or 5 bleeding. Conversely, advanced age, use of intra-aortic balloon pump, and baseline hemoglobin independently predicted both major/minor hemoglobin drop and BARC 3 or 5 bleeding, although for the latter predictor the association was directionally opposite.

Multivariate association of hemoglobin drop with all-cause mortality

Kaplan-Meier event curves showed a higher cumulative incidence of 1-year mortality in patients with major or minor hemoglobin drop compared with those with minimal or no hemoglobin drop with a similar trend in patients with and without overt bleeding **(Figure 2).** Multivariable association of hemoglobin drop with 30-day and 1-year mortality in patients with and without overt bleeding is reported in **Table 4** and displayed in **Figure 3** and in **the Central Illustration**. In general, hemoglobin drop in

patients with and without overt bleeding were independently associated with a graded association with mortality, which was higher for patients with overt bleeding as compared to patients without overt bleeding. Yet, patients without overt bleeding had an increased risk of 1-year mortality after both a minor (hazard ratio [HR]: 1.88; 95% confidence interval [CI]: 1.06-3.34; p=0.030) or a major hemoglobin drop (HR: 2.47; 95% CI: 1.02-5.99, p=0.046) as compared with those without hemoglobin drop. In patients with overt bleeding, the association of minor and major hemoglobin drop with 1-year mortality was directionally similar but had wider confidence intervals [minor: HR 2.17 (95% CI: 0.77-6.08), major: HR: 7.97 (95% CI: 2.08-30.54)]. The multivariable 1-year HR for mortality of hemoglobin drop modeled as a continuous variable was 1.13 per gram/dl decrease of hemoglobin for patients without overt bleeding (95% CI: 1-1.28; p=0.056) and of 1.28 for patients with overt bleeding (95% CI: 1.08-1.51; p=0.004), respectively. Results were directionally similar at 30-days.

Effects of randomized treatments on hemoglobin drop with or without bleeding

The effect of randomized treatments on in-hospital overt bleeding and in-hospital minor or major hemoglobin drop is reported in **Table 5**. The use of radial over femoral access was associated with a lower risk of in-hospital bleeding complications (odds ratio [OR]: 0.51; 95% CI: 0.45-0.59; p<0.001) and a numerically lower risk of minor or major hemoglobin reduction (OR: 0.85; 95% CI: 0.72-1.01; p=0.067). The use of bivalirudin was associated with a significantly reduced risk of in-hospital bleeding (OR: 0.77; 95% CI: 0.66-0.89; p<0.001) and minor or major hemoglobin reduction (OR: 0.77; 95% CI: 0.64-0.93; p=0.008) as compared with unfractionated heparin. The rates and proportions of patients with and without hemoglobin reduction receiving blood transfusions are reported in **eTable 7.**

DISCUSSION

In the present analysis, we comprehensively assessed, in an all-comer population of ACS patients managed invasively, the epidemiology, predictors and association with outcome of in-hospital hemoglobin drop, with and without overt bleeding,. The main findings are the following:

- In hospital hemoglobin drop of ≥ 3 g/dL, even in the absence of an adjudicated overt bleeding, showed a continuos, direct association with increased 1 year mortality. No association between minimal (below 3 g/dL) hemoglobin drop and mortality was observed.
- Patients with hemoglobin reduction ≥3 g/dL were proportionally more common (21% versus 7%) in the group with adjudicated bleeding. Yet, the prevalence of hemoglobin reduction ≥3 g/dL in patients without adjudicated bleeding was far higher than among patients with adjudicated bleeding (n=159 versus 400).
- Randomized bleeding minimization strategies tested in MATRIX (i.e., radial access and bivalirudin use) were associated with a lower risk of incurring in-hospital hemoglobin drop as compared with their control (i.e., femoral access on unfractionated heparin).

Possible Causes and Consequences of Hemoglobin Reductions in patients with ACS

In patients with ACS, multiple mechanisms may be responsible for in-hospital hemoglobin drop. Overt bleeding can complicate hospital course as a consequence of pharmacological as well as invasive procedures (10,11). Besides evident blood loss,

subtle bleeding can also occur due to the aggressive antithrombotic burden, with the primary source of bleeding remaining masked if not investigated appropriately. Also, a decline in hemoglobin after ACS can be caused by intense inflammatory status (12), stress polycythemia on admission (13), hemodilution secondary to volume repletion (14), or impaired bone marrow activity due to clinical factors (15).

In the early phase of ACS, anemia has been consistently associated with bleeding complications (16,17). However, its prognostic impact can also extend to nonbleeding outcomes and mortality (18–20) possibly by worsening myocardial ischemic insult (i.e., decreasing the oxygen supply to the jeopardized myocardium) (21), increasing myocardial oxygen demand (i.e., needing for higher cardiac output to maintain an adequate systemic oxygen delivery) (22), and inducing abnormal neurohormonal activation and cardiac remodeling (23). Previous studies showed that the presence of low hemoglobin levels before and/or after PCI is a powerful and independent predictor of future cardiovascular events (18–20). In a large pooled population of 39,922 patients with ACS, baseline hemoglobin level below 11 g/dL was associated with excess mortality of more than 4-fold compared with higher values (18). Evidence also indicates an adverse prognostic impact for in-hospital hemoglobin changes in this setting. Among 7,608 patients undergoing successful PCI from the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) (51.7% presenting with ACS) registry who had an in-hospital hemoglobin reduction ≥4.0 g/dL in the presence of overt bleeding was associated with a considerably increased risk of dying (24). In a prospective study involving 1,390 patients with myocardial infarction (15), in-hospital hemoglobin drop and nadir showed a significant and independent association with 2-year mortality. A relevant proportion of patients showed a decrease in hemoglobin levels during hospitalization in the

absence of bleeding, with a more than doubled proportion of patients having anemia at discharge (36.1%) than on admission (17.8%). In the TRIUMPH registry (25), including 2,909 patients with ACS and normal hemoglobin levels on admission, up to 45% of patients developed anemia during hospitalization, that if moderate-severe (below 11 g/dL in 26% of cases) was associated with worse mortality and health status at 1 year. Among patients who developed in-hospital anemia, 86% did not have overt bleeding. Finally, post-PCI drop in hemoglobin levels has been associated with acute kidney injury (26), which in turn has demonstrated to be a relevant driver of mortality in the setting of ACS (27,28).

However, no previous study addressed the prognostic impact of hemoglobin reduction *per se* (i.e., without concomitant overt bleeding) in the setting of ACS.

Prognostic effect of hemoglobin reductions in ACS patients without overt bleeding and implications for bleeding endpoint classifications

The present analysis extends previous evidence by examining the incidence and prognostic relevance of hemoglobin drop, with and without concomitant overt bleeding, in a large contemporary ACS population. In line with previous findings (15,25), the incidence of hemoglobin reduction was high in our population. In the absence of overt bleeding, a minor (between 3 and 5 g/dL) or major (more than 5 g/dL) hemoglobin drop was associated with an increase in the risk of dying up to 2.5 folds at 1 year, which was independent of several covariates including clinical and procedural factors and baseline hemoglobin concentrations. Conversely, a minimal hemoglobin reduction (less than 3 g/dL) was not associated with mortality.

Adjudication of bleeding endpoint in randomized controlled trials according to contemporary definitions mandate the presence of overt bleeding (29,30). This

modern approach deviates from historical frameworks, which considered a decrease in hemoglobin as minor hemorrhagic events even in the absence of overt bleeding (i.e., blood loss with no site identified) (31). Notably, most studies do not require systematic investigation of potential sources of hemoglobin loss. Thus, in clinical practice as well as in clinical research, many potential bleedings may remain occult. Moreover, bleeding events considered as prognostically relevant (such as BARC 3 to 5) are relatively infrequent (29,30), limiting study power (32).

The observation of an independent association with long-term mortality as well a measurable treatment effect on established bleeding minimization strategies support the concept that hemoglobin reductions ≥3 g/dL may be valid surrogate endpoints. As such, they could complement contemporary definitions of bleeding endpoints and be easily implemented due to the simple, reliable, and inexpensive measurement.

Study Limitations

Our findings should be interpreted in the context of several potential limitations. This is a post-hoc analysis from a prospective, randomized controlled trial, which was not powered to explore outcome differences across hemoglobin reduction sub-groups of patients. As such the results should only be considered hypothesis-generating. Qualifying hemoglobin values were missing in 7.1 % of patients. While the reason for this was not captured, the very high early mortality of these patients suggests that their very high-risk rather than data quality was the primary reason for data incompleteness. Specific conditions associated with or predisposing to chronic anemia were not assessed in detail in the study population and might have influenced our results. Another possible limitation is that some misclassification of hemoglobin reduction severity occurred in patients who received blood transfusions during the

hospital stay. Finally, in the MATRIX trial, data on hemoglobin at discharge and follow-up were not collected. Thus, we were not able to analyze the prognostic impact of transient (i.e., in-hospital only) versus persistent (i.e., after discharge) anemia.

CONCLUSIONS

In ACS patients managed invasively, in-hospital drop of hemoglobin levels ≥3 g/dL, even in the absence of overt bleeding events, were common and independently associated with an increased risk of all-cause mortality at 1 year. If confirmed, these results may help the identification of higher risk patients and inform contemporary bleeding definitions.

PERSPECTIVES

Competency in medical knowledge: in patients with ACS managed invasively, a drop of hemoglobin of at least 3 gr/dL, even in absence of a detectable bleeding, is common, independently associated with 1-year mortality, and may be sensitive to the effect of new treatments.

Translational Outlook: If confirmed, these findings may have implications for clinical practice and research. A drop of hemoglobin of at least 3 gr/dL drop may help identify higher risk patients and could compliment bleeding endpoint reporting in phase III clinical trials and may be a surrogate in mechanistic (phase I-II) trials.

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FIGURES

Figure 1. **Waterfall plot for the percent change in hemoglobin levels during hospitalization.** (A) Patients without overt bleeding. (B) Patients without overt bleeding. Data are shown for patients who had no hemoglobin reduction (light blue and light red), minimal hemoglobin reduction (blue and red), and major/minor hemoglobin reduction (intense blue and dark red). HB = hemoglobin.

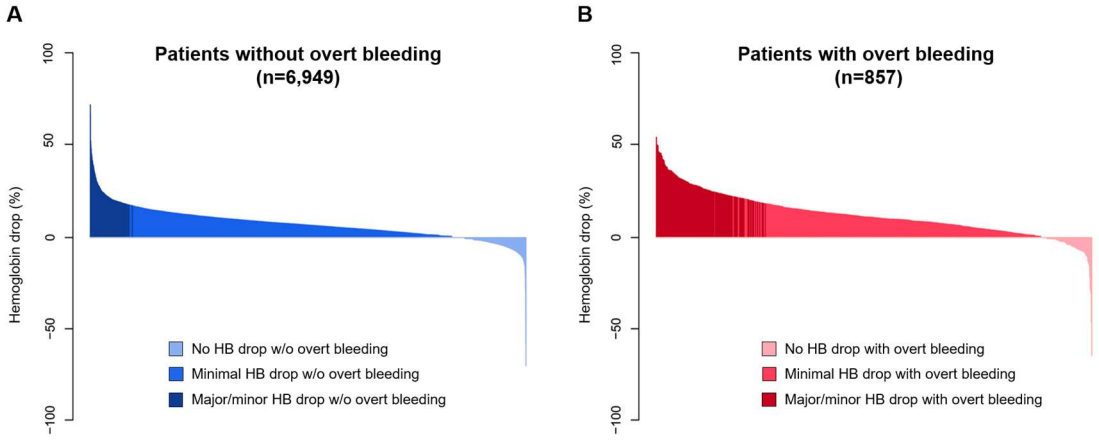


Figure 2. One-year mortality in patients with and without overt bleeding.

Kaplan-Meier event curves for all-cause mortality stratified by hemoglobin drop. (A) Patients without overt bleeding. (B) Patients with overt bleeding. HB = hemoglobin.

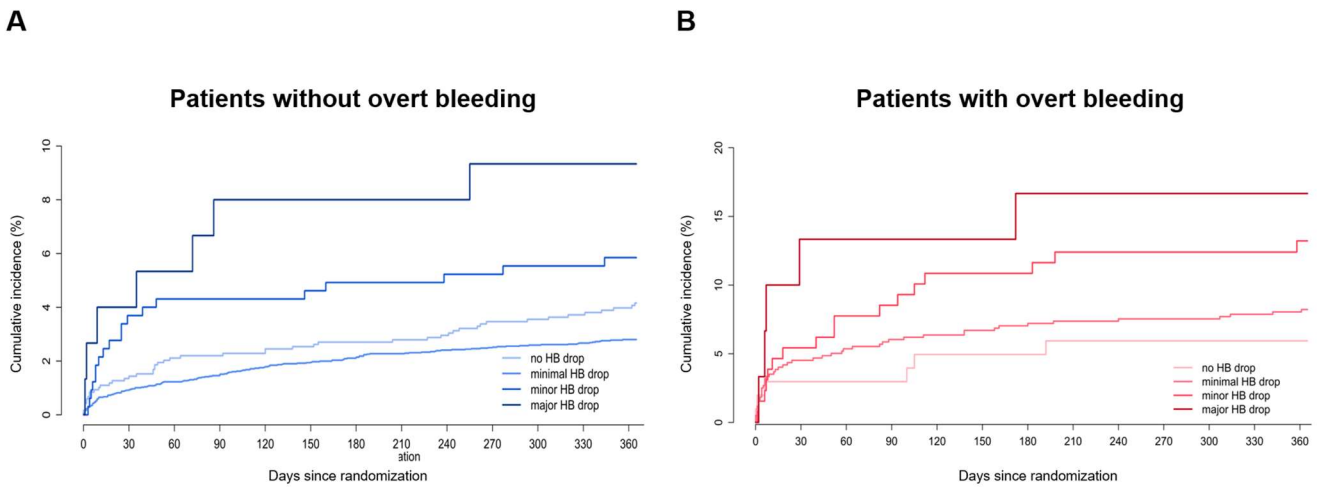
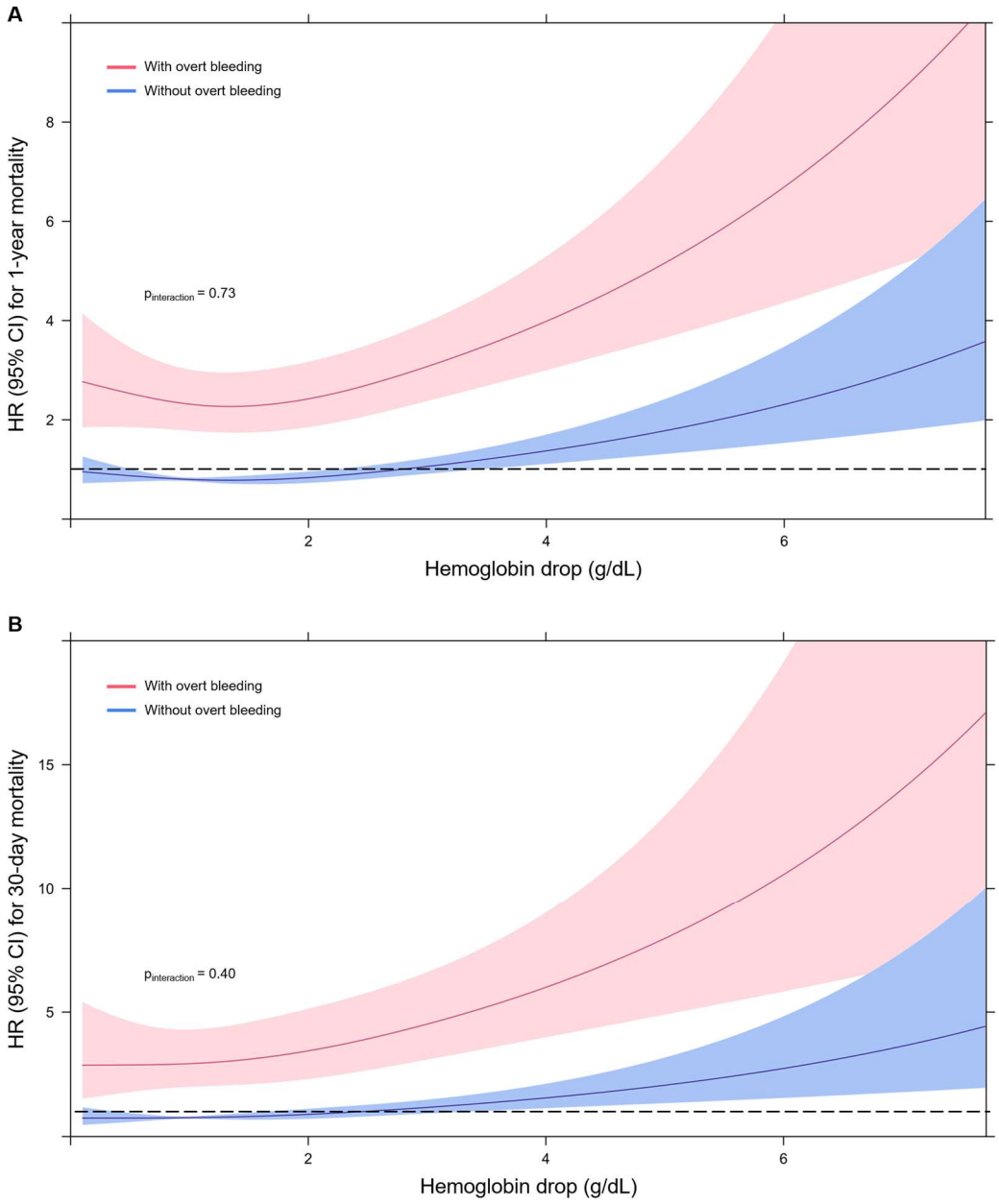


Figure 3. Spline functions of 1-year and 30-day mortality in patients with and without overt bleeding according to in-hospital hemoglobin drop. (A) Adjusted 1-year mortality. (B) Adjusted 30-day mortality. In pink, patients with overt bleeding; in blue, patients without overt bleeding. CI = confidence interval; HR = hazard ratio.



Central illustration. In-hospital hemoglobin drop in patients with and without overt bleeding in ACS. (A) Approximately 8 out of 10 patients invasively managed for ACS can develop an hemoglobin drop during the index hospitalization. In 7 of these 8 patients, an hemoglobin reduction is observed in the absence of overt bleeding. (B) Although patients without overt bleeding frequently have a minimal hemoglobin drop (below 3 g/dL), in view of the millions of individuals with ACS undergoing invasive management worldwide, a substantial number of patients can experience a minor (≥3 g/dL) or major (≥5 g/dL) hemoglobin drop. (C) Patients with an hemoglobin drop ≥3 g/dL showed a doubled risk of 1-year mortality, even in the absence of overt bleeding. HB = hemoglobin; HR = hazard ratio.

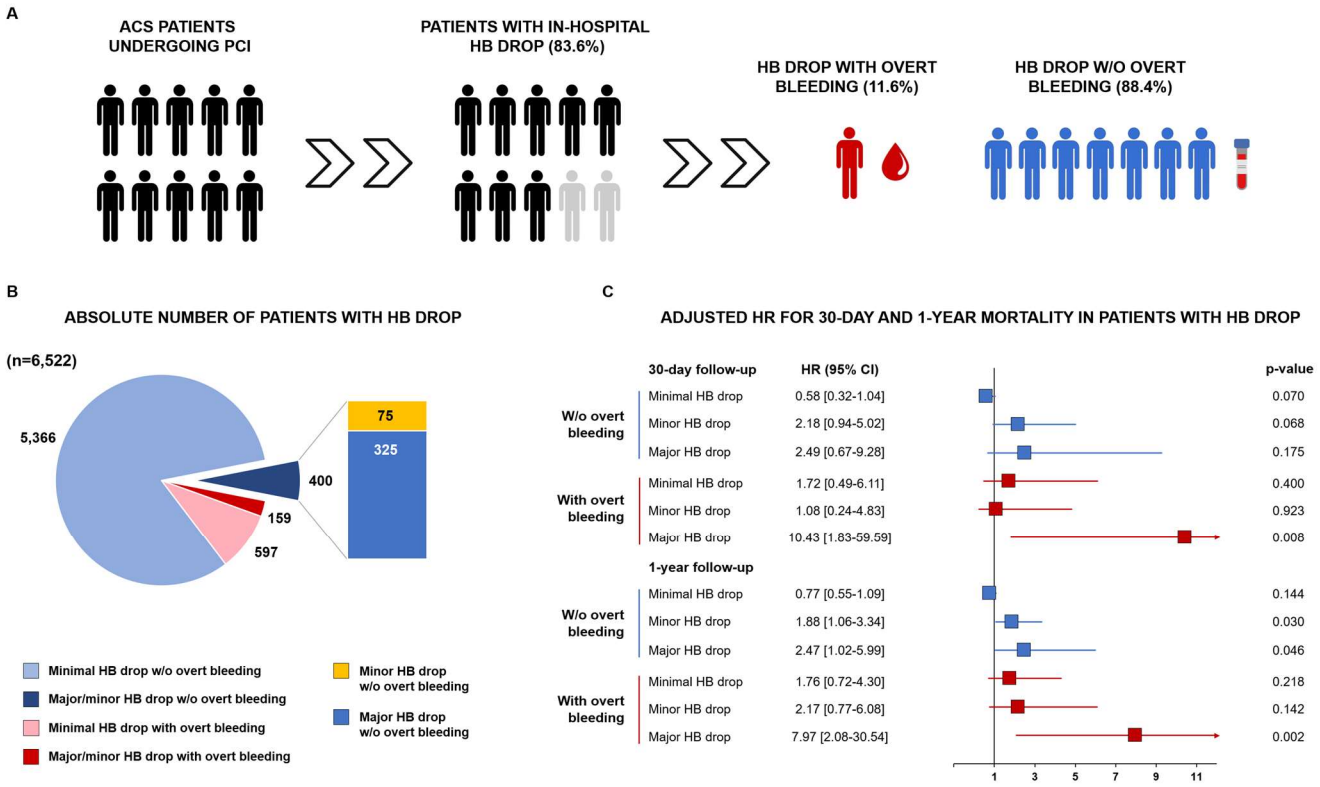


Table 1. Baseline characteristics of patients with hemoglobin reduction with and without overt bleeding.

	Hemoglobin drop without overt bleeding (n=5,766)	Hemoglobin drop with overt bleeding (n=756)	p-value
Age, years	65.3 (11.7)	68.5 (11.7)	<0.001
≥75	1,374 (23.8%)	280 (37%)	<0.001
Male sex	4,306 (74.7%)	511 (67.6%)	<0.001
Weight, kg	77.6 (14)	74.6 (13.8)	<0.001
Body-mass index, kg/m2	27.1 (4.2)	26.5 (4)	<0.001
≥25	3,870 (67.1%)	463 (61.2%)	0.001
Diabetes mellitus	1,281 (22.2%)	184 (24.3%)	0.20
Insulin-dependent	311 (5.4%)	48 (6.3%)	0.20
Current smoker	2,102 (36.5%)	219 (29%)	<0.001
Hypercholesterolemia	2,538 (44%)	331 (43.8%)	0.93
Hypertension	3,635 (63%)	508 (67.2%)	0.028
Family history of coronary artery disease	1,554 (27%)	203 (26.9%)	0.98
Previous myocardial infarction	790 (13.7%)	88 (11.6%)	0.13
Previous PCI	812 (14.1%)	81 (10.7%)	0.013
Radial access	121 (2.1%)	17 (2.2%)	0.013
Femoral access	414 (7.2%)	25 (3.3%)	
Both radial and femoral access	50 (0.9%)	2 (0.3%)	
Access site unknown	227 (3.9%)	37 (4.9%)	
Previous CABG	150 (2.6%)	24 (3.2%)	0.42
Previous transient ischemic attack or stroke	265 (4.6%)	48 (6.3%)	0.042
Peripheral vascular disease	443 (7.7%)	104 (13.8%)	<0.001
Chronic obstructive pulmonary disease	357 (6.2%)	58 (7.7%)	0.13
Renal failure	71 (1.2%)	10 (1.3%)	0.96
Dialysis	4 (0.1%)	1 (0.1%)	0.46
Cardiac arrest	108 (1.9%)	26 (3.4%)	0.007
Killip class			<0.001
I	5,242 (90.9%)	648 (85.7%)	
II	376 (6.5%)	66 (8.7%)	
III	109 (1.9%)	24 (3.2%)	
IV	39 (0.7%)	18 (2.4%)	
Previous lytic therapy	152 (2.6%)	10 (1.3%)	0.04
STEACS	2,923 (50.7%)	426 (56.3%)	0.004
NSTEACS	2,843 (49.3%)	330 (43.7%)	0.004
NSTEACS troponin-negative	323 (5.6%)	29 (3.8%)	0.05
Systolic arterial pressure, mmHg	138.9 (25.3)	141.3 (29.4)	0.039
Heart rate, bpm	76.4 (16.6)	77.3 (18.4)	0.18
Left ventricular ejection fraction, %	51.2 (9.5)	49.8 (10.5)	0.001
Hemoglobin, g/dL	14.2 (1.7)	13.9 (1.9)	<0.001
eGFR, ml/ min/1.73 m2	84 (25.3)	78.5 (24.8)	<0.001
eGFR <60	935 (16.2%)	177 (23.5%)	<0.001
eGFR <30	56 (1%)	7 (0.9%)	>0.99
Medications administered before catheterization			
Aspirin	5,437 (94.3%)	720 (95.2%)	0.32
Clopidogrel	2,709 (47%)	338 (44.7%)	0.25
Prasugrel	704 (12.2%)	97 (12.8%)	0.66
Ticagrelor	1,331 (23.1%)	197 (26.1%)	0.07
Enoxaparin	866 (15%)	123 (16.3%)	0.39
Fondaparinux	562 (9.7%)	72 (9.5%)	0.89
ACE inhibitors	1,659 (28.8%)	211 (27.9%)	0.65

Angiotensin II receptor blockers	593 (10.3%)	88 (11.6%)	0.27
Statins	2,417 (41.9%)	294 (38.9%)	0.12
Beta-blockers	2,292 (39.8%)	270 (35.7%)	0.036
Warfarin	89 (1.5%)	12 (1.6%)	>0.99
Proton pump inhibitors	2,897 (50.2%)	389 (51.5%)	0.55
Unfractionated heparin	1,745 (30.3%)	269 (35.6%)	0.003
Bivalirudin	3 (0.1%)	0 (0%)	>0.99
Glycoprotein IIb/IIIa inhibitors	10 (0.2%)	2 (0.3%)	0.64

Depicted are sample sizes (n) and counts (%); means (±standard deviations) or medians (25%-75% interquartile range). Chi-Square or Fisher Exact test if categorical variable; T-test or Wilcoxon test if continuous variables. ACE=angiotensin-converting-enzyme; CABG=coronary artery by-pass graft; eGFR=estimated glomerular filtration rate; NSTEACS=non-ST-segment elevation acute coronary syndrome; PCI=percutaneous coronary intervention; STEACS=ST-segment elevation acute coronary syndrome.

Table 2. Grade of hemoglobin drop in patients with and without overt bleeding.

	Hemoglobin drop without overt bleeding (n=5,766)	Hemoglobin drop with overt bleeding (n=756)	p-value
Minimal hemoglobin drop (<3 g/dL)	5,366 (93.1%)	597 (79%)	<0.001
Minor hemoglobin drop (≥3 g/dL and <5 gr/d)	325 (5.6%)	129 (17.1%)	<0.001
Major hemoglobin drop (≥5 gr/d)	75 (1.3%)	30 (4%)	<0.001
Δ hemoglobin drop, g/dL	1.2 (0.6-1.9)	1.7 (1-2.7)	<0.001

Depicted are sample sizes (n) and counts (%); medians (25%-75% interquartile range).
Chi-Square or Fisher Exact test if categorical variable; T-test or Wilcoxon test if continuous variables.

Table 3. Multivariate predictors of major/minor hemoglobin drop and BARC 3 or 5 type bleeding.

	Major/minor HB drop overall		Major/minor HB drop without overt bleeding		BARC 3 or 5 bleeding	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (for each increase of 10 years)	1.26 (1.15-1.39)	<0.001	1.18 (1.06-1.31)	0.003	1.31 (1.08-1.58)	0.005
Female sex	1.80 (1.41-2.28)	<0.001	1.93 (1.45-2.58)	<0.001	-	-
eGFR (for each increase of 10 ml/min)	-	-	-	-	0.81 (0.75-0.88)	<0.001
Hemoglobin at baseline (for each increase of 1 g/dL)	1.43 (1.34-1.53)	<0.001	1.56 (1.44-1.69)	<0.001	0.84 (0.77-0.91)	<0.001
Chronic obstructive pulmonary disease	-	-	1.79 (1.20-2.69)	0.005	-	-
Heart rate (for each increase of 10 bpm)	1.09 (1.03-1.15)	0.002	-	-	-	-
Left ventricular ejection fraction (for each increase of 10%)	0.83 (0.75-0.92)	<0.001	0.83 (0.74-0.94)	0.003	-	-
NSTE-ACS on admission	0.62 (0.49-0.79)	<0.001	0.49 (0.37-0.64)	<0.001	-	-
Troponin negative NSTE-ACS	-	-	0.31 (0.12-0.80)	0.016	-	-
Clopidogrel on admission	0.75 (0.62-0.92)	0.006	-	-	0.56 (0.39-0.81)	0.002
PCI not attempted after coronary angiography	10.43 (7.14-15.25)	<0.001	16.82 (10.79-26.20)	<0.001	-	-
Intra-aortic balloon pump	-	-	2.94 (1.70-5.08)	<0.001	5.20 (3.06-8.84)	<0.001
Full bivalirudin regimen post-PCI	-	-	-	-	0.19 (0.05-0.79)	0.022
Unfractionated heparin	1.35 (1.11-1.64)	0.002	-	-	-	-
Glycoprotein IIb/IIIa inhibitor	-	-	-	-	2.18 (1.43-3.34)	<0.001
≥1 complex lesion	-	-	-	-	1.95 (1.36-2.78)	<0.001
SYNTAX score (for each increase of 1 point)	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.001	-	-
TIMI 0-1 flow before PCI	1.41 (1.13-1.78)	0.003	-	-	-	-
Total contrast volume (for each 10 unit increase)	-	-	1.03 (1.01-1.04)	<0.001	-	-

eGFR=estimated glomerular filtration rate; NSTEACS=non-ST-segment elevation acute coronary syndrome; OR=odds ratio; PCI=percutaneous coronary intervention; STEACS=ST-segment elevation acute coronary syndrome; TIA=transient ischemic attack; TIMI=Thrombolysis in Myocardial Infarction.

Table 4. Multivariable association with 30-day and 1-year all-cause mortality of in-hospital hemoglobin reduction with and without overt bleeding.

	30-day mortality HR (95% CI)	p-value	1-year mortality HR (95% CI)	p-value
In-hospital hemoglobin drop without overt bleeding				
Hemoglobin drop (continuous variable), g/dL*	1.23 (1.01-1.49)	0.036	1.13 (1-1.28)	0.05
Minimal hemoglobin drop (<3 g/dL)	0.58 (0.32-1.04)	0.07	0.77 (0.55-1.09)	0.14
Minor hemoglobin drop (≥3 g/dL and <5 gr/d)	2.18 (0.94-5.02)	0.06	1.88 (1.06-3.34)	0.03
Major hemoglobin drop (≥5 gr/d)	2.49 (0.67-9.28)	0.17	2.47 (1.02-5.99)	0.046
In-hospital hemoglobin drop with overt bleeding				
Hemoglobin drop (continuous variable), g/dL*	1.20 (0.95-1.50)	0.12	1.28 (1.08-1.51)	0.004
Minimal hemoglobin drop (<3 g/dL)	1.72 (0.49-6.11)	0.40	1.76 (0.72-4.30)	0.21
Minor hemoglobin drop (≥3 g/dL and <5 gr/d)	1.08 (0.24-4.83)	0.92	2.17 (0.77-6.08)	0.14
Major hemoglobin drop (≥5 gr/d)	10.43 (1.83-59.59)	0.008	7.97 (2.08-30.54)	0.002

The reference group consisted of patients without hemoglobin reduction.
*If reduction <0 g/dL, consider 0. CI=confidence interval; HR=hazard ratio.

Table 5. Effect of radial versus femoral and of bivalirudin versus unfractionated heparin on in-hospital overt bleeding and in-hospital minor/major hemoglobin drop.

	In-hospital overt bleeding OR (95% CI) (n=8,404)	**p-value**	**In-hospital minor or major hemoglobin drop OR (95% CI) (n=7806)**	**p-value**
Radial access vs femoral access	0.51 (0.45-0.59)	<0.001	0.85 (0.72-1.01)	0.067
Bivalirudin vs unfractionated heparin	0.77 (0.66-0.89)	<0.001	0.77 (0.64-0.93)	0.008

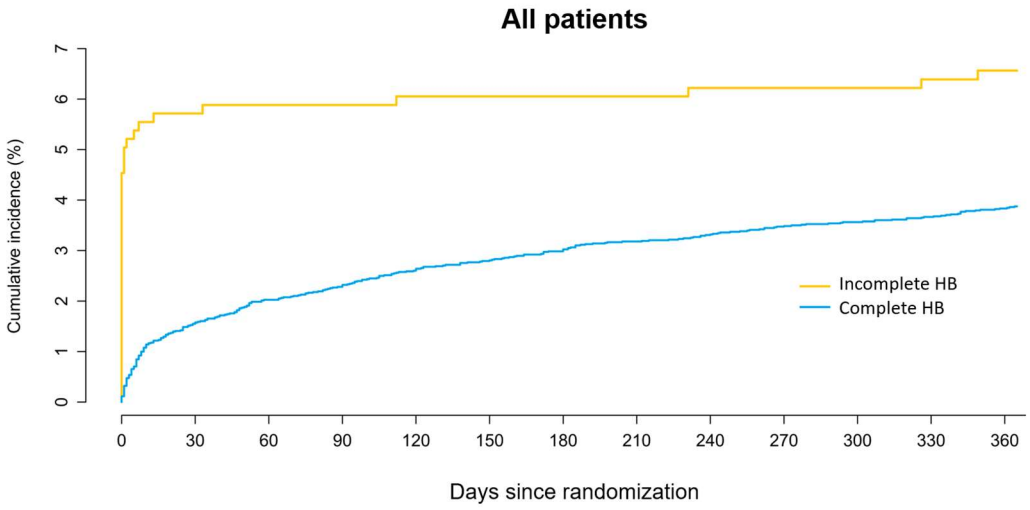
CI=confidence interval; OR=odds ratio.

SUPPLEMENTARY MATERIALS

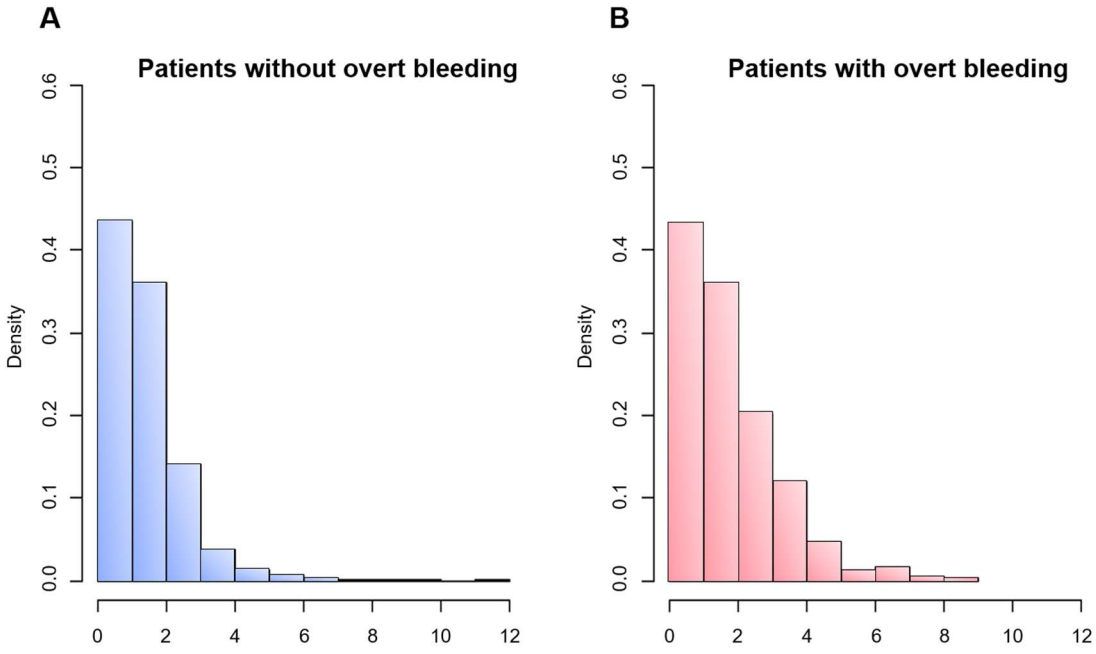
Incidence and Prognostic Implications of In-Hospital Hemoglobin Reductions With and Without Overt Bleeding in Patients With Acute Coronary Syndrome Managed Invasively

Leonardi S et al.

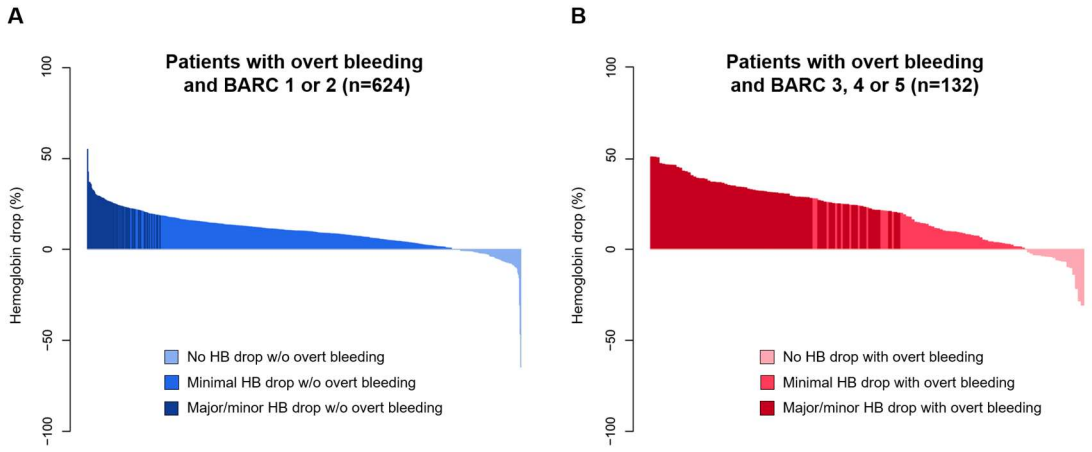
eFigure 1. One-year mortality in patients with complete or incomplete hemoglobin information. Kaplan-Meier event curves for all-cause mortality at 1 year. HB = hemoglobin.



eFigure 2. Distribution of hemoglobin drop in patients with and without overt bleeding.



eFigure 3. Waterfall plot for the percent change in hemoglobin levels during hospitalization in patients with overt bleeding stratified by BARC severity. (A) Patients with BARC 1 or 2 bleeding. (B) Patients with BARC 3, 4 or 5 BARC bleeding. Data are shown for patients who had no hemoglobin reduction (light blue and light pink), minimal hemoglobin reduction (blue and pink), and major/minor hemoglobin reduction (dark blue and dark pink). BARC = Bleeding Academic Research Consortium; HB = hemoglobin.



eTable 1. Baseline characteristics of patients with and without hemoglobin drop and with incomplete hemoglobin information.

	No hemoglobin drop (n=1,284)	Hemoglobin drop (n=6,522)	p-value*	Incomplete Hemoglobin (n=598)
Age, years	66.5 (11.9)	65.6 (11.8)	0.018	65.4 (12.2)
≥75 years	377 (29.4%)	1,654 (25.4%)	0.003	151 (25.3%)
Male sex	940 (73.2%)	4,817 (73.9%)	0.65	415 (69.4%)
Weight, kg	77.2 (13.2)	77.2 (14)	0.99	77.2 (14.4)
Body-mass index, kg/m2	27.2 (4.1)	27.1 (4.2)	0.29	27.1 (4.3)
≥25 kg/m2	883 (68.8%)	4,333 (66.4%)	0.11	405 (67.7%)
Diabetes mellitus	311 (24.2%)	1,465 (22.5%)	0.18	127 (21.2%)
Insulin-dependent	76 (5.9%)	359 (5.5%)	0.18	31 (5.2%)
Current smoker	377 (29.4%)	2,321 (35.6%)	<0.001	189 (31.6%)
Hypercholesterolemia	568 (44.2%)	2,869 (44%)	0.89	254 (42.5%)
Hypertension	817 (63.6%)	4,143 (63.5%)	0.96	351 (58.7%)
Family history of coronary artery disease	363 (28.3%)	1,757 (26.9%)	0.34	173 (28.9%)
Previous myocardial infarction	240 (18.7%)	878 (13.5%)	<0.001	85 (14.2%)
Previous PCI	217 (16.9%)	893 (13.7%)	0.003	85 (14.2%)
Radial access	49 (3.8%)	138 (2.1%)	0.003	16 (2.7%)
Femoral access	91 (7.1%)	439 (6.7%)	0.003	32 (5.4%)
Both radial and femoral access	18 (1.4%)	52 (0.8%)	0.003	1 (0.2%)
Access site unknown	59 (4.6%)	264 (4%)	0.003	36 (6%)
Previous CABG	71 (5.5%)	174 (2.7%)	<0.001	12 (2%)
Previous transient ischemic attack or stroke	74 (5.8%)	313 (4.8%)	0.16	38 (6.4%)
Peripheral vascular disease	125 (9.7%)	547 (8.4%)	0.12	41 (6.9%)
Chronic obstructive pulmonary disease	84 (6.5%)	415 (6.4%)	0.85	34 (5.7%)
Renal failure	20 (1.6%)	81 (1.2%)	0.43	4 (0.7%)
Dialysis	3 (0.2%)	5 (0.1%)	0.13	0 (0%)
Cardiac arrest	21 (1.6%)	134 (2.1%)	0.38	13 (2.2%)
Killip class				
I	1,169 (91%)	5,890 (90.3%)		537 (89.8%)
II	87 (6.8%)	442 (6.8%)	0.20	40 (6.7%)
III	24 (1.9%)	133 (2%)		10 (1.7%)
IV	4 (0.3%)	57 (0.9%)		11 (1.8%)
Previous lytic therapy	25 (1.9%)	162 (2.5%)	0.294	11 (1.8%)
STEACS	406 (31.6%)	3,349 (51.3%)	<0.001	255 (42.6%)
NSTEACS	878 (68.4%)	3,173 (48.7%)	<0.001	343 (57.4%)
NSTEACS troponin negative	103 (8%)	352 (5.4%)	<0.001	53 (8.9%)
Systolic arterial pressure, mmHg	137.8 (24.8)	139.2 (25.9)	0.05	134.6 (24)
Heart rate, bpm	74.8 (16.2)	76.5 (16.9)	0.001	75.6 (15.9)
Left ventricular ejection fraction, %	51 (9.8)	51 (9.7)	0.95	51.8 (9.4)
Hemoglobin, g/dL	13 (1.8)	14.2 (1.7)	<0.001	13.7 (2)
eGFR, ml/ min/1.73 m2	84.9 (26.5)	83.3 (25.3)	0.05	85.9 (24.6)
eGFR <60	226 (17.6%)	1,112 (17.1%)	0.66	77 (14%)
eGFR <30	15 (1.2%)	63 (1%)	0.60	6 (1.1%)
Medications administered before catheterization				
Aspirin	1,199 (93.4%)	6,157 (94.4%)	0.17	554 (92.6%)
Clopidogrel	685 (53.3%)	3,047 (46.7%)	<0.001	280 (46.8%)
Prasugrel	105 (8.2%)	801 (12.3%)	<0.001	47 (7.9%)
Ticagrelor	327 (25.5%)	1,528 (23.4%)	0.12	152 (25.4%)
Enoxaparin	316 (24.6%)	989 (15.2%)	<0.001	124 (20.7%)
Fondaparinux	181 (14.1%)	634 (9.7%)	<0.001	81 (13.5%)
ACE inhibitors	467 (36.4%)	1,870 (28.7%)	<0.001	217 (36.3%)
Angiotensin II receptor blockers	162 (12.6%)	681 (10.4%)	0.025	69 (11.5%)

Statins	666 (51.9%)	2,711 (41.6%)	<0.001	298 (49.8%)
Beta-blockers	623 (48.5%)	2,562 (39.3%)	<0.001	284 (47.5%)
Warfarin	28 (2.2%)	101 (1.5%)	0.13	7 (1.2%)
Proton pump inhibitors	749 (58.3%)	3,286 (50.4%)	<0.001	315 (52.7%)
Unfractionated heparin	316 (24.6%)	2,014 (30.9%)	<0.001	146 (24.4%)
Bivalirudin	0 (0%)	3 (0%)	>0.99	3 (0.5%)
Glycoprotein IIb/IIIa inhibitors	2 (0.2%)	12 (0.2%)	>0.99	0 (0%)

Depicted are sample sizes (n) and counts (%); means (±standard deviations) or medians (25%-75% interquartile range). *Chi-Square or Fisher Exact test if categorical variable; T-test or Wilcoxon test if continuous variables for the comparison of patients with or without hemoglobin drop.
ACE=angiotensin-converting-enzyme; CABG=coronary artery by-pass graft; eGFR=estimated glomerular filtration rate; NSTEACS=non-ST-segment elevation acute coronary syndrome; PCI=percutaneous coronary intervention; STEACS=ST-segment elevation acute coronary syndrome;

eTable 2. Procedural characteristics of patients with and without hemoglobin drop and with incomplete hemoglobin information.

	No hemoglobin drop (n=1284)	Hemoglobin drop (n=6522)	p-value*	Incomplete hemoglobin (n=598)
No PCI attempted after coronary angiography	323 (25.2%)	1155 (17.7%)	<0.001	192 (32.1%)
CABG	34 (2.6%)	233 (3.6%)	0.11	43 (7.2%)
Patient with significant lesion and medical treatment	214 (16.7%)	660 (10.1%)	<0.001	115 (19.2%)
Patient without significant lesion	75 (5.8%)	262 (4%)	0.004	34 (5.7%)
PCI attempted	961 (74.8%)	5366 (82.3%)	<0.001	399 (66.7%)
PCI completed	961 (74.8%)	5366 (82.3%)	<0.001	397 (66.4%)
Intra-aortic balloon pump	15 (1.2%)	149 (2.3%)	0.015	22 (3.7%)
Medications in and after the catheterization laboratory				
Aspirin	92 (7.2%)	359 (5.5%)	0.023	30 (5%)
Clopidogrel	81 (6.3%)	413 (6.3%)	1	29 (4.8%)
Prasugrel	86 (6.7%)	522 (8%)	0.12	18 (3%)
Ticagrelor	107 (8.3%)	594 (9.1%)	0.40	75 (12.5%)
Glycoprotein IIb/IIIa inhibitor	97 (7.6%)	953 (14.6%)	<0.001	45 (7.5%)
Bailout GPI	23 (1.8%)	265 (4.1%)	<0.001	16 (2.7%)
Planned GPI	74 (5.8%)	688 (10.5%)	<0.001	29 (4.8%)
Unfractionated heparin	556 (43.3%)	3073 (47.1%)	0.013	267 (44.6%)
Unfractionated heparin, units/kg	78.8 (27)	75.1 (30.3)	<0.001	68.9 (25.8)
Sub-therapeutic regimen <50 units/kg	55 (10.9%)	473 (16.2%)	0.003	49 (20.4%)
Therapeutic regimen ≥ 50 units/kg	451 (89.1%)	2442 (83.8%)	0.003	191 (79.6%)
Bivalirudin	503 (39.2%)	2734 (41.9%)	0.07	190 (31.8%)
Prolonged infusion post-PCI	234 (18.2%)	1410 (21.6%)	0.007	96 (16.1%)
Average duration of post-PCI bivalirudin infusion	394.1 (254.6)	370.1 (251.1)	0.97	334.8 (260.2)
Full bivalirudin regimen post-PCI	92 (7.2%)	491 (7.5%)	0.69	43 (7.2%)
Average duration of full bivalirudin regimen	256.3 (98)	267 (231.7)	0.83	266.5 (126.3)
Low bivalirudin regimen post-PCI	142 (11.1%)	919 (14.1%)	0.004	53 (8.9%)
Average duration of low bivalirudin regimen	483.3 (283.8)	425.2 (243.8)	0.048	390.3 (322.2)
PCIs	961	5366		397
TIMI 3 flow post-procedure in all treated lesions	923 (96%)	5096 (95%)	0.17	371 (93.5%)
Coronary stenosis after PCI <30% in all treated lesions	919 (95.6%)	5132 (95.6%)	>0.99	371 (93.5%)
Procedural success in all treated lesions	905 (94.2%)	4978 (92.8%)	0.13	357 (89.9%)
Duration of procedure, min	54.3 (25.5)	54.5 (28.6)	0.86	57.8 (28.9)
Total amount of injected contrast, ml	185.7 (82.3)	181.7 (81.2)	0.15	188 (102)
Treated vessel(s) per patient				
Left main coronary artery	43 (4.5%)	206 (3.8%)	0.40	22 (5.5%)
Left anterior descending artery	491 (51.1%)	2654 (49.5%)	0.38	189 (47.6%)
Left circumflex artery	284 (29.6%)	1401 (26.1%)	0.03	128 (32.2%)

Right coronary artery	301 (31.3%)	1818 (33.9%)	0.12	118 (29.7%)
Bypass graft	17 (1.8%)	37 (0.7%)	0.002	2 (0.5%)
≥2 vessels treated	155 (16.1%)	676 (12.6%)	0.004	58 (14.6%)
Lesions treated per patient				
1	730 (76%)	4254 (79.4%)	0.035	312 (78.6%)
2	189 (19.7%)	905 (16.9%)		71 (17.9%)
≥3	42 (4.4%)	202 (3.8%)		14 (3.5%)
≥1 complex lesion	504 (52.4%)	2792 (52.1%)	0.86	176 (44.3%)
Median number of stents per patient	1 (1 - 2)	1 (1 - 2)	0.98	1 (1 - 2)
Overall stent length per patient,	69.7 (43.7)	70.4 (44.2)	0.67	64.3 (41.5)
Total syntax score	13.4 (9.8)	13.5 (9.1)	0.71	12.3 (9.1)
Lesions[§]				
Number of lesions with PCI	1241	6707		498
Lesions stented	1121 (90.3%)	6104 (91%)	0.47	448 (90%)
≥1 drug-eluting stent	846 (68.2%)	4414 (65.8%)	0.14	347 (69.7%)
≥1 bare-metal stent	275 (22.2%)	1690 (25.2%)	0.05	101 (20.3%)
Lesions not stented	120 (9.7%)	603 (9%)	0.47	50 (10%)
TIMI flow before PCI				
0 or 1	383 (30.9%)	2699 (40.2%)	<0.001	171 (34.3%)
2	161 (13%)	837 (12.5%)	0.64	63 (12.7%)
3	697 (56.2%)	3171 (47.3%)	<0.001	264 (53%)
TIMI flow after PCI				
0 or 1	22 (1.8%)	114 (1.7%)	0.86	12 (2.4%)
2	18 (1.5%)	169 (2.5%)	0.03	19 (3.8%)
3	1201 (96.8%)	6424 (95.8%)	0.12	467 (93.8%)
Coronary stenosis after PCI <30%	1195 (96.3%)	6456 (96.3%)	0.92	468 (94%)
Procedural success	1180 (95.1%)	6291 (93.8%)	0.09	452 (90.8%)
Number of lesions stented	1121	6104		448
Total stent length per lesion, mm	25.7 (14.2)	26.1 (14.4)	0.48	25 (14.1)
Average stent diameter per lesion, mm	3.1 (0.5)	3.1 (0.5)	0.28	3.1 (0.5)
≥1 direct stenting	231 (20.6%)	1394 (22.8%)	0.12	73 (16.3%)
Post-stenting dilatation	487 (43.4%)	2756 (45.2%)	0.33	200 (44.6%)
Large vessel caliber	771 (68.8%)	4324 (70.9%)	0.16	303 (67.6%)
Proximal location	587 (52.4%)	3452 (56.6%)	0.009	236 (52.7%)
Thrombus	313 (27.9%)	2369 (38.8%)	<0.001	155 (34.6%)

Depicted are sample sizes (n) and counts (%); means (±standard deviations) or medians (25%-75% interquartile range). [*]Chi-Square or Fisher Exact test if categorical variable for the comparison of patients with or without hemoglobin drop; T-test or Wilcoxon test if continuous variable. [§]p-values from mixed models accounting for lesion nested within patients. CABG=coronary artery by-pass graft; GPI=glycoprotein IIb/IIIa inhibitors; PCI=percutaneous coronary intervention; TIMI=Thrombolysis in Myocardial Infarction.

eTable 3. Medications at discharge of patients with and without hemoglobin drop and of those with incomplete hemoglobin information.

	No hemoglobin drop (n=1,284)	**Hemoglobin drop (n=6,522)**	**p-value***	**Incomplete Hemoglobin (n=598)**
Aspirin	1,204 (94.9%)	6,172 (95.7%)	0.23	521 (92.7%)
Ticlopidine	3 (0.2%)	16 (0.2%)	>0.99	2 (0.4%)
Clopidogrel	494 (38.9%)	2,340 (36.3%)	0.07	177 (31.5%)
Prasugrel	170 (13.4%)	1,313 (20.4%)	<0.001	65 (11.6%)
Ticagrelor	380 (29.9%)	1,908 (29.6%)	0.81	210 (37.4%)
$P2Y_{12}$ inhibitors	1,046 (82.4%)	5,577 (86.5%)	<0.001	454 (80.8%)
ACE inhibitors or angiotensin II receptor blockers	1,029 (81.1%)	5,121 (79.4%)	0.18	423 (75.3%)
Statins	1142 (90%)	5,900 (91.5%)	0.10	488 (86.8%)
Beta-blockers	1,020 (80.4%)	5,280 (81.8%)	0.23	446 (79.4%)
Warfarin	45 (3.5%)	231 (3.6%)	>0.99	13 (2.3%)
Diuretics	337 (26.6%)	1,765 (27.4%)	0.58	85 (15.1%)
Oral hypoglycemic drugs	125 (9.9%)	616 (9.5%)	0.77	58 (10.3%)
Proton pump inhibitors	1,105 (87.1%)	5,688 (88.2%)	0.29	458 (81.5%)
H2 blockers	41 (3.2%)	256 (4%)	0.24	21 (3.7%)

Depicted are sample sizes (n) and counts (%). Chi-Square or Fisher Exact test if categorical variable; T-test or Wilcoxon test if continuous variables for the comparison of patients with or without hemoglobin drop. ACE=angiotensin-converting-enzyme.

eTable 4. Procedural characteristics of patients with hemoglobin drop with and without overt bleeding.

	Hemoglobin drop without overt bleeding (n=5,766)	Hemoglobin drop with overt bleeding (n=756)	p-value
No PCI attempted after coronary angiography	1,070 (18.6%)	85 (11.2%)	<0.001
CABG	218 (3.8%)	15 (2%)	0.016
Patient with significant lesion and medical treatment	628 (10.9%)	32 (4.2%)	<0.001
Patient without significant lesion	224 (3.9%)	38 (5%)	0.16
PCI attempted	4,696 (81.4%)	670 (88.6%)	<0.001
PCI completed	4,696 (81.4%)	670 (88.6%)	<0.001
Intra-aortic balloon pump	97 (1.7%)	52 (6.9%)	<0.001
Medications in and after the catheterization laboratory			
Aspirin	309 (5.4%)	50 (6.6%)	0.18
Clopidogrel	358 (6.2%)	55 (7.3%)	0.29
Prasugrel	469 (8.1%)	53 (7%)	0.31
Ticagrelor	523 (9.1%)	71 (9.4%)	0.82
Glycoprotein IIb/IIIa inhibitor	775 (13.4%)	178 (23.5%)	<0.001
Bailout GPI	211 (3.7%)	54 (7.1%)	<0.001
Planned GPI	564 (9.8%)	124 (16.4%)	<0.001
Unfractionated heparin	2,665 (46.2%)	408 (54%)	<0.001
Unfractionated heparin, units/kg	74.4 (29.8)	80.1 (32.9)	<0.001
Sub-therapeutic regimen <50 units/kg	415 (16.5%)	58 (14.7%)	0.42
Therapeutic regimen ≥ 50 units/kg	2,106 (83.5%)	336 (85.3%)	0.42
Bivalirudin	2,436 (42.2%)	298 (39.4%)	0.14
Prolonged infusion post-PCI	1,251 (21.7%)	159 (21%)	0.71
Average duration of post-PCI bivalirudin infusion	369.7 (241)	373.4 (320.6)	0.89
Full bivalirudin regimen post-PCI	469 (8.1%)	22 (2.9%)	<0.001
Average duration of full bivalirudin regimen	269.8 (236.1)	207.1 (80.7)	0.002
Low bivalirudin regimen post-PCI	782 (13.6%)	137 (18.1%)	0.001
Average duration of low bivalirudin regimen	429.6 (223.6)	400.2 (336.5)	0.001
PCIs	4,696	670	
TIMI 3 flow post-procedure in all treated lesions	4,477 (95.3%)	619 (92.4%)	0.002
Coronary stenosis after PCI <30% in all treated lesions	4,500 (95.8%)	632 (94.3%)	0.09
Procedural success in all treated lesions	4,373 (93.1%)	605 (90.3%)	0.01
Duration of procedure, min	53.5 (28)	61.3 (31.8)	<0.001
Total amount of injected contrast, ml	179.8 (79.6)	195 (90.4)	<0.001
Treated vessel(s) per patient			
Left main coronary artery	166 (3.5%)	40 (6%)	0.003
Left anterior descending artery	2,311 (49.3%)	343 (51.3%)	0.35
Left circumflex artery	1,227 (26.2%)	174 (26%)	0.97
Right coronary artery	1,583 (33.7%)	235 (35.1%)	0.50
Bypass graft	32 (0.7%)	5 (0.7%)	0.80
≥2 vessels treated	564 (12%)	112 (16.7%)	0.001
Lesions treated per patient			0.1
1	3,736 (79.6%)	518 (77.3%)	
2	790 (16.8%)	115 (17.2%)	
≥3	165 (3.5%)	37 (5.5%)	
≥1 complex lesion	2,416 (51.5%)	376 (56.1%)	0.028
Median number of stents per patient	1 (1 - 2)	1 (1 - 2)	0.009
Overall stent length per patient,	69.4 (43.5)	77.7 (48.1)	<0.001
Total syntax score	13.2 (8.8)	15.7 (10.6)	<0.001
Lesions[§]			

Number of lesions with PCI	5,842	865	
Lesions stented	5,327 (91.2%)	777 (89.8%)	0.22
≥1 drug-eluting stent	3,846 (65.8%)	568 (65.7%)	0.70
≥1 bare-metal stent	1,481 (25.4%)	209 (24.2%)	0.79
Lesions not stented	515 (8.8%)	88 (10.2%)	0.22
TIMI flow before PCI			
0 or 1	2,349 (40.2%)	350 (40.5%)	0.80
2	739 (12.6%)	98 (11.3%)	0.33
3	2,754 (47.1%)	417 (48.2%)	0.69
TIMI flow after PCI			
0 or 1	94 (1.6%)	20 (2.3%)	0.13
2	137 (2.3%)	32 (3.7%)	0.02
3	5,611 (96%)	813 (94%)	0.008
Coronary stenosis after PCI <30%	5,632 (96.4%)	824 (95.3%)	0.13
Procedural success	5,497 (94.1%)	794 (91.8%)	0.017
Number of lesions stented	5327	777	
Total stent length per lesion, mm	25.8 (14.2)	27.7 (15.4)	<0.001
Average stent diameter per lesion, mm	3.1 (0.5)	3.1 (0.5)	0.63
≥1 direct stenting	1,269 (23.8%)	125 (16.1%)	<0.001
Post-stenting dilatation	2,370 (44.5%)	386 (49.7%)	0.012
Large vessel caliber	3,780 (71%)	544 (70.1%)	0.68
Proximal location	3,002 (56.4%)	450 (57.9%)	0.41
Thrombus	2,063 (38.7%)	306 (39.4%)	0.65

Depicted are sample sizes (n) and counts (%); means (±standard deviations) or medians (25%-75% interquartile range). Chi-Square or Fisher Exact test if categorical variable; T-test or Wilcoxon test if continuous variables. §p-values from mixed models accounting for lesion nested within patients
CABG=coronary artery by-pass graft; GPI=glycoprotein IIb/IIIa inhibitors; PCI=percutaneous coronary intervention; TIMI=Thrombolysis in Myocardial Infarction.

eTable 5. Medications at discharge of patients with hemoglobin drop with and without overt bleeding.

	Hemoglobin drop without overt bleeding (n=5,766)	**Hemoglobin drop with overt bleeding (n=756)**	**p-value**
Aspirin	5,475 (95.6%)	697 (96.4%)	0.35
Ticlopidine	16 (0.3%)	0 (0%)	0.24
Clopidogrel	2,023 (35.3%)	317 (43.8%)	<0.001
Prasugrel	1,192 (20.8%)	121 (16.7%)	0.012
Ticagrelor	1,703 (29.7%)	205 (28.4%)	0.47
$P2Y_{12}$ inhibitors	4,934 (86.1%)	643 (88.9%)	0.044
ACE inhibitors or angiotensin II receptor blockers	4,539 (79.2%)	582 (80.5%)	0.46
Statins	5,246 (91.6%)	654 (90.5%)	0.34
Beta-blockers	4,686 (81.8%)	594 (82.2%)	0.85
Warfarin	198 (3.5%)	33 (4.6%)	0.16
Diuretics	1487 (26%)	278 (38.5%)	<0.001
Oral hypoglycemic drugs	547 (9.5%)	69 (9.5%)	>0.99
Proton pump inhibitors	5,045 (88.1%)	643 (88.9%)	0.54
H2 blockers	230 (4%)	26 (3.6%)	0.65

Depicted are sample sizes (n) and counts (%). Chi-Square or Fisher Exact test if categorical variable; T-test or Wilcoxon test if continuous variables. ACE=angiotensin-converting-enzyme.

eTable 6. Type of BARC bleeding in patients with hemoglobin drop and overt bleeding.

	Hemoglobin drop and overt bleeding (n=756)
BARC 1	369 (48.8%)
Δ hemoglobin drop, g/dL	1.6 (0.9-2.3)
BARC 2	276 (36.5%)
Δ hemoglobin drop, g/dL	1.7 (1-2.4)
BARC 3	112 (14.8%)
Δ hemoglobin drop, g/dL	3.4 (1.9-4.5)
BARC 4	7 (0.9%)
Δ hemoglobin drop, g/dL	3.9 (1.8-5.7)
BARC 5	16 (2.1%)
Δ hemoglobin reduction, g/dL	1.7 (0.9-2.9)

Depicted are sample sizes (n) and counts (%); medians (25%-75% interquartile range).
BARC=Bleeding Academic Research Consortium.

eTable 7. In-hospital blood transfusion in patients stratified by hemoglobin reduction severity.

	In-hospital hemoglobin drop			
	Absent	**Minimal**	**Minor**	**Major**
Yes	6 (0.5%)	40 (0.7%)	33 (7.3%)	17 (16.2%)
No	1,278 (99.5%)	5,923 (99.3%)	421 (92.7%)	88 (83.8%)

Depicted are sample sizes (n) and counts (%).
*p-value <0.001