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Relationship between baseline haemoglobin and major bleeding complications in acute coronary syndromes

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Aims In patients with acute coronary syndromes (ACS), the negative impact of baseline haemoglobin levels on ischaemic events, particularly death, is well established, but the association with bleeding risk is less well studied. The aim of this study was to assess the impact of baseline haemoglobin levels on major bleeding complications.

Methods and results Pooled analysis of OASIS 5 and 6 data involving 32 170 patients with ACS with and without ST-segment elevation was performed. The association between baseline haemoglobin and major bleeding or ischaemic events was examined using multiple regression model. Main outcome measures were 30-day rates of major bleeding, death, and death/myocardial infarction (MI) analysed according to baseline haemoglobin levels. Baseline haemoglobin level independently predicted the risk of overall, procedure-related, and non-procedure-related major bleedings at 30 days [odds ratio (OR) 0.94, 95% CI 0.90–0.98; OR 0.94, 95% CI 0.90–0.99; and OR 0.89, 95% CI 0.83–0.95, respectively, per 1 g/dL haemoglobin increment above 10 g/dL]. In addition, a curvilinear relationship between baseline haemoglobin levels and death at 30 days was observed with a 6% decrease in the risk for every 1 g/dL haemoglobin increment above 10 g/dL up to 15.9 g/dL (OR 0.94, 95% CI 0.90–0.98) and a 19% increase above this value (OR 1.19, 95% CI, 0.98–1.43). A similar relationship for the composite outcome of death/MI was observed.

Conclusion A low baseline haemoglobin level is an independent predictor of the risk of major bleeding in ACS as well as of the risk of death and death and MI. Among other predictors of bleeding risk, baseline haemoglobin should be taken into account in patients presenting with ACS.

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http://clinicaltrials.gov/ct2/show/NCT00139815?term=NCT00139815&rank=1.

Keywords Anaemia • Angina • Anticoagulants • Infarction

Introduction

Anaemia is associated with a higher risk of short- and long-term mortality across the whole spectrum of patients with coronary artery disease, including chronic stable angina, ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndromes (NSTE-ACS),[1] and those undergoing percutaneous coronary interventions (PCI).[2,3]

The relation between baseline haemoglobin and ischaemic outcomes was shown to be curvilinear,[1,4] with the lowest rate of

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ischaemic events and death occurring in patients with a baseline haemoglobin level of ~15 g/dL, and higher rates in patients with haemoglobin levels below and above this value.[1] An association between anaemia and adverse outcome has also been described in patients with heart failure,[5–7] renal failure,[7–10] diabetes,[10–12] undergoing various types of surgery,[13–15] including cardiac surgery,[16] malignancy,[17] the elderly,[18] in women,[19] and in the general population.[20] In addition, low baseline haemoglobin level was shown in some reports to be an independent predictor of bleeding.[21,22] However, the impact of baseline haemoglobin level on the risk of bleeding in ACS, with or without ST-segment elevation, has never been addressed in a large cohort. Indeed, the presence of low haemoglobin level at admission may mirror the presence of unrecognized haemorrhagic diathesis, which may lead to an increased risk of bleeding, given that anticoagulants and antiplatelet agents are important components of the treatment of these syndromes.

The goal of our study was to assess the impact of baseline haemoglobin levels on major bleeding complications, and secondarily on death and death/MI at 30 days in a cohort of over 32 000 patients from the OASIS 5 and 6 trials.

Methods

The OASIS 5 and OASIS 6 cohorts of patients were pooled together for the purpose of this analysis. The design and methods of the OASIS 5 and OASIS 6 trials have been reported in detail.[23,24] In brief, OASIS 5 was a randomized, double-blind, placebo-controlled, parallel group trial of fondaparinux vs. enoxaparin in 20 078 patients with unstable angina or non-ST elevation MI. Patients were eligible for inclusion if they presented to hospital with symptoms of NSTE-ACS, with at least two of the following criteria: age ≥60 years, troponin T or I or CKMB above upper limit of normal or ECG changes suggestive of ischaemia (ST depression >1 mm in two contiguous leads or T-wave inversion >3 mm or dynamic shift in ST-segment or transient ST elevation). Patients were excluded if they had a contraindication to low molecular weight heparin or fondaparinux, or haemorrhagic stroke within the previous 12 months or severe renal insufficiency (serum creatinine >3 mg/dL or 265 mmol/L). Patients were followed for a minimum of 90 days and a maximum of 180 days. The primary efficacy outcome (assessed at 9 days) was a composite of death, MI, and refractory ischaemia. The primary safety outcome was major bleeding at 9 days. Information on both outcomes was available at 30 days and 90–180 days.

OASIS 6 was a randomized, double-blind trial of fondaparinux vs. usual care in 12 092 patients with STEMI. Exclusion criteria were the same as used in OASIS 5. Treatment allocation was randomized and stratified by indication for the use of unfractionated heparin (UFH) based on the investigator's judgement. The 5658 patients of stratum 1 (no indication for UFH) were assigned to receive blinded fondaparinux 2.5 mg (or 5.0 mg in case of PCI without the use of a glycoprotein IIb/IIIa inhibitor) or matching placebo once daily, given intravenously for the first dose, and subcutaneously thereafter for up to 8 days or hospital discharge. The 6434 patients in stratum 2 (indication for UFH) were assigned to receive either fondaparinux or UFH in a double-blind design. As in OASIS 5, patients were followed up for a minimum of 90 and a maximum of 180 days. The primary efficacy outcome was death or re-infarction at 30 days, and the safety outcome was major bleeding.

In both trials, outcome events were adjudicated by a committee blinded to treatment allocation. The definitions of MI, stroke and bleeding, and the classification of deaths have been previously published. In brief, major bleeding was defined as clinically overt bleeding that is either fatal or symptomatic intracranial haemorrhage, retroperitoneal haemorrhage, intraocular haemorrhage leading to significant vision loss, decrease in haemoglobin of at least 3.0 g/dL (with each blood transfusion unit counting for 1.0 g/dL of haemoglobin), or bleed requiring transfusion of two or more units of red blood cells or equivalent of whole blood.

For the purpose of this study, major bleeding complications were categorized as overall, procedure-related, and non-procedure-related major bleeding. Procedure-related bleeding referred to any non-CABG major bleeding induced by any diagnostic or therapeutic invasive procedure, such as coronary angiography, PCI, intra-aortic balloon pumping, among others. Special attention was paid to blood transfusions, which were a component of the definition of major and minor bleeding. Patients with low haemoglobin levels at baseline may have been transfused in the absence of overt bleeding. Therefore, transfusion of packed red blood cells or whole blood (regardless of number of units given) in the absence of overt bleeding and/or at least 1 g/dL fall in haemoglobin was not considered as bleeding. All the endpoints of interest (death, MI, and bleeding) were assessed at 30 days.

Statistical analysis

All analyses were performed using SAS software, version 9.1 (SAS institute Inc., Cary, NC, USA).

Baseline characteristics

Patients were divided into groups according to 1 g/dL increments in haemoglobin levels from <10 up to >17 g/dL. The number of patients and their baseline characteristics and in-hospital treatments within each haemoglobin category were compared using a χ^2 test for categorical variables and ANOVA for continuous variables. ANOVA was used to analyse the statistical significance of the relationship, if any, between baseline haemoglobin and baseline characteristics (age, heart rate, systolic blood pressure, previous history of MI, diabetes, hypertension, heart failure, smoking, serum creatinine and creatinine clearance, GRACE risk score), as well as the relationship between baseline haemoglobin and rate of co-interventions, PCI, beta blockers, angiotensin-converting enzyme (ACE)-inhibitors, and angiotensin receptor blockers (ARB).

Association between baseline haemoglobin and outcomes

The number and proportion of patients who suffered from overall, procedure-related, and non-procedure-related major bleeding, death, MI, the composite of death, or MI were examined in different haemoglobin categories using a χ^2 test. To evaluate the relationship between baseline haemoglobin categories and outcome, we graphically explored and fitted piece-wise with one slope until haemoglobin of 15.9 g/dL and a different slope above that value. We obtained two odds ratios (ORs) for the two ranges, estimating the effect of 1 g/dL increase in haemoglobin on the outcome under consideration. Separate multivariable

logistic regression models were used to determine independent predictors of overall, procedure-related, and non-procedure-related major bleedings, as well as independent predictors of death and death/MI at 30 days, with adjustment for baseline demographics, prior medical history, cardiovascular risk factors, randomized treatment allocation, and co-interventions.

For each model, we pre-specified baseline characteristics and co-interventions that were believed to be associated with baseline haemoglobin or with the outcome of interest based on biology, pharmacology, and clinical experience. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the OASIS 5 and OASIS 6 cohorts have been reported elsewhere.[23,24] In the combined OASIS 5 and 6 cohort, anaemia (as defined according to the WHO definition, baseline haemoglobin <13 g/dL for men and <12 g/dL for women[25]) was present in 6565 (20.5%) patients [4083/20 981 (19.5%) men and 2482/10 958 (22.6%) women, $P < 0.0001$]. However baseline haemoglobin <10 g/dL was found in only 805 (2.5%) patients, of whom 370 (46%) were men.

The baseline characteristics, treatment, procedures, and events occurring during the hospital phase according to baseline haemoglobin are presented in categories by increments of 1 g/dL from <10 to 17 g/dL in *Tables 1–3*. There were significant differences in baseline characteristics and co-interventions according to baseline haemoglobin levels. Patients with lower baseline haemoglobin levels tended to be older, were more frequently females, and had a lower body weight, higher heart rate, and lower systolic and diastolic blood pressure than patients with higher levels. They tended also to have more co-morbidities than patients with higher levels of baseline haemoglobin, as shown by the more frequent previous history of coronary artery disease (MI, PCI, or CABG), higher rates of diabetes, hypertension, and heart failure. The rates of current or former smokers were lower among patients with lower levels of haemoglobin and increased gradually above 15 g/dL of baseline haemoglobin. Creatinine clearance tended to be lower in individuals with low baseline haemoglobin levels. There was a significant inverse correlation between GRACE risk score and baseline haemoglobin levels ($r = -0.20$; $P < 0.0001$). Finally, patients with lower levels of baseline haemoglobin were less likely to undergo coronary angiography and PCI during hospitalization than those with higher levels or to receive beta-blockers and ACE-inhibitors and were more prone to receive ARB.

The rates of major bleeding were significantly higher with lower levels of baseline haemoglobin, with a progressive increase in the rates of overall, procedure-related, and non-procedure-related major bleeding from the highest to the lowest levels of baseline haemoglobin in the whole cohort as well as in NSTE-ACS and STEMI populations (*Figure 1*). This trend was not apparent when bleeding was graded according to the TIMI major scale. This may be because this scale lacks sensitivity, as shown by the very low rates of TIMI severe bleeding. The frequency of the clinical components of the definition of major bleeding was well balanced over the four quartiles (*Table 4*). However, transfusions of more than 2 units of red blood cells were observed more frequently

Table 1 OASIS 5 and 6: baseline characteristics and medical history by levels of baseline haemoglobin (g/dL)

	Overall	<10	10–<11	11–<12	12–<13	13–<14	14–<15	15–<16	16–<17	≥17	*P*-value
Randomized	31 939 (100)	805 (100)	1017 (100)	2490 (100)	4893 (100)	7119 (100)	7482 (100)	5101 (100)	2204 (100)	828 (100)	
Age, years	64.7 ± 11.7	68.4 ± 11.8	69.6 ± 11.3	69.6 ± 11.0	67.8 ± 11.0	66.0 ± 10.9	63.4 ± 11.4	60.9 ± 11.4	59.9 ± 11.5	58.9 ± 12.0	<0.01
Male (%)	65.7	46.0	43.9	40.7	46.0	58.3	74.6	85.9	92.0	90.8	<0.01
Heart rate, b.p.m.	74.2 ± 13.9	78.1 ± 14.3	77.2 ± 14.1	75.2 ± 14.1	74.1 ± 13.8	73.3 ± 13.8	73.4 ± 13.8	74.2 ± 14.0	75.0 ± 13.8	77.2 ± 14.4	<0.01
SBP, mmHg	135.6 ± 22.8	133.2 ± 23.4	134.2 ± 23.1	133.9 ± 24.0	135.2 ± 22.8	134.9 ± 22.6	135.3 ± 22.5	137.2 ± 22.5	137.9 ± 22.4	139.3 ± 24.3	<0.01
Cr.Cl, mL/min	77.4 ± 29.8	58.9 ± 27.3	58.8 ± 26.2	62.5 ± 25.8	69.1 ± 27.0	75.2 ± 27.7	82.5 ± 29.3	88.2 ± 29.8	89.0 ± 29.7	88.5 ± 31.4	<0.01
MI, *n* (%)	6640 (20.8)	178 (22.1)	257 (25.3)	607 (24.4)	1085 (22.2)	1552 (21.8)	1488 (19.9)	930 (18.2)	402 (18.2)	141 (17.0)	<0.01
Previous PCI, *n* (%)	2681 (8.4)	72 (8.9)	109 (10.7)	230 (9.2)	432 (8.8)	643 (9.0)	614 (8.2)	388 (7.6)	145 (6.6)	48 (5.8)	<0.01
CABG surgery, *n* (%)	1777 (5.6)	54 (6.7)	78 (7.7)	146 (5.9)	314 (6.4)	424 (6.0)	389 (5.2)	244 (4.8)	97 (4.4)	31 (3.7)	<0.01
Heart failure, *n* (%)	4452 (13.9)	163 (20.2)	231 (22.7)	487 (19.6)	817 (16.7)	944 (13.3)	874 (11.7)	555 (10.9)	262 (11.9)	119 (14.4)	<0.01
Hypertension, *n* (%)	19 955 (62.5)	494 (61.4)	715 (70.3)	1729 (69.4)	3334 (68.1)	4554 (64.0)	4386 (58.6)	2931 (57.5)	1307 (59.3)	505 (61.0)	<0.01
Diabetic, *n* (%)	7179 (22.5)	260 (32.3)	348 (34.2)	734 (29.5)	1300 (26.6)	1575 (22.1)	1504 (20.1)	940 (18.4)	386 (17.5)	132 (15.9)	<0.01
Current smoker, *n* (%)	9266 (29.0)	146 (18.1)	170 (16.7)	388 (15.6)	944 (19.3)	1775 (24.9)	2484 (33.2)	1993 (39.1)	968 (43.9)	398 (48.1)	<0.01
GRACE risk score		128	130	127	121	116	110	105	105	104	<0.01

b.p.m., beats per minute; SBP, systolic blood pressure; Cr.Cl, creatinine clearance; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.
Age, heart rate, SBP, and Cr.Cl. are presented as mean ± SD.

Table 2 OASIS 5 and 6: medications and procedures since randomization in hospital by levels of baseline haemoglobin (g/dL)

	Overall	<10	10–<11	11–<12	12–<13	13–<14	14–<15	15–<16	16–<17	≥17	*P*-value
Randomized	31 939 (100)	805 (100)	1017 (100)	2490 (100)	4893 (100)	7119 (100)	7482 (100)	5101 (100)	2204 (100)	828 (100)	
Medications											
ASA	31 052 (97.2)	766 (95.2)	983 (96.7)	2401 (96.4)	4749 (97.1)	6934 (97.4)	7271 (97.2)	4980 (97.6)	2164 (98.2)	804 (97.1)	NS
Clop/Ticlo	21 496 (67.3)	566 (70.3)	659 (64.8)	1582 (63.5)	3229 (66.0)	4752 (66.7)	5151 (68.9)	3595 (70.5)	1434 (65.0)	528 (63.8)	NS
B-blockers	27 547 (86.2)	650 (80.7)	831 (81.7)	2028 (81.4)	4164 (85.1)	6179 (86.8)	6492 (86.8)	4519 (88.6)	1964 (89.1)	720 (87.0)	<0.01
ARB agents	1909 (6.0)	72 (8.9)	94 (9.2)	188 (7.6)	359 (7.3)	413 (5.8)	402 (5.4)	247 (4.8)	107 (4.9)	27 (3.3)	<0.01
ACE inhib.	23 338 (73.1)	553 (68.7)	736 (72.4)	1815 (72.9)	3575 (73.1)	5194 (73.0)	5432 (72.6)	3761 (73.7)	1635 (74.2)	637 (76.9)	<0.01
Procedures											
Angio	17 864 (55.9)	326 (40.5)	396 (38.9)	1137 (45.7)	2478 (50.6)	4007 (56.3)	4531 (60.6)	3190 (62.5)	1339 (60.8)	460 (55.6)	<0.01
PCI	11 252 (35.2)	159 (19.8)	208 (20.5)	621 (24.9)	1424 (29.1)	2462 (34.6)	2972 (39.7)	2186 (42.9)	914 (41.5)	306 (37.0)	<0.01
CABG	2005 (6.3)	40 (5.0)	70 (6.9)	143 (5.7)	273 (5.6)	444 (6.2)	510 (6.8)	347 (6.8)	123 (5.6)	55 (6.6)	NS

Clop/Ticlo, clopidogrel or ticlopidine; B-blockers, beta-blockers; inhib, inhibitors; Angio, coronary angiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table 3 OASIS 5 and 6: 30-day events by levels of baseline haemoglobin (g/dL)

	Overall	<10	10–<11	11–<12	12–<13	13–<14	14–<15	15–<16	16–<17	≥17	*P*-value
Randomized	31 939 (100)	805 (100)	1017 (100)	2490 (100)	4893 (100)	7119 (100)	7482 (100)	5101 (100)	2204 (100)	828 (100)	<0.01
Death/MI	2537 (7.9)	93 (11.6)	126 (12.4)	268 (10.8)	479 (9.8)	535 (7.5)	518 (6.9)	307 (6.0)	139 (6.3)	72 (8.7)	<0.01
Death	1633 (5.1)	72 (8.9)	97 (9.5)	200 (8.0)	316 (6.5)	344 (4.8)	307 (4.1)	168 (3.3)	84 (3.8)	45 (5.4)	<0.01
MI	1112 (3.5)	31 (3.9)	39 (3.8)	94 (3.8)	208 (4.3)	228 (3.2)	258 (3.4)	161 (3.2)	63 (2.9)	30 (3.6)	NS
Stroke	289 (0.9)	6 (0.7)	4 (0.4)	26 (1.0)	45 (0.9)	73 (1.0)	65 (0.9)	42 (0.8)	20 (0.9)	8 (1.0)	NS
Major bleed	1066 (3.3)	54 (6.7)	65 (6.4)	123 (4.9)	171 (3.5)	242 (3.4)	228 (3.0)	119 (2.3)	46 (2.1)	18 (2.2)	<0.01
Procedure-related major bleed	653 (2.0)	23 (2.9)	36 (3.5)	60 (2.4)	107 (2.2)	158 (2.2)	155 (2.1)	75 (1.5)	28 (1.3)	11 (1.3)	<0.01
Non-procedure-related major bleed	412 (1.3)	31 (3.9)	29 (2.9)	63 (2.5)	64 (1.3)	84 (1.2)	73 (1.0)	44 (0.9)	18 (0.8)	6 (0.7)	<0.01
TIMI major bleed	183 (0.6)	4 (0.5)	6 (0.6)	10 (0.4)	27 (0.6)	45 (0.6)	46 (0.6)	042 (0.8)	20 (0.9)	8 (1.0)	NS

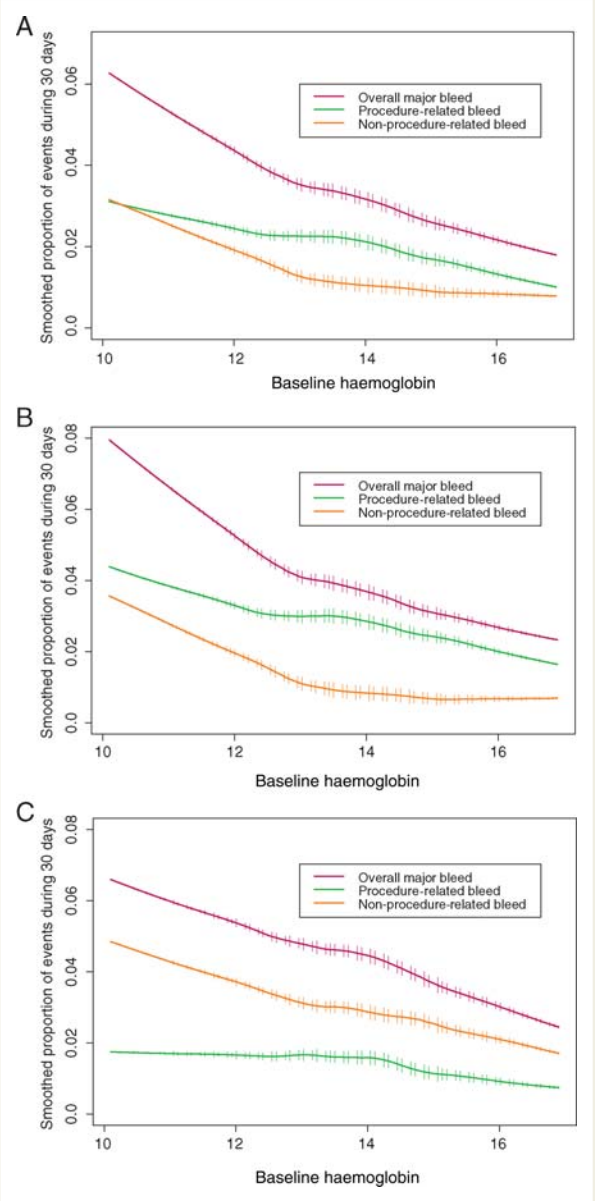

Figure 1 Relationship between baseline haemoglobin and overall, procedure-related, and non-procedure-related bleedings at 30 days in the overall population (*A*), in non-ST-segment elevation acute coronary syndromes (*B*), and in ST-segment elevation myocardial infarction (*C*).

from the lowest to the highest haemoglobin level. Since transfusion without overt bleeding or with at least <1 g/dL haemoglobin drop was not counted as a bleeding event, one can reasonably assume that a haemoglobin loss in the lowest haemoglobin levels triggered transfusion at an earlier stage in patients with already low haemoglobin levels (*Table 4*). Baseline haemoglobin was identified as an independent and a strong predictor of the risk of overall, procedure-related, and non-procedure-related major bleedings at 30 days (OR 0.94, 95% CI 0.90–0.98; OR 0.94, 95% CI 0.90–0.99; and OR 0.89, 95% CI 0.83–0.95, respectively, per every 1 g/dL haemoglobin increment above 10 g/dL), along with treatment allocation, age, creatinine clearance in all categories of bleeding. Gender and diabetes (overall major bleed) and heart failure (procedure-related and non-procedure-related bleedings) were also found to be independent predictors (*Table 5*).

In addition, a curvilinear relationship between baseline haemoglobin levels and death at 30 days was observed with a 6% decrease in the risk for every 1 g/dL haemoglobin increment above 10 g/dL up to 15.9 g/dL (OR 0.94, 95% CI 0.90–0.98) and a 19% increase above this value (OR 1.19, 95% CI 0.98–1.43) (*Figure 2*). This curvilinear relation was also observed for the composite endpoint of death/MI (OR 0.96, 95% CI 0.93–0.99 up to 15.9 g/dL baseline haemoglobin; OR 1.15, 95% CI 0.99–1.34 above this value).

Baseline haemoglobin was shown to be an independent predictor of death, death/MI, at 30 days along with treatment allocation (fondaparinux vs. enoxaparin/UFH/placebo), heart failure and diabetes at baseline, the use of PCI, and creatinine clearance (*Table 6*).

Discussion

The main finding of this study is the inverse relation between baseline haemoglobin and major bleeding risk in the whole cohort as well as in NSTE-ACS and STEMI populations (*Table 3* and *Figure 1*). Anaemia as defined according to the WHO criteria[25] is frequent in ACS and may be present in 5–10% of patients with NSTE-ACS. However, much higher rates were found in many instances, 19.5% of men and 22.6% of women in this report, in 30.6% of cases of ACS patients in another study,[1] and in up to 43% in elderly patients with acute MI.[26] Anaemia is associated with older age[27–29] and co-morbidities, such as presence of diabetes,[11] renal failure,[8] and heart failure,[5,6] but also with non-cardiovascular conditions such as haemorrhagic diathesis or malignancies,[17] which may have an impact on outcome. In this report, low baseline haemoglobin levels were associated with more co-morbidities, higher risk population, and suboptimal treatment. However, the relation between haemoglobin levels and outcome persisted after adjustment on a broad range of clinical, biological, and procedural characteristics including creatinine clearance. After adjustment, baseline haemoglobin remained an independent predictor of overall, procedure-related, and non-procedure-related major bleeding risk.

Low baseline haemoglobin has already been reported to be an independent predictor of bleeding,[21,22] although previous studies have focused primarily on the link between anaemia and ischaemic events, with little or no emphasis on bleeding, which has been only recently perceived as a major contributor to the short- and long-term prognosis of patients suffering from ACS.[21,22] Baseline haemoglobin level was shown to independently predict bleeding, with an inverse relation between baseline haemoglobin levels and bleeding risk in other reports.[30,31] Low baseline haemoglobin level may be a marker of occult gastro-intestinal bleeding, inflammatory state, or haemorrhagic diathesis that may account for propensity to bleeding in such situation. In addition, haematocrit level has an influence on primary haemostasis. Increasing haematocrit levels were shown to lead, on the one hand, to increased platelet deposition to the arterial wall and, on the other hand, to increased blood viscosity and increased shear forces that may lead, in turn, to the activation of platelet functions through ADP release by erythrocytes,[32–34] all factors that may have protective effects against

Table 4 Details of major bleeds at 30 days (g/dL)

	Overall	<10	10–<11	11–<12	12–<13	13–<14	14–<15	15–<16	16–<17	≥17
Fatal bleed	126 (0.4)	3 (0.4)	6 (0.6)	9 (0.4)	23 (0.5)	31 (0.4)	26 (0.3)	19 (0.4)	5 (0.2)	3 (0.4)
Symptomatic internal haemorrhage	43 (0.1)	0 (0)	1 (0.1)	1 (0)	7 (0.1)	16 (0.2)	10 (0.1)	5 (0.1)	1 (0)	2 (0.2)
Retroperitoneal haemorrhage	57 (0.2)	3 (0.4)	3 (0.3)	9 (0.4)	8 (0.2)	14 (0.2)	7 (0.1)	9 (0.2)	2 (0.1)	2 (0.2)
Vision loss	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiac tamponade	101 (0.3)	1 (0.1)	4 (0.4)	6 (0.2)	20 (0.4)	25 (0.4)	18 (0.2)	21 (0.4)	4 (0.2)	1 (0.1)
Requiring surgical intervention	182 (0.6)	8 (1)	11 (1.1)	14 (0.6)	18 (0.4)	44 (0.6)	45 (0.6)	30 (0.6)	10 (0.5)	2 (0.2)
Hb drop ≥3 g/dL	618 (1.9)	23 (2.9)	18 (1.8)	52 (2.1)	100 (2.1)	146 (2.1)	156 (2.1)	77 (1.5)	32 (1.5)	12 (1.5)
Blood transfusion ≥2 units	690 (2.2)	52 (6.5)	57 (5.6)	98 (4.0)	117 (2.4)	148 (2.1)	135 (1.8)	52 (1.0)	20 (0.9)	6 (0.7)

Hb, haemoglobin.

bleeding. The use of aggressive antiplatelet and antithrombin treatments as well as invasive procedures may play the role of precipitating factor. Of note also is the fact that the risk of major bleeding sharply increased for baseline haemoglobin levels below 12–13 g/dL (lower limit of normal according to the WHO definition of anaemia), as shown in *Table 3* and *Figure 1*. This implies that even modestly low baseline haemoglobin levels should be factored into the therapeutic decisions in patients with ACS and lead clinicians to select procedures or treatments with known reduced risk of bleeding.

In addition, a link between low baseline haemoglobin and death, and death/MI at 30 days was confirmed in our study, with a gradual decrease in the risk from the lowest levels of baseline haemoglobin up to 15.9 g/dL and an increase above this value. A J-shaped relationship between baseline haemoglobin levels and death or death/MI across the whole spectrum of ACS has already been shown, with poorer prognosis at lower baseline haemoglobin levels.[1,18] As expected, age, gender, treatment allocation, creatinine clearance, diabetes, history of heart failure, and the use of PCI were also strong predictors of the risk of death and death/MI at 30 days.

The practical implications are that baseline haemoglobin level should be taken into account in the initial risk assessment of ACS patients. The impact of baseline haemoglobin on the risk of bleeding compared with other predictors of bleeding may appear quite weak. Actually, a 1 SD decrease in baseline haemoglobin led to a 13% increase in bleeding risk. Comparatively, a 1 SD decrease in creatinine clearance or 1 SD increase in age, respectively, led to a 25 and 41% increase in bleeding risk. As bleeding has been shown to increase several-fold the risk of death and MI,[23,35–37] the prevention of bleeding complications has become as important an objective as the prevention of ischaemic events in ACS.[38] Drugs and/or procedures that are associated with a reduced risk of bleeding should be favoured. In this regard, fondaparinux was confirmed in this report to carry a 30–36% lower risk of major bleeding compared with control treatment (enoxaparin/UFH/placebo), depending on the type of bleeding (*Table 5*). In addition, a radial rather than femoral approach should be favoured whenever possible, as it was shown to reduce the risk of procedure-related bleeding, need for transfusion, and death.[39,40] Lastly, as transfusion of stored blood might have deleterious effect, a restrictive policy for blood transfusion should be implemented, with a trigger for transfusion in stable patients set at 7–8 g/dL haemoglobin level as recommended in the most recent guidelines for the management of NSTE-ACS.[38]

Table 5 Independent predictors of overall, procedure-related, and non-procedure-related major bleeding at 30 days

Effect	OR estimates	
	Point estimate	95% Wald confidence limits
Overall major bleeding		
Baseline haemoglobin*	0.94	0.90–0.98
Treatment allocation	0.67	0.59–0.77
Age	1.02	1.01–1.03
Male sex	0.82	0.72–0.95
Diabetes	1.17	1.0–1.35
Creatinine clearance	0.93	0.92–0.94
Procedure-related bleeding		
Baseline haemoglobin*	0.94	0.90–0.99
Treatment allocation	0.70	0.60–0.83
Age	1.02	1.01–1.03
Heart failure	0.62	0.47–0.80
Creatinine clearance	0.93	0.92–0.95
Non-procedure-related bleeding		
Baseline haemoglobin*	0.89	0.83–0.95
Treatment allocation	0.64	0.52–0.78
Age	1.04	1.03–1.05
Heart failure	1.55	1.21–1.99
Creatinine clearance	0.92	0.90–0.94

*Per every 1 g/dL increment above 10 g/dL, age: per 1 year increase; creatinine clearance: per 5 units decrease.

Limitations

This was a pooled analysis of NSTE-ACS and STEMI, which do not share the same therapeutic options and prognosis at least for the

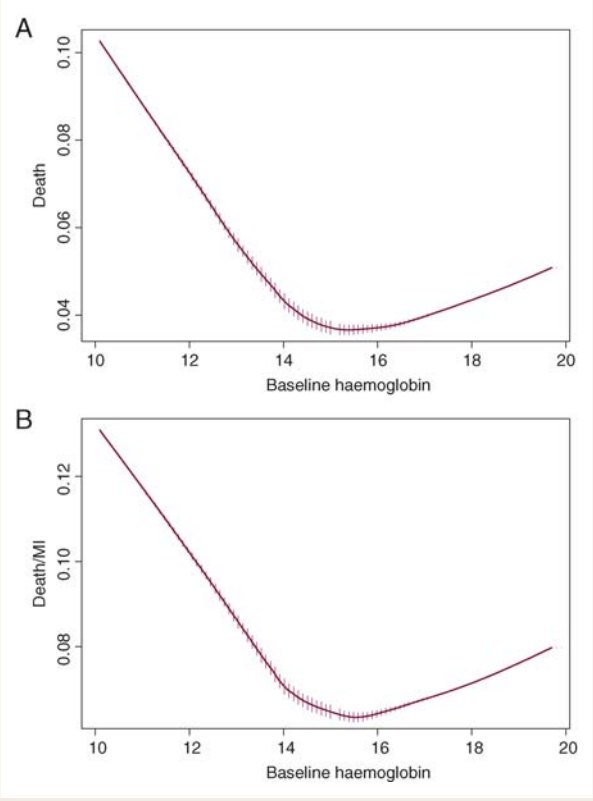

Figure 2 Relationship between baseline haemoglobin and death (*A*), and death/myocardial infarction (*B*) at 30 days.

Table 6 Independent predictors of death and death/MI at 30 days

	Death at 30 days (OR, 95% CI)	Death/MI at 30 days (OR, 95% CI)
Treatment allocation	0.83, 0.75–0.93	0.86, 0.79–0.94
Baseline haemoglobin <15.9 g/dL	0.94, 0.90–0.98	0.96, 0.93–0.99
Baseline haemoglobin >15.9 g/dL	1.19, 0.98–1.43	1.15, 0.99–1.34
Age	1.03, 1.02–1.04	1.03, 1.02–1.04
Heart failure	2.04, 1.81–2.31	1.71, 1.54–1.90
PCI	0.52, 0.41–0.67	0.84, 0.71–0.99
Diabetes	1.19, 1.06–1.34	1.18, 1.07–1.30
Creatinine clearance	0.97, 0.97–0.98	0.98, 0.98–0.99

Age: per 1 year increase, Creatinine clearance: per 5 units decrease.

short, 30-day evolution. However, the data collected and the definition of endpoints, both bleeding and ischaemic, were common in the two cohorts and hence the analysis was carried out on a homogenous database. Great attention was paid to avoid classifying as bleeding events patients who may have been transfused merely because of anaemia at admission. Transfusion administered without overt bleeding was not considered a bleeding event. One important limitation was that it was not possible to analyse the impact of blood transfusion on outcome according to baseline haemoglobin levels, since transfusions were part of the definition of bleeding. Causality between baseline haemoglobin and adverse outcomes cannot be established in our observational study and it is possible that the association was confounded by other baseline characteristics associated with both low baseline haemoglobin levels and adverse outcome. However, our analyses after adjustment for all known confounders demonstrate that low baseline haemoglobin levels is a marker of an increased risk of major bleeding. Lastly, it was not possible to determine the cause of low baseline haemoglobin levels from this database. Malignancy and known haemorrhagic diathesis were exclusion criteria for entry into the two studies. Most of the conditions known to influence haemoglobin levels were collected, including diabetes and renal function, so that we can reasonably assume that confounding factors were taken into account for the statistical analysis, as far as possible. Lastly, it was not possible to assess from the data collected in these two trials the adequacy of the dosing of non-study drugs.

Conclusions

Low baseline haemoglobin levels were shown in this report to be associated with an increased risk of major bleeding. After adjustment for a broad range of baseline characteristics, in-hospital treatments, and co-interventions, baseline haemoglobin was shown to be a strong independent predictor of overall, procedure-related, and non-procedure related major bleeding risk. These findings should prompt clinicians to incorporate baseline haemoglobin level in the initial risk assessment of patients presenting with ACS, for both bleeding and ischaemic risks.

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Conflict of interest: J.-P.B. reports receiving honoraria and consultancy fees from GlaxoSmithKline, Eli Lilly Inc., and Sanofi-Aventis. J.E. reports having received honoraria and research funding from Bayer, GSK, and Sanofi-Aventis. L.W. reports having received institutional research grants from Astra-Zeneca, Boehringer-Ingelheim, BMS, Lilly, GSK, and Sanofi-Aventis. R.P. reports speakers bureau and honoraria with several pharmaceutical companies, and advisory board with Sanofi-Aventis. A.B. reports receiving research grants from GlaxoSmithKline and Sanofi-Aventis, honoraria with GlaxoSmithKline and Sanofi-Aventis, and advisory boards with GlaxoSmithKline and Sanofi-Aventis. K.A.A.F. reports receiving research grants from Sanofi-Aventis, Bristol-Myers Squibb, and GlaxoSmithKline, honoraria from Sanofi-Aventis, Bristol-Myers Squibb, and GlaxoSmithKline, and

advisory boards with Sanofi-Aventis and GlaxoSmithKline. C.D.J. reports receiving a research grant from Sanofi-Aventis. C.B.G reports receiving research grants from Aventis and Bristol-Myers Squibb and advisory boards with Aventis and GlaxoSmithKline. S.M. reports receiving research grants from GlaxoSmithKline and Sanofi-Aventis, honoraria from GlaxoSmithKline, Sanofi-Aventis, and Bristol-Myers Squibb, and advisory boards with GlaxoSmithKline, Sanofi-Aventis, and Bristol-Myers Squibb. S.Y. reports that the OASIS 5 Study was funded by GlaxoSmithKline and Sanofi. He has received honoraria from several pharmaceutical companies for lectures and has been a consultant with GlaxoSmithKline and Sanofi-Aventis. R.A. and S.C. have no conflicts of interest to disclose.

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CARDIOVASCULAR FLASHLIGHT

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Collaboration between cardiac computed tomography and echocardiography in complex anomalies

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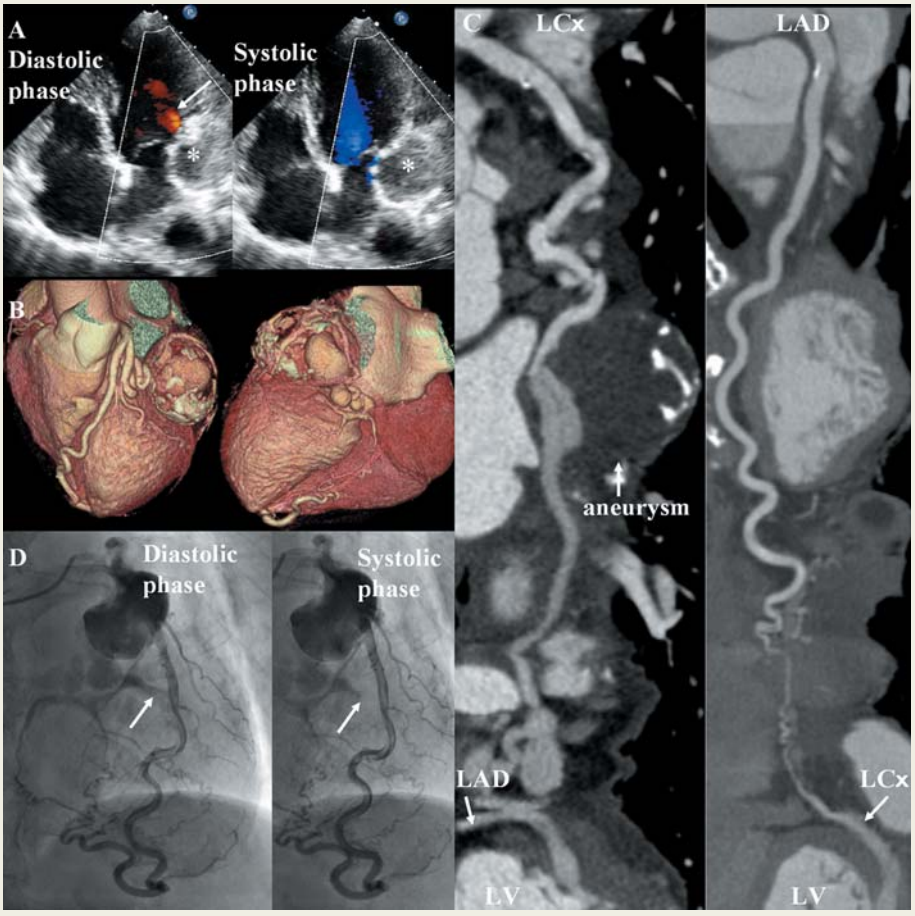

A 69-year-old woman carrying the hepatitis C virus was admitted to our hospital because of atypical chest pain. Electrocardiogram was normal, except for right axis deviation. Trans-thoracic echocardiography revealed a tumour-like image behind the left atrium (*Panel A*, asterisk) and a flow towards the inferior wall of the left ventricle (LV) during diastolic phase (*Panel A*, arrow). A cardiac computed tomography (CT) revealed coronary aneurysm in the left circumflex artery (LCx) (*Panel B*). Distal portion of LCx was communicated with the left anterior descending artery (LAD) and left ventricular cavity in diastolic phase (*Panel C*). These findings suggested that the tumour-like image was coronary aneurysm formed in LCx, and LCx was merged to LAD at the distal portion and flowed into LV. Coronary angiography (CAG) unequivocally showed the coronary aneurysm of LCx and coronary fistula. The flow from coronary artery to LV was detected in diastolic phase, but not in systolic phase (*Panel D*, arrow). With the technological advances of multidetector row CT (MDCT) angiography, cardiac anomalies and atherosclerotic coronary artery disease are evaluated with markedly improved temporal and spacial resolution. However, MDCT cannot provide the precise information of the blood flow direction because we have to fill in contrast material to coronary arteries at the time of scanning. On the other hand, colour flow imaging using routine 2D images of echocardiography is used to identify blood flow within the heart. Thus, by collaboration between cardiac CT and echocardiography, we could evaluate complex anomalies without invasive procedures in this patient.