JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 77, NO. 4, 2021

PUBLISHED BY ELSEVIER

Prognostic Implications of Declining Hemoglobin Content in Patients Hospitalized With Acute Coronary Syndromes

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ABSTRACT

BACKGROUND Contemporary definitions of bleeding endpoints are restricted mostly to clinically overt events. Whether hemoglobin drop per se, with or without overt bleeding, adversely affects the prognosis of patients with acute coronary syndrome (ACS) remains unclear.

OBJECTIVES The aim of this study was to examine in the MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial the incidence, predictors, and prognostic implications of in-hospital hemoglobin drop in patients with ACS managed invasively stratified by the presence of in-hospital bleeding.

METHODS Patients were categorized by the presence and amount of in-hospital hemoglobin drop on the basis of baseline and nadir hemoglobin values and further stratified by the occurrence of adjudicated in-hospital bleeding. Hemoglobin drop was defined as minimal (<3 g/dl), minor (≥3 and <5 g/dl), or major (≥5 g/dl). Using multivariate Cox regression, we modeled the association between hemoglobin drop and mortality in patients with and without overt bleeding.

RESULTS Among 7,781 patients alive 24 h after randomization with available hemoglobin data, 6,504 patients (83.6%) had hemoglobin drop, of whom 5,756 (88.5%) did not have overt bleeding and 748 (11.5%) had overt bleeding. Among patients without overt bleeding, minor (hazard ratio [HR]: 2.37; 95% confidence interval [CI]: 1.32 to 4.24; p = 0.004) and major (HR: 2.58; 95% CI: 0.98 to 6.78; p = 0.054) hemoglobin drop were independently associated with higher 1-year mortality. Among patients with overt bleeding, the association of minor and major hemoglobin drop with 1-year mortality was directionally similar but had wider CIs (minor: HR: 3.53 [95% CI: 1.06 to 11.79]; major: HR: 13.32 [95% CI: 3.01 to 58.98]).

CONCLUSIONS Among patients with ACS managed invasively, in-hospital hemoglobin drop ≥3 g/dl, even in the absence of overt bleeding, is common and is independently associated with increased risk for 1-year mortality. (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox; NCT01433627) (J Am Coll Cardiol 2021;77:375–88) © 2021 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2020.11.046

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ACS = acute coronary syndrome(s)

BARC = Bleeding Academic Research Consortium

CI = confidence interval

eGFR = estimated glomerular filtration rate

HR = hazard ratio

OR = odds ratio

PCI = percutaneous coronary intervention

STEACS = ST-segment elevation acute coronary syndrome

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

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It is unclear, however, whether a hemoglobin reduction per se, in patients without overt bleeding, is independently associated 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 PROGRAM DESIGN. MATRIX (NCT01433627) was a program of 3 nested randomized controlled trials enrolling a total of 8,404 all-comer patients with ACS, with or without ST-segment elevation, receiving invasive management (7). The study protocol of the MATRIX trial was approved by the institutional ethics committees of participating institutions and the central regulatory body of each of the centers and was conducted according to the Declaration of Helsinki and Good Clinical Practice. Detailed study design, methods, and enrollment criteria have been previously published (7). In brief, the first study, MATRIX Access, randomized 8,404 patients with ACS to radial access or femoral access (5). The second study, MATRIX Antithrombin, randomized 7,213 patients comparing an antithrombotic strategy of bivalirudin versus unfractionated heparin (with optional glycoprotein IIb/IIIa inhibitors) (8). The third study, 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 h of symptom onset or between 12 and 24 h with evidence of continuing ischemia or previous fibrinolytic treatment and if they had ST-segment elevation ≥1 mm in 2 or more contiguous electrocardiographic 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 histories consistent with new or worsening cardiac ischemia, occurring at rest or with minimal activity within 7 days before randomization and fulfilled at least 2 high-risk criteria among the following: age ≥60 years, elevation of cardiac biomarkers, electrocardiographic changes consistent with cardiac ischemia, and 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 program who: 1) did not experience fatal events during the first 24 h after randomization, to minimize the risk for immortal time bias; and 2) had qualifying in-hospital hemoglobin information available, including values at baseline and 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 positive differences between baseline and nadir hemoglobin values (i.e., the baseline was higher than the nadir). If this difference was zero 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

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 27, 2020; revised manuscript received November 12, 2020, accepted November 13, 2020.

stratified on the basis of 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 and <5 g/dl, and major if ≥5 g/dl.

STUDY ENDPOINTS. The primary endpoint for this analysis was all-cause mortality occurring from 24 h to 1 year from randomization. As secondary endpoint, all-cause mortality from 24 h to 30 days was also evaluated. An independent clinical events committee 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 was submitted to the clinical events committee for potential unreported bleeding events.

STATISTICAL ANALYSIS. Differences across groups were assessed using Student's *t*-test or the Wilcoxon-Mann-Whitney *U* test for continuous variables and the chi-square or Fisher exact test for categorical data. The incidence, distribution, and degree of hemoglobin reduction in the study population were assessed. Independent predictors of hemoglobin drop and Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding were selected with multivariate stepwise selection ($p < 0.01$), starting with forward selection and followed by backward selection. We applied a multivariate Cox proportional hazards model to evaluate the association of hemoglobin drops during index hospitalization (as a categorical and a continuous variable) with all-cause mortality from 24 h to 1 year from randomization in patients with and without overt bleeding. Patients without hemoglobin drop and no overt bleeding were the reference category to compute hazard ratios (HRs) for those with hemoglobin drop without overt bleeding. Patients without hemoglobin drop who bled were used as reference for the hemoglobin drop and overt bleeding group. Covariates tested in the model were chosen among the previously validated predictors of death in ACS populations, including those reported in the GRACE (Global Registry of Acute Coronary Events) risk score (9). The final multivariate 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. The Kaplan-Meier method was used to estimate cumulative rates of events from 24 h to 30 days and 1 year of 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 prespecified randomization subgroups to estimate possible effects of radial access versus femoral access and bivalirudin versus heparin on: 1) in-hospital bleeding and; 2) 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 and sensitivity analyses in patients without known anemia at baseline. The analyses were done using Stata release 14.1 (StataCorp, College Station, Texas) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the 8,404 patients enrolled in the MATRIX trial, 568 (6.7%) were excluded because of incomplete hemoglobin values (baseline, nadir, or both) and 55 (0.6%) because they died within 24 h of randomization. Of the 7,781 patients alive at 24 h with complete hemoglobin information, 83.6% (n = 6,504) experienced hemoglobin drop during the index hospitalization, and 16.4% (n = 1,277) 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 Supplemental Tables 1 to 3. Unadjusted mortality rates of patients with or without qualifying hemoglobin values are shown in Supplemental Figure 1, indicating higher in-hospital mortality for patients with incomplete compared with complete hemoglobin information.

Of the 6,504 patients with in-hospital hemoglobin drop, 748 (11.5%) had at least 1 adjudicated overt bleeding event. Baseline characteristics, procedural data, and medications at discharge of patients with and without hemoglobin drop stratified by the presence or absence of overt bleeding are shown in **Table 1** and Supplemental Tables 4 and 5. Among patients with no hemoglobin reduction, patients who bled were older, more frequently had histories

TABLE 1 Baseline Characteristics of Patients With and Without Hemoglobin Drop Stratified by the Presence or Absence of Overt Bleeding

	Hemoglobin Drop Without Overt Bleeding (n = 5,756)	Hemoglobin Drop With Overt Bleeding (n = 748)	p Value	No Hemoglobin Drop Without Overt Bleeding (n = 1,178)	No Hemoglobin Drop With Overt Bleeding (n = 99)	p Value
Age, yrs	65.2 ± 11.7	68.4 ± 11.7	<0.001	66.2 ± 11.9	69.5 ± 11.3	0.007
≥75 yrs	1,368 (23.8)	273 (36.5)	<0.001	335 (28.4)	37 (37.4)	0.078
Male	4,298 (74.7)	509 (68.0)	<0.001	857 (72.8)	78 (78.8)	0.23
Weight, kg	77.6 ± 14	74.7 ± 13.7	<0.001	77.5 ± 13.2	74.3 ± 12.9	0.014
Body mass index, kg/m^2	27.1 ± 4.2	26.5 ± 4	<0.001	27.2 ± 4.1	26.5 ± 3.5	0.068
≥25 kg/m^2	3,865 (67.1)	460 (61.5)	0.002	814 (69.1)	65 (65.7)	0.55
Diabetes mellitus	1,279 (22.2)	181 (24.2)	0.24	293 (24.9)	17 (17.2)	0.11
Insulin dependent	310 (5.4)	46 (6.1)	0.20	72 (6.1)	4 (4.0)	0.092
Current smoking	2,101 (36.5)	219 (29.3)	<0.001	344 (29.2)	30 (30.3)	0.90
Hypercholesterolemia	2,535 (44.0)	330 (44.1)	>0.99	521 (44.2)	46 (46.5)	0.74
Hypertension	3,629 (63.0)	501 (67.0)	0.039	745 (63.2)	67 (67.7)	0.44
Family history of coronary artery disease	1,552 (27.0)	203 (27.1)	0.95	333 (28.3)	28 (28.3)	>0.99
Previous myocardial infarction	790 (13.7)	87 (11.6)	0.12	212 (18.0)	27 (27.3)	0.032
Previous PCI	812 (14.1)	80 (10.7)	0.013	197 (16.7)	20 (20.2)	0.45
Radial access	121 (2.1)	17 (2.3)	0.013	46 (3.9)	3 (3.0)	0.45
Femoral access	414 (7.2)	24 (3.2)		82 (7.0)	9 (9.1)	
Both radial and femoral access	50 (0.9)	2 (0.3)		16 (1.4)	2 (2.0)	
Access site unknown	227 (3.9)	37 (4.9)		53 (4.5)	6 (6.1)	
Previous CABG	150 (2.6)	24 (3.2)	0.40	62 (5.3)	9 (9.1)	0.17
Previous transient ischemic attack or stroke	265 (4.6)	47 (6.3)	0.053	68 (5.8)	5 (5.1)	0.94
Peripheral vascular disease	442 (7.7)	101 (13.5)	<0.001	112 (9.5)	12 (12.1)	0.50
Chronic obstructive pulmonary disease	357 (6.2)	57 (7.6)	0.15	72 (6.1)	10 (10.1)	0.18
Renal failure	70 (1.2)	10 (1.3)	0.91	17 (1.4)	2 (2.0)	0.65
Dialysis	4 (0.1)	1 (0.1)	0.45	3 (0.3)	0 (0.0)	>0.99
Cardiac arrest	108 (1.9)	26 (3.5)	0.006	21 (1.8)	0 (0.0)	0.40
Killip class			<0.001			0.40
I	5,238 (91)	643 (86)		1,077 (91.4)	89 (89.9)	
II	372 (6.5)	65 (8.7)				
III	109 (1.9)	22 (2.9)		1,077 (91.4)	89 (89.9)	
IV	37 (0.6)	18 (2.4)				
Previous lytic therapy	152 (2.6)	10 (1.3)	0.043	22 (1.9)	2 (2.0)	0.70
STEACS	2,915 (50.6)	420 (56.1)	0.005	367 (31.2)	33 (33.3)	0.73
NSTEACS	2,841 (49.4)	328 (43.9)	0.005	811 (68.8)	66 (66.7)	
NSTEACS, troponin negative	323 (5.6)	29 (3.9)	0.059	97 (8.2)	6 (6.1)	0.56
Systolic arterial pressure, mm Hg	139 ± 25.3	141.4 ± 29.5	0.038	138.2 ± 24.6	134.3 ± 26.4	0.22
Heart rate, beats/min	76.4 ± 16.6	77.4 ± 18.5	0.15	74.7 ± 16.1	74.4 ± 15.8	0.84
Left ventricular ejection fraction, %	51.2 ± 9.5	49.8 ± 10.5	0.001	51.2 ± 9.6	49.9 ± 10.9	0.28
Hemoglobin, g/dl	14.2 ± 1.7	13.9 ± 1.9	<0.001	13 ± 1.8	13 ± 2	0.83
eGFR, ml/min/1.73 m^2	84 ± 25.3	78.6 ± 24.9	<0.001	85.5 ± 26.5	80.3 ± 23.6	0.07
<60 ml/min/1.73 m^2	929 (16.2)	175 (23.5)	<0.001	198 (16.8)	23 (23.2)	0.14
<30 ml/min/1.73 m^2	55 (1.0)	7 (0.9)	>0.99	13 (1.1)	0 (0.0)	0.61

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of myocardial infarction, and more often received intra-aortic balloon pump support than patients without overt bleeding. Compared with patients without hemoglobin drop or 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 more often received clopidogrel at discharge. Baseline, procedural, and treatment characteristics of patients stratified by hemoglobin drop levels are detailed in Supplemental Tables 6 to 8. The distribution of hemoglobin drop in patients with and without overt bleeding is presented in Supplemental Figure 2. The proportion of patients with minor or major hemoglobin drop was higher among those with overt bleeding (15.1% and 3.5%, respectively) compared with those without overt bleeding (4.7% and 1.1%, respectively; $p < 0.001$) (**Figure 1, Table 2**). In contrast, a minor or major hemoglobin drop without overt bleeding was observed in 399 patients compared with 158 patients with the same level of hemoglobin drop and concomitant overt bleeding

TABLE 1 Continued

	Hemoglobin Drop Without Overt Bleeding (n = 5,756)	Hemoglobin Drop With Overt Bleeding (n = 748)	p Value	No Hemoglobin Drop Without Overt Bleeding (n = 1,178)	No Hemoglobin Drop With Overt Bleeding (n = 99)	p Value
Medications administered before catheterization						
Aspirin	5,428 (94.3)	713 (95.3)	0.29	1,097 (93.1)	96 (97.0)	0.20
Clopidogrel	2,706 (47)	336 (44.9)	0.29	625 (53.1)	56 (56.6)	0.57
Prasugrel	703 (12.2)	97 (13.0)	0.59	94 (8.0)	10 (10.1)	0.58
Ticagrelor	1,331 (23.1)	194 (25.9)	0.097	301 (25.6)	25 (25.3)	>0.99
Enoxaparin	866 (15.0)	122 (16.3)	0.39	283 (24.0)	31 (31.3)	0.13
Fondaparinux	561 (9.7)	72 (9.6)	0.96	163 (13.8)	17 (17.2)	0.44
ACE inhibitors	1,659 (28.8)	210 (28.1)	0.70	427 (36.2)	39 (39.4)	0.60
Angiotensin II receptor blockers	592 (10.3)	87 (11.6)	0.28	146 (12.4)	16 (16.2)	0.35
Statins	2,416 (42.0)	293 (39.2)	0.15	611 (51.9)	54 (54.5)	0.68
Beta-blockers	2,292 (39.8)	267 (35.7)	0.033	575 (48.8)	47 (47.5)	0.88
Warfarin	89 (1.5)	12 (1.6)	>0.99	25 (2.1)	2 (2.0)	>0.99
Proton pump inhibitors	2,896 (50.3)	385 (51.5)	0.57	683 (58.0)	63 (63.6)	0.32
Unfractionated heparin	1,742 (30.3)	265 (35.4)	0.005	288 (24.4)	25 (25.3)	0.95
Bivalirudin	3 (0.1)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	>0.99
Glycoprotein IIb/IIIa inhibitors	10 (0.2)	2 (0.3)	0.64	1 (0.1)	1 (1.0)	0.14

Values are mean ± SD or n (%). The chi-square or Fisher exact test was used for categorical variables; Student's *t*-test or the Wilcoxon test was used for continuous variables.

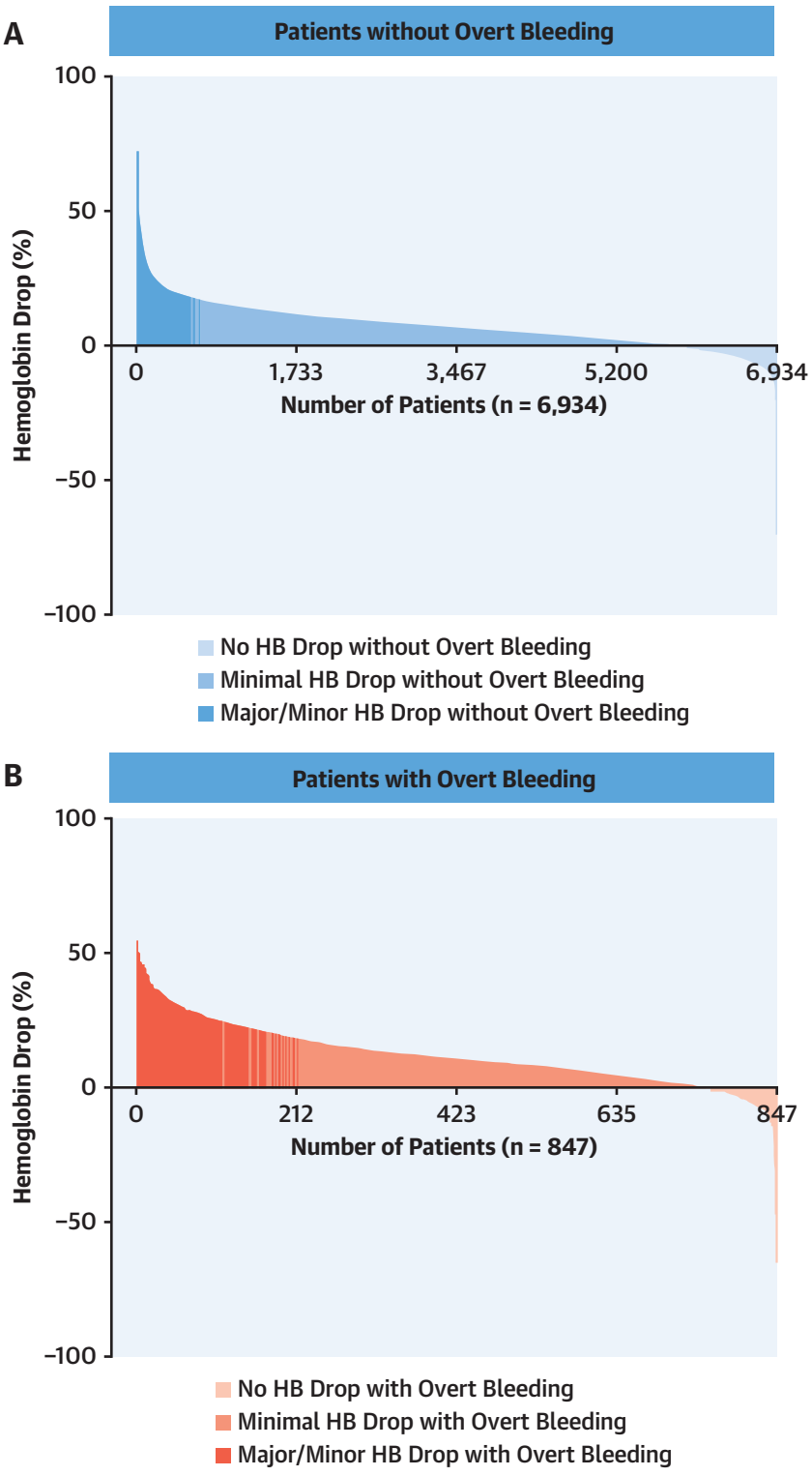
ACE = angiotensin-converting-enzyme; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; NSTEACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEACS = ST-segment elevation acute coronary syndrome.

(**Table 2**). Among patients with overt bleeding, 36.8% had BARC type 2 bleeding, while 16.4% had BARC type 3 or 5 bleeding (Supplemental Table 9). The percentage changes in hemoglobin levels in patients with overt bleeding stratified by BARC type severity (type 1 or 2 vs. type 3, 4, or 5) is reported in Supplemental Figure 3.

PREDICTORS OF MAJOR OR MINOR HEMOGLOBIN DROP AND BARC TYPE 3 OR 5 BLEEDING. To comprehensively characterize the potential use of hemoglobin drop as surrogate, multivariate predictors at baseline of major or minor hemoglobin drop as well as of BARC type 3 or 5 type bleeding were assessed (**Table 3**). Predictors of major or minor hemoglobin drop included age, female sex, body mass index, diabetes, non-ST-segment elevation ACS presentation, heart rate, clopidogrel on admission, and Killip class at presentation. Notably, baseline hemoglobin independently predicted both major or minor hemoglobin drop and BARC type 3 or 5 bleeding but with a directionally opposite association.

MULTIVARIATE ASSOCIATION OF HEMOGLOBIN DROP WITH ALL-CAUSE MORTALITY. Kaplan-Meier event curves showed a higher cumulative incidence of mortality from 24 h to 1 year in patients with major or minor hemoglobin drop compared with those with minimal or no hemoglobin drop, with a similar pattern in patients with and without overt bleeding (**Figure 2**). Multivariate 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 the **Central Illustration**. In general, hemoglobin drop in patients with and without overt bleeding was independently associated with a graded association with mortality, which was higher for patients with overt bleeding compared with those without overt bleeding. Yet patients without overt bleeding had a higher risk for 1-year mortality after a minor (HR: 2.37; 95% confidence interval [CI]: 1.32 to 4.24; p = 0.004) or a major (HR: 2.58; 95% CI: 0.98 to 6.78, p = 0.054) hemoglobin drop, respectively, compared with those without hemoglobin drop and without overt bleeding. Among patients with overt bleeding, the hazard of 1-year mortality for minor and major hemoglobin drop, compared with patients without hemoglobin drop, was directionally similar but had wider CIs (minor: HR: 3.53 [95% CI: 1.06 to 11.79; p = 0.040]; major: HR: 13.32 [95% CI: 3.01 to 58.98; p = 0.001]). The multivariate 1-year HR for mortality of hemoglobin drop modeled as a continuous variable was 1.18 per g/dl decrease in hemoglobin for patients without overt bleeding (95% CI: 1.04 to 1.34; p = 0.010) and 1.41 for patients with overt bleeding (95% CI: 1.19 to 1.67; p < 0.001). Results were directionally similar at 30 days as well as restricting the population to those without known anemia at baseline (excluding 1,536 patients with baseline anemia) (Supplemental Table 10).

FIGURE 1 Waterfall Plot for the Percentage Change in Hemoglobin Level During Hospitalization



(A) Patients without overt bleeding. **(B)** Patients with overt bleeding. Data are shown for patients alive 24 h after randomization who had no hemoglobin (Hb) reduction **(light blue and light red)**, minimal hemoglobin reduction **(blue and red)**, and major or minor hemoglobin reduction **(dark blue and dark red)**. The y-axis shows percentage of hemoglobin drop. The x-axis shows absolute number of patients per group.

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 for in-hospital bleeding complications (odds ratio [OR]: 0.51; 95% CI: 0.44 to 0.59; p < 0.001) and a numerically lower risk for minor or major hemoglobin reduction (OR: 0.85; 95% CI: 0.71 to 1.01; p = 0.065). The use of bivalirudin was associated with a significantly reduced risk for in-hospital bleeding (OR: 0.77; 95% CI: 0.67 to 0.89; p < 0.001) and minor or major hemoglobin reduction (OR: 0.78; 95% CI: 0.64 to 0.94; p = 0.010) compared with unfractionated heparin. The rates and proportions of patients with and without hemoglobin reduction receiving blood transfusions are reported in Supplemental Table 11.

TABLE 2 Grade of Hemoglobin Drop in Patients With and Without Overt Bleeding

	Patients Without Overt Bleeding (n = 6,934)	Patients With Overt Bleeding (n = 847)	p Value
No hemoglobin drop	1,178 (17)	99 (11.7)	<0.001
Minimal hemoglobin drop (<3 g/dl)	5,357 (77.3)	590 (69.7)	
Minor hemoglobin drop (≥3 and <5 g/dl)	325 (4.7)	128 (15.1)	
Major hemoglobin drop (≥5 g/dl)	74 (1.1)	30 (3.5)	

Values are n (%). The chi-square or Fisher exact test was used for categorical variable; Student's *t*-test or the Wilcoxon test was used for continuous variables.

DISCUSSION

In the present analysis, we comprehensively assessed, in an all-comer population of patients with ACS 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.

First, an in-hospital hemoglobin drop of ≥3 g/dl, even in the absence of adjudicated overt bleeding, showed a continuous, direct association with increased 1-year mortality. No independent association between minimal (<3 g/dl) hemoglobin drop and mortality was observed.

Second, patients with hemoglobin reduction ≥3 g/dl were proportionally more common (19% vs. 6%) 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 = 158 vs. n = 399).

Third, randomized bleeding minimization strategies tested in MATRIX (i.e., radial access and bivalirudin use) were associated with a lower risk for incurring in-hospital hemoglobin drop 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

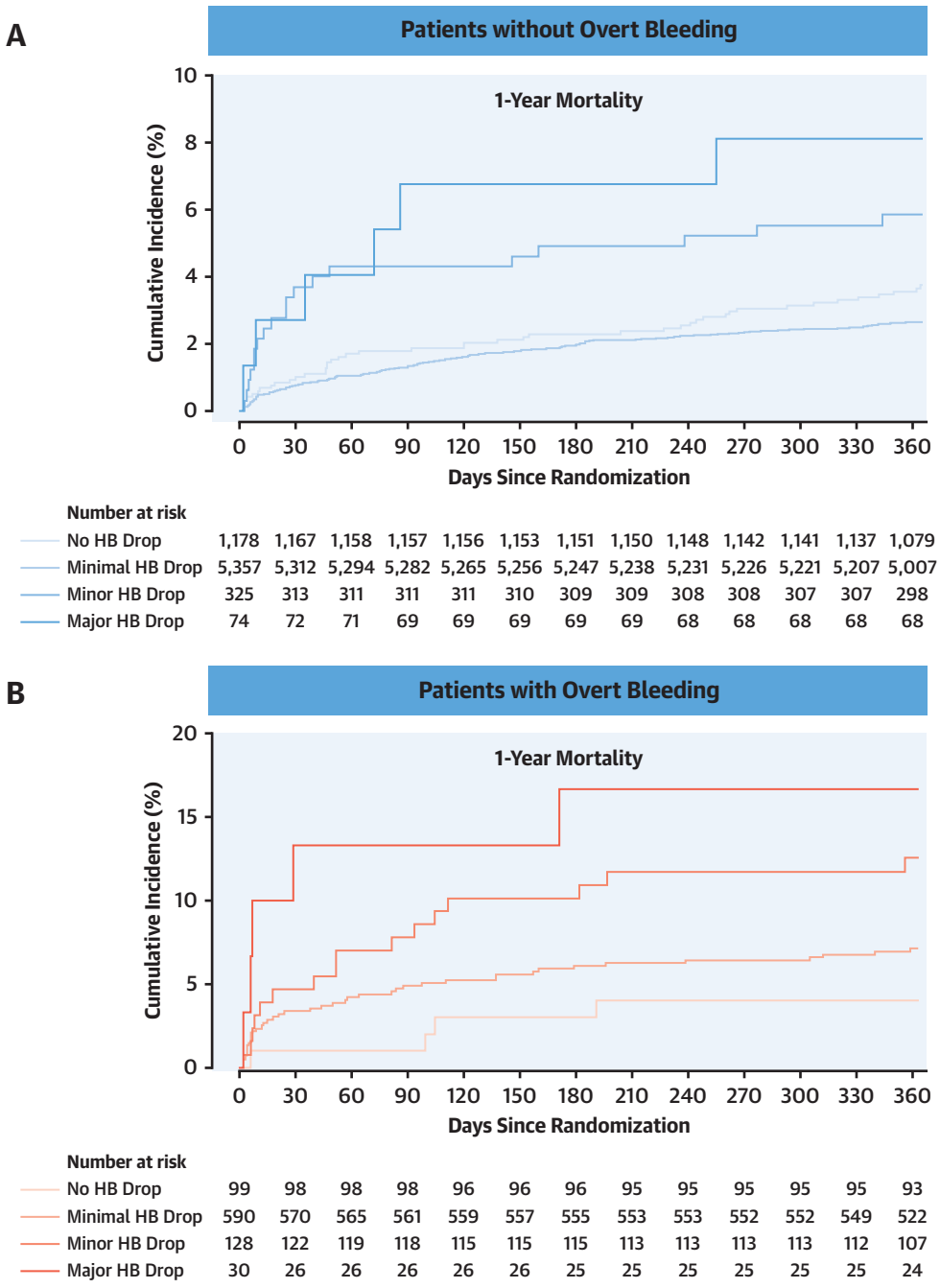
TABLE 3 Multivariate Predictors of Major or Minor Hemoglobin Drop and BARC Type 3 or 5 Bleeding

	Major/Minor HB Drop*		BARC Type 3 or 5 Bleeding*	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age (for each increase of 10 yrs)	1.31 (1.20–1.42)	<0.001	1.54 (1.29–1.83)	<0.001
Female sex	1.52 (1.22–1.90)	<0.001	–	–
Body mass index (for each increase of 1 kg/m^2)	0.96 (0.94–0.99)	0.001	–	–
Peripheral vascular disease	–	–	2.46 (1.58–3.82)	<0.001
Diabetes mellitus	1.28 (1.01–1.63)	0.047	–	–
Insulin-dependent diabetes mellitus	2.10 (1.48–2.98)	<0.001	–	–
Killip class II (vs. class I)	1.45 (1.07–1.99)	0.020	–	–
Killip class III (vs. class I)	1.43 (0.83–2.48)	0.17	–	–
Killip class IV (vs. class I)	3.43 (1.83–6.43)	<0.001	–	–
NSTEACS on admission	0.63 (0.52–0.76)	<0.001	0.49 (0.34–0.70)	<0.001
Troponin-negative NSTEACS	0.43 (0.22–0.82)	0.011	–	–
Hemoglobin at baseline (for each increase of 1 g/dl)	1.51 (1.41–1.60)	<0.001	0.82 (0.75–0.90)	<0.001
Heart rate (for each increase of 10 beats/min)	1.11 (1.06–1.17)	<0.001	–	–
Clopidogrel on admission	0.76 (0.63–0.92)	0.005	0.57 (0.39–0.83)	0.003

*Multivariate analysis included all patients with complete hemoglobin data (n = 7,806).

BARC = Bleeding Academic Research Consortium; CI = confidence interval; HB = hemoglobin; NSTEACS = non-ST-segment elevation acute coronary syndrome; OR = odds ratio.

FIGURE 2 1-Year Mortality in Patients With and Without Overt Bleeding



Kaplan-Meier event curves for all-cause mortality stratified by hemoglobin (Hb) drop from 24 h to 1 year. **(A)** Patients without overt bleeding. **(B)** Patients with overt bleeding.

complicate hospital course as a consequence of pharmacological as well as invasive procedures (10,11). Besides evident blood loss, subtle bleeding can also occur because of 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 blood loss during the index procedure, intense inflammatory status (12), stress polycythemia on admission (13), hemodilution secondary to volume

TABLE 4 Multivariate 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
Patients without overt bleeding				
No hemoglobin drop*	Reference	—	Reference	—
Minimal hemoglobin drop (<3 g/dl)	0.78 (0.40–1.56)	0.48	0.85 (0.60–1.22)	0.39
Minor hemoglobin drop (≥3 and <5 g/dl)	4.30 (1.71–10.78)	0.002	2.37 (1.32–4.24)	0.004
Major hemoglobin drop (≥5 g/dl)	3.39 (0.68–16.85)	0.13	2.58 (0.98–6.78)	0.054
Continuous hemoglobin drop (for each increase of 1 g/dl)†	1.41 (1.16–1.70)	0.001	1.18 (1.04–1.34)	0.010
Patients with overt bleeding				
No hemoglobin drop‡	Reference	—	Reference	—
Minimal hemoglobin drop (<3 g/dl)	4.19 (0.52–34.04)	0.18	2.41 (0.82–7.08)	0.11
Minor hemoglobin drop (≥3 and <5 g/dl)	3.22 (0.33–31.63)	0.31	3.53 (1.06–11.79)	0.040
Major hemoglobin drop (≥5 g/dl)	33.8 (2.84–402.35)	0.005	13.32 (3.01–58.98)	0.001
Continuous hemoglobin drop (for each increase of 1 g/dl)†	1.44 (1.13–1.84)	0.003	1.41 (1.19–1.67)	<0.001

*The reference group consisted of patients without hemoglobin drop and without overt bleeding. †If reduction <0 g/dl, consider 0 g/dl. ‡The reference group consisted of patients without hemoglobin drop and with overt bleeding.
CI = confidence interval; HR = hazard ratio.

repletion (14), or impaired bone marrow activity due to clinical factors (15).

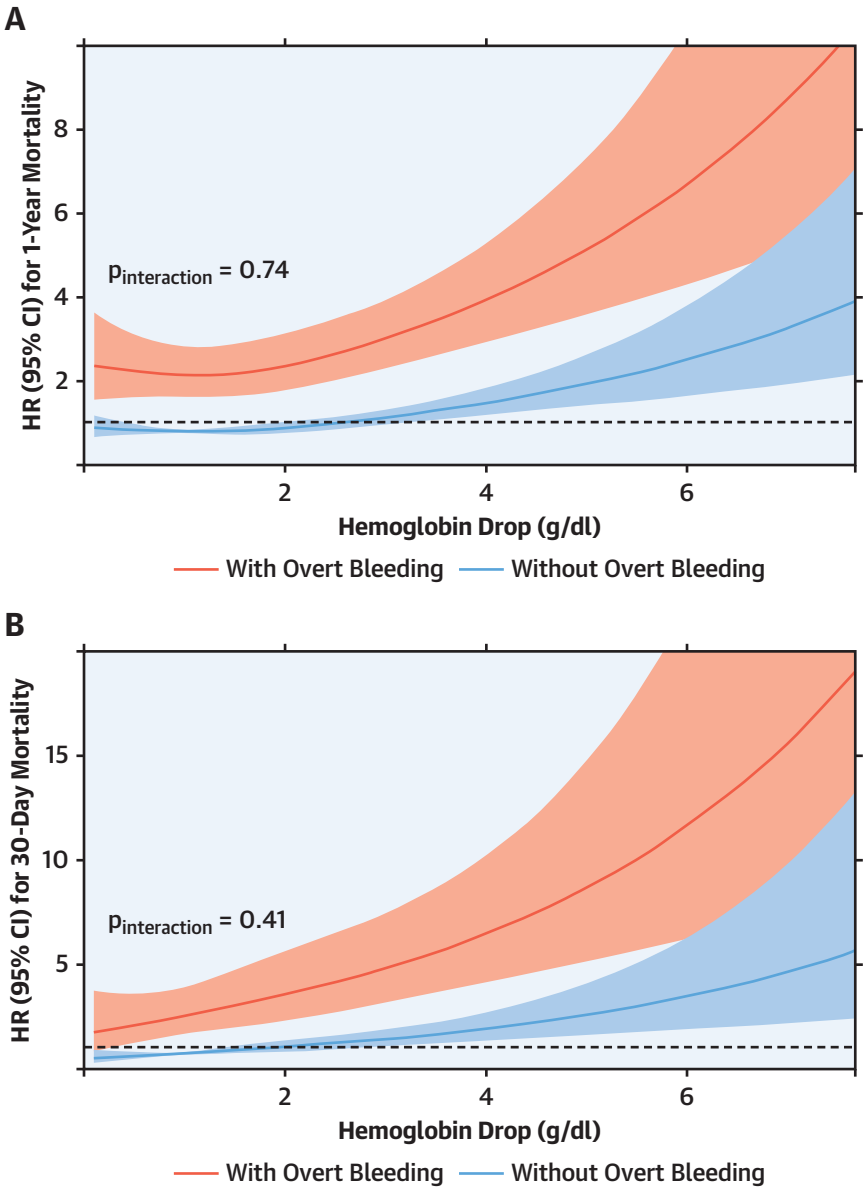
In the early phase of ACS, anemia has been consistently associated with bleeding complications (16,17). However, its prognostic impact can also extend to nonbleeding outcomes and mortality (18–20), possibly by worsening myocardial ischemic insult (i.e., decreasing the oxygen supply to the jeopardized myocardium) (21), increasing myocardial oxygen demand (i.e., need 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 <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) registry (51.7% presenting with ACS), in-hospital hemoglobin reduction ≥4.0 g/dl in the presence of overt bleeding was associated with considerably increased risk for 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 decreases 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, which if moderate to severe (<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 PATIENTS WITH ACS 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 patients without adjudicated bleeding, a heightened risk for mortality was apparent at a hemoglobin threshold of approximately 3 g/dl. Thus, 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 for dying of about 2.5-fold at 1 year, which was independent of

FIGURE 3 Spline Functions of 1-Year and 30-Day Mortality in Patients With and Without Overt Bleeding According to In-Hospital Hemoglobin Drop

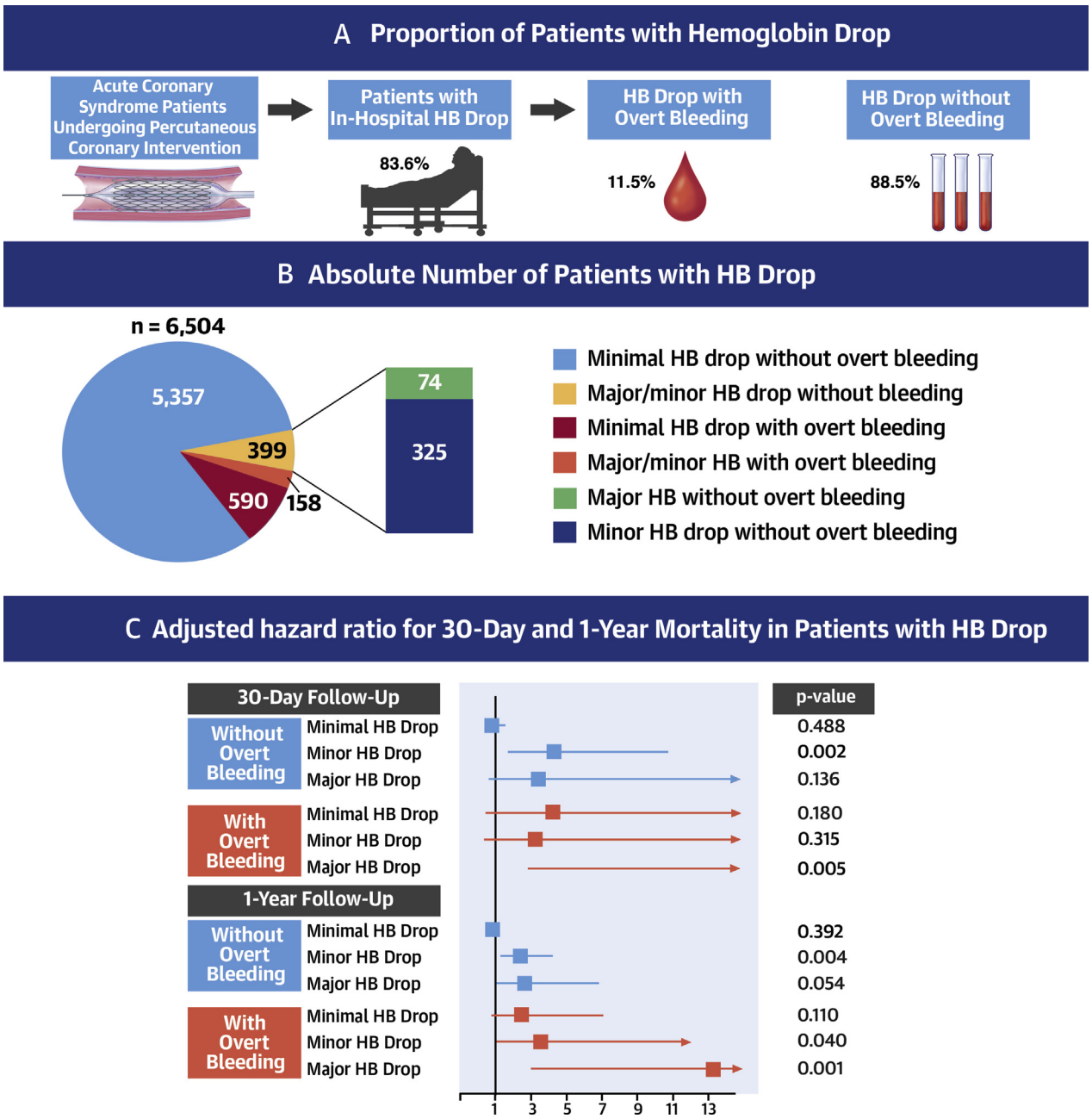


(A) Adjusted mortality risk from 24 h to 1 year. **(B)** Adjusted mortality risk from 24 h to 30 days. **Red** indicates patients with overt bleeding; **blue** indicates patients without overt bleeding. CI = confidence interval; HR = hazard ratio.

several covariates, including clinical and procedural factors and, importantly, baseline hemoglobin concentrations. Conversely, a minimal hemoglobin reduction (<3 g/dl) was not associated with mortality. In contrast, life-threatening bleeding such as intracranial hemorrhage or cardiac tamponade may occur with modest blood loss. This might in part explain why, in patients with adjudicated bleeding, an increase in the risk for mortality in multivariate analysis (although nonsignificant) was apparent even for minimal hemoglobin drop.

Adjudication of bleeding endpoints in most randomized controlled trials according to contemporary definitions mandates the presence of overt bleeding (29,30). This modern approach deviates from historical frameworks, which considered a decrease in hemoglobin as a minor hemorrhagic event even in the absence of overt bleeding (i.e., blood loss with no site

CENTRAL ILLUSTRATION **In-Hospital Hemoglobin Drop in Patients With and Without Overt Bleeding in Acute Coronary Syndrome**



Leonardi, S. et al. J Am Coll Cardiol. 2021;77(4):375–88.

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

TABLE 5 Effect of Radial Versus Femoral Access and of Bivalirudin Versus Unfractionated Heparin on In-Hospital Overt Bleeding and In-Hospital Minor or Major Hemoglobin Drop

	In-Hospital Overt Bleeding OR (95% CI) (n = 8,349)	p Value	In-Hospital Minor or Major Hemoglobin Drop OR (95% CI) (n = 7,781)	p Value
Radial access vs. femoral access	0.51 (0.44–0.59)	<0.001	0.85 (0.71–1.01)	0.065
Bivalirudin vs. unfractionated heparin	0.77 (0.67–0.89)	<0.001	0.78 (0.64–0.94)	0.010

Abbreviations as in Table 3.

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 bleeding events may remain occult. Moreover, bleeding events considered prognostically relevant (such as BARC type 3 to 5) are relatively infrequent (29,30), limiting study power (32).

The observation of a direct, continuous, independent association with long-term mortality as well as a measurable treatment effect on established bleeding minimization strategies supports the concept that a threshold of in-hospital hemoglobin reduction higher than 3 g/dl may serve as a valid surrogate endpoint (33). As such, this level of hemoglobin reduction could complement contemporary definitions of bleeding endpoints and be easily implemented because of the simple, reliable, and inexpensive measurement.

Finally, a strength of this study is the inclusion of baseline hemoglobin as a covariate. The directionally inverse association of baseline hemoglobin with major or minor hemoglobin drop in patients without overt bleeding (vs. those with adjudicated bleeding) likely reflects the definition of hemoglobin drop (i.e., the higher the baseline value, the more likely a hemoglobin drop is observed) and supports the inclusion of baseline hemoglobin in the multivariate model with death as outcome (Table 4).

Therefore, regardless of baseline hemoglobin, a hemoglobin drop ≥3 g/dl, even in the absence of detectable bleeding, appears prognostically relevant.

STUDY LIMITATIONS. This was a post hoc analysis from a prospective, randomized controlled trial, which was not powered to explore outcome differences across hemoglobin reduction subgroups of patients. As such, the results should only be considered hypothesis generating. Qualifying hemoglobin values were missing in 7.1% of patients. Although the reason for this was not captured, the high early mortality rate of these patients indicates that an early fatal event prevented the collection of hemoglobin values in many of them. 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 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 patients with ACS managed invasively, in-hospital decreases in hemoglobin levels ≥3 g/dl, even in the absence of overt bleeding events, were common and independently associated with an increased risk for all-cause mortality at 1 year. If confirmed, these results may help the identification of higher risk patients and inform contemporary bleeding definitions.

AUTHOR DISCLOSURES

The MATRIX trial was sponsored by Società Italiana di Cardiologia Invasiva (a nonprofit organization), which received grant support from The Medicines Company and Terumo. This substudy did not receive any direct or indirect funding. Dr. Leonardi has received grants and personal fees from AstraZeneca, Bristol Myers Squibb/Pfizer, and Chiesi; and has received personal fees from Bayer outside the submitted work. Dr. Gragnano has received research grant support from the European Society of Cardiology outside the submitted work. Dr. Gargiulo has received consultant fees from Daiichi-Sankyo outside the submitted work. Dr. Vranckx has received personal fees from AstraZeneca, Terumo, CSL Behring, Daiichi-Sankyo, and 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 the 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, visit the University of Bern Web site (and see Research, Declaration of Interest). Dr. Windecker has received research and educational grants to the institution from Abbott, Amgen, Bristol Myers Squibb, Bayer, Boston Scientific,

Biotronik, Cardinal Health, CSL Behring, Daiichi-Sankyo, Edwards Lifesciences, Johnson & Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, and Sinomed outside the submitted work. Dr. Valgimigli has received grants and personal fees from Abbott, Terumo, AstraZeneca; has received personal fees from Chiesi, Bayer, Daiichi-Sankyo, Amgen, Alvimedica, Biosensors, and Idorsia; and has received grants from Medicure outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In invasively managed patients with ACS, a decrease in hemoglobin content of ≥3 g/dl is associated with 1-year mortality even in the absence of overt bleeding.

TRANSLATIONAL OUTLOOK:

A declining hemoglobin level may be a useful surrogate for other bleeding-related endpoints in clinical trials investigating treatment strategies for patients with ACS undergoing invasive management.

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KEY WORDS acute coronary syndromes, bleeding, hemoglobin, percutaneous coronary intervention

APPENDIX For supplemental tables and figures, please see the online version of this paper.