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▶ **To cite this version:**

P. Deharo, G. Ducrocq, C. Bode, M. Cohen, T. Cuisset, et al.. Blood transfusion and ischaemic outcomes according to anemia and bleeding in patients with non-ST-segment elevation acute coronary syndromes: Insights from the TAO randomized clinical trial. International Journal of Cardiology, 2020, 318, pp.7-13. 10.1016/j.ijcard.2020.06.020 . hal-03155477

HAL Id: hal-03155477
https://hal.inrae.fr/hal-03155477

Submitted on 21 Sep 2022

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Version of Record: https://www.sciencedirect.com/science/article/pii/S0167527320333982
Manuscript_605ac08a1c4ff4a10e9181f505d9b211

Blood transfusion and ischaemic outcomes according to anemia and bleeding in patients with Non-ST-Segment Elevation Acute Coronary Syndromes: Insights from the TAO Randomized Clinical Trial

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Word count: 3602

Disclosures: under full completion

M SABATINE Research grant support through Brigham and Women's Hospital from: Amgen; AstraZeneca; Bayer; Daiichi-Sankyo; Eisai; Intarcia; Medicines Company; MedImmune; Merck; Novartis; Pfizer; Quark Pharmaceuticals. Consulting for: Amgen; Anthos Therapeutics; AstraZeneca; Bristol-Myers Squibb; CVS Caremark; DalCor; IFM Therapeutics; Intarcia; Medicines Company; MedImmune; Merck. Additionally, Dr. Sabatine is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from: Abbott, Aralez, Roche, and Zora Biosciences. C POLLACK Consultant to Janssen Pharma, Boehringer Ingelheim. At the time TAO was done was a consultant to Sanofi. JW JUKEMA None SV RAO None P DEHARO None Y ELBEZ None T CUISSET None

Fundings: TAO trial was funded by Sanofi. For this analysis, no funding source to declare.

Acknowledgment: To the TAO investigators

Running title: Blood transfusion in NSTEMI

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Fundings: TAO trial was funded by Sanofi. For this analysis, no funding source to declare.

Acknowledgment: To the TAO investigators

Running title: Blood transfusion in NSTEMI

Abstract

Background: The benefits and risks of blood transfusion in patients with acute myocardial infarction who are anemic or who experience bleeding are debated. We sought to study the association between blood transfusion and ischemic outcomes according to haemoglobin nadir and bleeding status in patients with NST-elevation myocardial infarction (NSTEMI).

Methods: The TAO trial randomized patients with NSTEMI and coronary angiogram scheduled within 72h to heparin plus eptifibatide versus otamixaban. After exclusion of patients who underwent coronary artery bypass surgery, patients were categorized according to transfusion status considering transfusion as a time-varying covariate.
The primary ischemic outcome was the composite of all-cause death or MI within 180 days of randomization. Subgroup analyses were performed according to pre-transfusion hemoglobin nadir and bleeding status.

Results: 12,547 patients were enrolled. Among these, blood transfusion was used in 489 (3.9%) patients. Patients who received transfusion had a higher rate of death or MI (29.9% vs. 8.1%, p<0.01). This excess risk persisted after adjustment on GRACE score and nadir of hemoglobin (HR 3.36 95%CI 2.63-4.29 p<0.01). Subgroup analyses showed that blood transfusion was associated with a higher risk in patients without overt bleeding (adjusted HR 6.25 vs. 2.85; p-interaction0.001) as well as in those with hemoglobin nadir > 9.0 g/dl (HR 4.01; p-interaction<0.0001).

Conclusion: In patients with NSTEMI, blood transfusion was associated with an overall increased risk of ischaemic events. However, this was mainly driven by patients without overt bleeding and those hemoglobin nadir > 9.0g/dl. This suggests possible harm of transfusion in those groups.

Key words: Non ST elevation Myocardial Infarction, percutaneous coronary intervention, blood transfusion.

Introduction

In patients with acute coronary syndrome (ACS), the presence of anemia, with or without active bleeding, may jeopardize oxygen delivery to the myocardium, (1-3). Red blood cell (RBC) transfusion is the only treatment available that rapidly increases hemoglobin level (4). However, RBC transfusions are also associated with potentially deleterious effects in the acute phase of an ACS (5-7). Therefore, the indications of RBC transfusion are still debated and clinical management of anemia or bleeding varies widely in this population (8).
The most recent guidelines from the American College of Cardiology/ American Heart Association and of the European Society of cardiology for the management of patients with NSTEMI both recommend a restrictive use of transfusion with avoidance of routine RBC transfusion in patients with hemoglobin levels over 7.0 g/dL for European (Class IIb Level C)

and 8.0 g/dl (Class III Level B for transfusion if hemoglobin > 8.0 g/dl) for American (9-10). However, those guidelines are not based on randomized data but on observational studies of outcomes in patients requiring transfusion in the setting of myocardial infarction (MI). Yet, these studies have yielded inconsistent results, with transfusion being associated with either improved or worsened subsequent cardiovascular outcomes (11, 12).
We hypothesized that the presence or absence of active bleeding and the severity of anemia may affect the benefits and risks of RBC transfusion in patients with ACS.

Using a large contemporary trial cohort, derived from a recent international randomized trial in NSTEMI patients, we aimed to assess the association between blood transfusion and ischaemic events overall as well as according to hemoglobin nadir and bleeding status.

Methods

Study population

The methods and results of the TAO trial (Treatment of Acute Coronary Syndrome With Otamixaban) have been previously described. Briefly, TAO was a large international trial randomizing patients with moderate to high-risk NSTEMI with coronary angiography planned in the first 72 hours, to heparin plus eptifibatide versus otamixaban. Patients were randomized to the UFH plus eptifibatide group or to 1 of 2 otamixaban dosing groups (intravenous bolus of 0.080 mg/kg followed by an infusion of either 0.100mg/kg per hour or 0.140mg/kg per hour) in a 1:1:1 ratio. A planned interim analysis performed after 1969 randomized patients in each group led the investigators to define the higher-dose otamixaban as optimal, discontinue enrolment in the lower dose and to continue enrolment in the higher dose until study end in a 1:1 ratio compared to placebo.
Eligibility criteria for the study were patients with NSTEMI scheduled to undergo an invasive strategy (angiography and PCI, if indicated, to be performed at the latest within 72 hours of randomization).
The main exclusion criteria were a revascularization procedure already performed for the qualifying event; acute ST–segment elevation myocardial infarction; receipt of a therapeutic dose of injectable anticoagulant for more than 24 hours before randomization; or treatment with abciximab. The main results of the trial have been previously published: otamixaban did not reduce the rate of the primary outcomes of death plus MI but did increase bleeding in comparison with heparin plus eptifibatide (13, 14).

PCI is currently the main revascularisation modality in patients with NSTEMI (15-17). The use of CABG is currently marginal in this setting and is associated with higher bleeding rate (15-18). In patients undergoing CABG, the use of transfusion is much more frequent than in the overall NSTEMI population (between 30 to 90% according to local protocols) and has recently been evaluated in a dedicated randomized trial (18). For those reasons, patients who underwent CABG as treatment of the index event were excluded from the present analysis.

Bleeding definition and Transfusion

Bleeding events were reported if clinically overt, of unanticipated/unexpected quantity, prompting medical attention, evaluation or treatment. Bleeds were categorized using the Thrombosis in Myocardial Infarction (TIMI) classification into major and minor bleeding (19). In case of reported bleeding, hemoglobin and hematocrit before and after the event were reported (13). Hemoglobin nadir is defined as the lowest hemoglobin value and was categorized as ≤7.0, 7.1-8.0, 8.1-9.0, 9.1-10.0, >10.0 g/dl.

The indication for transfusion and the number of packed red blood cells or whole blood units transfused were left to the discretion of the treating physicians. The number of red blood cell units transfused was reported.

Outcomes:

The primary ischemic outcome studied was the same as the primary endpoint of the TAO trial: a composite of all-cause death or new MI. For the present analysis, the longest follow-up available was considered for the primary endpoint (i.e. 180 days compared to 7 days for the TAO trial).
Secondary efficacy outcome measures included the same composite ischaemic endpoint at day 30. All-cause death, cardiovascular death, non-fatal MI, stroke, rehospitalization or prolongation of the hospitalization due to MI and stent thrombosis (ST) were analysed separately at day 30. ST were categorized according to the Academic Research Consortium classification and MIs were categorized according to the 2007 universal definition (20, 21). Efficacy outcomes, were adjudicated by a central clinical event committee (TIMI Study Group); the committee members were unaware of study treatment assignments.
In order to explore potential mechanisms in outcome differences, we evaluated the incidence of antiplatelet cessation according to transfusion status, bleeding and hemoglobin nadir. All antiplatelet agents were considered (aspirin, clopidogrel and ticagrelor). A patient fulfilled criteria for antiplatelet cessation when receiving a given antiplatelet at the time of randomization but not at any subsequent time point of index hospitalization.

Ethics:

All patients provided written informed consent. In each country, the study was approved by ethics committees in accordance with local guidelines.

Statistical analysis:

Patients were categorized into two groups according to their transfusion status during entire study follow up. Descriptive statistics are reported as means ± standard deviations for continuous variables and patient numbers with percentages for categorical variables. Categorical variables across groups were compared by chi-square tests and continuous variables by analyses of variance. Events rates comparisons across groups were performed by chi-square tests. Primary and secondary outcomes were adjusted according to several multivariable logistic models including predefined variables and considering transfusion as a time-varying covariate. Model 1 was adjusted on GRACE score. Model 2 on GRACE score and nadir of hemoglobin. Model 3 included adjustment on GRACE score, region, sex, atrial fibrillation, peripheral artery disease and smoking status. Outcomes were adjusted on models 1, 2 and 3. We also present in supplemental analysis an analysis of the primary endpoint and according to bleeding status and nadir of hemoglobin with addition to the

model 3 (GRACE score, region, sex, atrial fibrillation, peripheral artery disease, smoking status) of body mass index, treatment with percutaneous coronary intervention and TAO trial allocated treatment (i.e. heparin and eptifibatide vs. otamixaban).
Given the lower number of events, subgroup analyses according to bleeding status were adjusted on model 1 only. For the subgroup analysis according to nadir hemoglobin, an additional model (model 4) was built for adjustment on GRACE score and baseline hemoglobin.
Comparisons between transfused and non-transfused patients were performed according to bleeding status (TIMI minor and major or no bleeding) occurring within 7 days after randomization, and according to the hemoglobin nadir.
The interactions between bleeding subgroups, as well as hemoglobin nadir subgroups and transfusion status were assessed by introducing interaction terms in the logistic models.
P values were reported for all statistical tests, with a cut off of 0.05 to consider a statistical significance, except for p values of interaction where the cut off of significance was set as 0.10. All statistical analyses were performed using the statistical software SAS, version 9.3 (Statistical Analyses System, SAS Institute Inc., Cary, NC, USA).

Results

Baseline and procedural characteristics

In the TAO trial, 13,229 patients with NSTEMI were randomized. Of these, 682 (5.1%) underwent CABG and were excluded from analysis. Within the study population of 12,547 patients, 12,058 (96.1%) did not receive any transfusion during the study follow up, while 489 patients (3.9%) received at least one RBC transfusion (**Supplemental Figure 1**).

Table 1 describes the baseline characteristics of the study population. Patients with transfusion were frailer (older and with lower body mass index) and sicker (higher Killip and GRACE scores and lower creatinine clearance). Vascular disease, cardiovascular risk factors and atrial fibrillation were more prevalent in this group. These patients also received less frequently aspirin or P2Y12 blockers and had lower rates of PCI following the acute MI (p=0.05). Finally, cessation of an antiplatelet agent was reported in 20.3% (n=97) of transfused patients versus 5.3% (n=627) of non-transfused patients (p<0.001) (**Supplemental table 1**).

Outcomes

Ischaemic outcomes

Unadjusted outcomes are presented in **Supplemental Table 2**. In the overall population, at 180 days, the primary efficacy endpoint occurred in 719 patients (6.0%) in the non-transfused cohort and 116 (23.7%) in the transfused cohort (p<0.001).
When transfusion status was introduced as a time-varying covariate in the Cox model the unadjusted HR for the primary endpoint was 7.35 (95%CI 6.00-9.015, p<0.01) (**Figure 1**). The increase in ischaemic risk associated with transfusion persisted after adjustment across all models: model 1 (GRACE score), model 2 (GRACE score and nadir of haemoglobin) as well on model 3 (GRACE score, region, sex, atrial fibrillation, peripheral artery disease history, smoking status) (adjusted HR 6.17 (4.98-7.65), p<0.001; 3.36 (2.63-4.29), p<0.001 and 5.65 (4.54-7.03), p<0.001 respectively) (**Figure 1**). In each model, the rates of MI and of death were higher in patients who had received RBC transfusion that in patients who were not transfused (**Supplemental figure 2**).

Ischaemic outcomes according to bleeding status

In the transfusion group, 85 patients (17.4%) experienced a TIMI major (65 patients) or minor (22 patients) bleed during follow up, versus 231 (1.9%) (19 TIMI major and 214 TIMI minor) in the non-transfused group.
Unadjusted outcomes according to bleeding status are presented in **Figure 2**. Patients transfused despite not having experienced a bleeding event had a higher risk of the primary endpoint than those with bleeding (HR 7.49 95%CI (5.97-9-41) vs. HR 3.20 95%CI (1.93-5.32)). After adjustment on model 1 (GRACE score), this excess risk persisted (HR 6.25 (4.91-7.95) vs HR 2.85 (1.70-4.80) p value for interaction 0.0066) (**Figure 2**). This increased

incidence of the primary endpoint was driven by an increased risk of recurrent MI in patients with transfusion (5.52 (4.05-7.53) vs 2.24 (1.11-4.55) p value for interaction 0.02) whereas there was no excess mortality risk (5.37 (3.80-7.60) vs 6.56 (3.35-12.82) p value for interaction 0.549) (**Supplemental figure 3**).
Within the transfused cohort, no difference in any antiplatelet cessation according to bleeding status was reported: 16 (19.3%) patients with bleeding vs. 81 (20.5%) patients without bleeding (p=0.80).

Ischaemic outcomes according to hemoglobin nadir

To further explore the association between RBC transfusion and risk of death and MI we stratified analyses according to the nadir of haemoglobin.
Unadjusted outcomes are presented in **Figure 3** and show worse ischaemic outcomes for patients who received transfusion but had the highest haemoglobin nadir (p interaction 0.0018).
After adjustment on GRACE score (model 1) and GRACE score and baseline hemoglobin (model 4), a graded association between blood transfusion and the primary endpoint was observed for patients with nadir of haemoglobin > 9.0 g/dl (p value for interaction 0.006 in model 1 and <0.0001 in model 2). Above a certain Hb value (Hb > 8.0 g/dl in model 1 and haemoglobin > 9 g/dl in model 2) RBC transfusion was associated with a higher risk of all cause death or MI (**Figure 3**). The two components of the primary endpoint are presented in **supplemental figures 4 and 5**. In model 1, the rates of recurrent non-fatal MI were significantly influenced by RBC transfusion (p value interaction 0.0009) while in model 2 both all-cause death and MI were independently associated with RBC transfusion (p 0.008 and p<0.001 respectively).
Within the transfused cohort, hemoglobin nadir was not associated with antiplatelet cessation (p=0.09).

Supplemental figure 6 presents the results adjusted on GRACE score, region, sex, AF, PAD history, smoking status body mass index, treatment with percutaneous coronary intervention and TAO trial allocated treatment (i.e. heparin and eptifibatide vs. otamixaban) showing similar results than in the main analysis.

Discussion

In the present analysis, RBC transfusion in NSTEMI patients was associated with increased risks of death and MI. This increase in ischemic events was mainly driven by patients transfused without overt bleeding and those with hemoglobin nadir > 9.0 g/dl.

In theory, RBC transfusion, because it quickly increases hemoglobin level, should increase oxygen delivery to ischemic myocardium and limit myocardial injury during the acute phase of MI. However, data suggest that RBCs have high oxygen affinity and low 2,3-diphosphoglycerate, and, as a consequence, oxygen delivery may in fact not be improved in patients receiving RBC transfusions (22, 23). In addition, during storage, packed RBCs are rapidly depleted of nitric oxide, leading to attenuation of physiologic vasodilation in hypoxic areas, impairment of erythrocyte function and deformability, and disruption of normal oxygen delivery in the microcirculation (24-26). There is also evidence of increased platelet reactivity resulting from RBC transfusion (27). Therefore, transfusion may actually be deleterious at least in some patients during acute coronary syndrome. There is a need to better understand whether RBC transfusion is associated with benefit or harm and in which types of patients.
Currently, both European and American guidelines recommend a restrictive approach to transfusion in patients with ACS which implies withholding transfusion if the hemoglobin level exceeds 7.0 g/dL to 8.0 g/dL (9, 10). However, few clinical data are available to support this recommendation. The only two randomized studies performed in this setting were underpowered (45 and 110 patients respectively) and showed conflicting results (28, 29). Currently available randomized data on blood transfusion in MI patients are therefore scarce and rely on very small datasets, precluding any definitive conclusion.

A recent meta-analysis of randomized trials examining optimal thresholds for RBC transfusion among inpatients with various conditions found no difference in 30 day mortality between liberal and restrictive transfusion strategies (30). However, the specific sub-analysis of the 2 small randomized trials in ACS patients showed a trend favouring liberal strategy (RR 3.88; 95% CI 0.83-18.13). This subanalysis only included 154 patients and is underpowered as attested by the large confidence interval. However, those data suggests that ACS might be a specific setting in which the balance of benefit and risk of transfusion may differ from other clinical situations and deserves to be analyzed separately.

Most of the available clinical evidence derives from observational data, which tend to support a restrictive rather than a liberal transfusion strategy in ACS (11, 12, 31, and 32). Three large meta-analyses of observational data, including both STEMI and NSTEMI patients, have concluded that RBC transfusion is associated with higher short and long-term mortality after ACS (11, 12, and 33). In 2 out of these 3 meta-analyses, RBC transfusion at hemoglobin below 8 g/dL appeared to be beneficial, and its use at hemoglobin above 10.0 g/dL was associated

with an increased risk of mortality (11, 33). One of the main hypotheses for such conflicting results is that both anemia and bleeding, which drive transfusion indications, are themselves associated with a worse prognosis in patients with MI, and confound the association of transfusion with outcomes (34). There might be some heterogeneity in the effect of transfusion in ACS patients according to different clinical characteristics. Recent observational data suggest worse outcome in patients with RBC transfusion only in case of STEMI but no difference in case of NSTEMI (8).

To the best of our knowledge, a differential effect of transfusion according to the presence of active bleeding has never been explored. In the present analysis, we observed that, in NSTEMI patients, RBC transfusion was associated with increased ischemic hazard mostly in patients without bleeding or with high hemoglobin levels. After statistical adjustment, we identified significant interaction between transfusion and bleeding, meaning that patients transfused without having experienced significant bleeding had a worse prognosis. Same results were observed with nadir of hemoglobin above 9.0 g/dl.

It is conceivable that in patient with active bleeding and lowest hemoglobin levels the balance between beneficial and deleterious effects of RBC transfusion is positive, whereas it is negative in others. A confounding component of the increased ischemic risk in the transfused group could be the need to discontinue antithrombotic drugs when bleeding or anemia occur. An increase in platelet reactivity combined with discontinuation in dual antiplatelet therapy could explain the higher risk for recurrent MI after transfusion (26, 27). In the present analysis, we observed a nearly four-time higher rate in antiplatelet cessation in patients receiving transfusion compared to non-transfused patients. This can at least partly explain the increased ischemic risk in transfused patients.

We observed, however, no differences in antiplatelet cessation in transfused patients according to bleeding or hemoglobin status. This suggests that the heterogeneity of outcomes observed in these subgroups is more likely related to the effect of transfusion than to the confounding component of antiplatelet cessation.

Patients undergoing surgical revascularization were excluded from this analysis. The question of transfusion in patients undergoing CABG has been specifically addressed in several adequately powered randomized trial and recent evidence is in favor of a restrictive RBC transfusion approach in this setting (18). In our cohort we observed that in the transfused cohort the majority of patients were treated medically. While, in the non-transfused cohort NSTEMI patients were more often treated invasively. Therefore, the occurrence of transfusion do impact the treatment strategy in acute coronary syndrome. Indeed, patients undergoing transfusion are more often managed medically.

Limitations

Although multivariable adjustment was used to correct for measured differences between the groups, we cannot exclude the presence of unmeasured confounders. It is important to

note that this study is a post hoc analysis, and our findings should therefore be interpreted as hypothesis-generating only. The indications for transfusion were not prespecified in TAO trial and varied across centers.
Patients with RBC transfusion were at higher baseline risk and had different antithrombotic regimen characterized by reduced use of aspirin and clopidogrel.
Consequently, only large randomized controlled trials will be able to address this issue definitively. Currently, 2 randomized trials are ongoing and will provide high quality evidence regarding optimal strategies for RBC transfusion in ACS patients. The REALITY (REstrictive And LIberal Transfusion Strategies in Patients With Acute mYocardial Infarction) trial (NCT02648113) is randomizing 630 ACS patients in a restrictive transfusion strategy (RBC transfusion if hemoglobin < 8.0 g/dl with objective 8.0 to 10.0 g/dl) vs. liberal strategy (RBC transfusion if hemoglobin < 10.0 g/dl with objective of 11.0 g/dl) (35) and will evaluate a 30-day composite of all-cause death, non-fatal stroke, nonfatal recurrent MI, and emergency revascularization. The MINT (Myocardial Ischemia and Transfusion) trial (NCT02981407) aims to randomize 3500 patients with MI and anemia to a restrictive (hemoglobin < 8.0 g/dl) vs. liberal strategy (hemoglobin < 10.0 g/dl) (36). The primary outcome will be a 30-day composite of all-cause mortality or nonfatal MI.

Conclusion

In patients with NSTEMI, RBC transfusion was associated with an increase of risk of death or MI at 180 days. This worse outcome appeared more pronounced in case of transfusion without overt bleeding and for hemoglobin level > 9.0 g/dl. This suggests that it may be prudent to refrain from RBC transfusion in those patients who do not have overt bleeding and have preserved hemoglobin levels. Randomized trials are required to better define patients who will benefit from RBC transfusion after a NSTEMI.

Acknowledgements: To our nurses' team and technicians in executing this study. To the TAO investigators.

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Table 1: Baseline characteristics and procedural characteristics of the population, according to transfusion status.

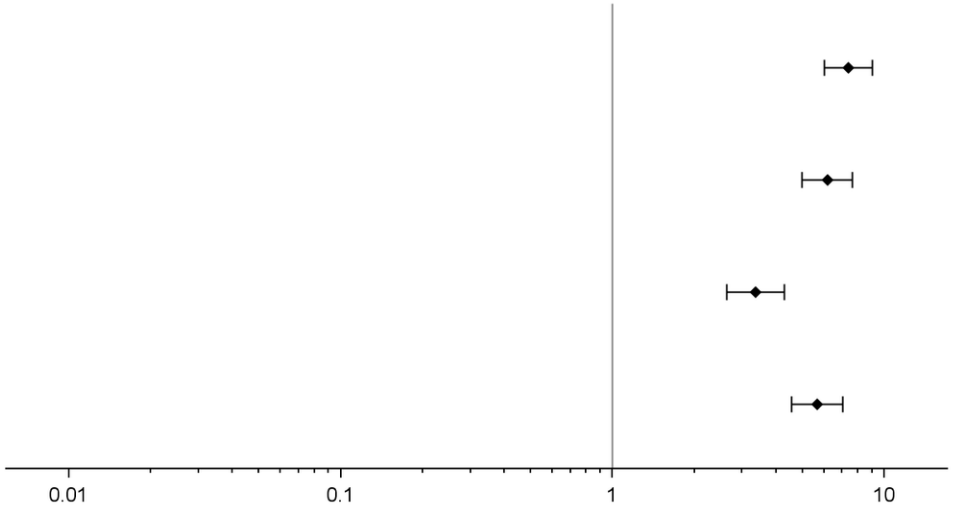
Figure 1: Unadjusted and adjusted hazard ratio of primary outcome at 180 days comparing transfused vs. not transfused patients (reference). Adjustment covariates are: GRACE score (model 1) GRACE score and nadir of hemoglobin (model 2) and GRACE score, Region, Sex, AF, PAD history, Smoking status (model 3). Transfusion status has been introduced as time varying covariate in the model.

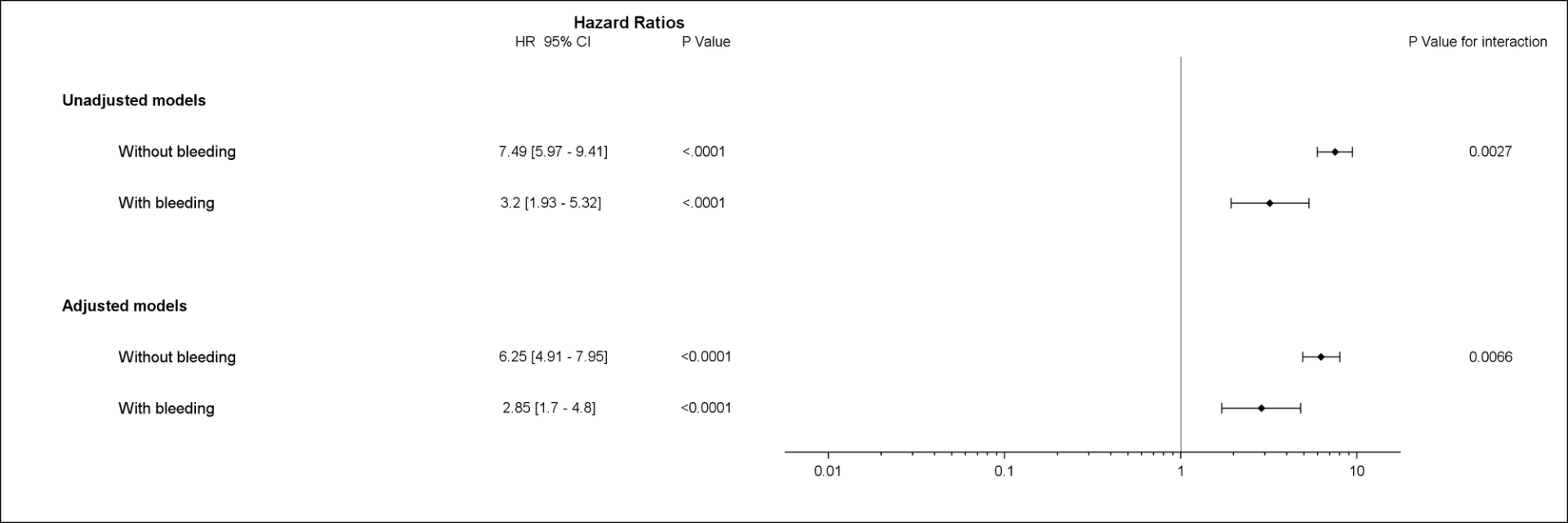
Figure 2: Unadjusted and adjusted hazard ratio of primary endpoint at 180 days comparing transfused vs. not transfused patients stratified by status of bleeding events occurring in the 7 days after randomization. Transfusion status has been introduced as time varying covariate in the model. The analysis was performed adjusted with GRACE score (model 1).

Figure 3: Unadjusted and adjusted hazard ratio of primary endpoint at 180 days comparing transfused vs. not transfused patients stratified by group of nadir of hemoglobin. Transfusion status has been introduced as time varying covariate in the model. The primary efficacy outcome, all cause death and non-fatal MI was analyzed until 180 days The analysis was performed adjusted with GRACE score (model 1) GRACE score and Baseline Hemoglobin (model 4)

Hazard Ratios

	HR 95% CI	P Value
Unadjusted	7.35 [6.00 - 9.01]	<0.0001
Model 1	6.17 [4.98 - 7.65]	<0.0001
Model 2	3.36 [2.63 - 4.29]	<0.0001
Model 3	5.65 [4.54 - 7.03]	<.0001




Hazard Ratios
HR 95% CI
P Value
P Value for interaction
Unadjusted models
Without bleeding
7.49 [5.97 - 9.41]
<.0001
0.0027
With bleeding
3.2 [1.93 - 5.32]
<.0001
Adjusted models
Without bleeding
6.25 [4.91 - 7.95]
<0.0001
0.0066
With bleeding
2.85 [1.7 - 4.8]
<0.0001
0.01
0.1
1
10

Hazard Ratios

	HR 95% CI	P Value	P Value for interaction
Unadjusted models			
nadir : <=70	2.87 [1.2 - 6.87]	0.0177	0.0018
nadir : 70 - 80	1.62 [0.78 - 3.37]	0.199	
nadir : 80 - 90	2.17 [1.28 - 3.68]	0.0041	
nadir : 90 - 100	2.98 [1.76 - 5.04]	<.0001	
nadir > 100	5.97 [3.77 - 9.44]	<.0001	
Adjusted models (1)			
nadir : <=70	2.51 [1.02 - 6.18]	0.0447	0.006
nadir : 70 - 80	1.32 [0.62 - 2.83]	0.4771	
nadir : 80 - 90	1.93 [1.12 - 3.32]	0.0187	
nadir : 90 - 100	3.49 [2.04 - 5.97]	<0.0001	
nadir > 100	5.29 [3.25 - 8.61]	<0.0001	
Adjusted models (2)			
nadir : <=70	1.87 [0.63 - 5.59]	0.2622	<0.0001
nadir : 70 - 80	1.31 [0.61 - 2.83]	0.4886	
nadir : 80 - 90	1.53 [0.84 - 2.81]	0.1667	
nadir : 90 - 100	4.01 [2.19 - 7.35]	<0.0001	
nadir > 100	6.8 [4.9 - 9.42]	<0.0001	

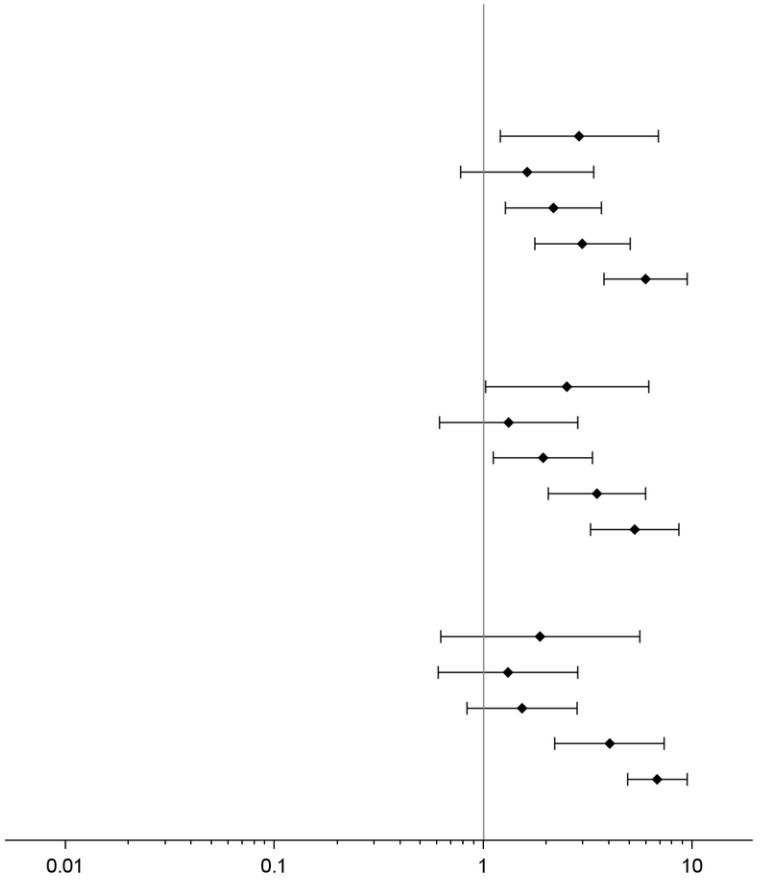


Table 1: Baseline characteristics and procedural characteristics of the population, according to transfusion status.

	No transfusion N= 12058	Transfusion N= 489	p-value
Clinical presentation:			
Age, mean (sd) y	61.66 (11.22)	66.22 (11.34)	<0.001
Body weight, mean (sd) kg	80.75 (16.7)	75.92 (15.7)	<0.001
Body mass index, mean (sd) , kg/m^2	28.26 (5.02)	27.7 (4.92)	0.007
Male gender, n (%)	8430 (69.9%)	279 (57.1%)	<0.001
Systolic BP, mean (SD), mmHg	131.88 (19.55)	132.13 (21.91)	0.941
Diastolic BP, mean (SD), mmHg	77.09 (11.95)	75.1 (13.53)	0.002
Heart rate, mean (SD), bpm	72.01 (12.92)	76.08 (14.5)	<0.001
Killip class, n (%):			<0.001
I	11218 (93.5%)	405 (82.8%)	
II	675 (5.6%)	63 (12.9%)	
III	98 (0.8%)	19 (3.9%)	
IV	10 (0.1%)	2 (0.4%)	
Cardiac arrest at admission, n (%)	70 (0.6%)	3 (0.6%)	0.930
Atrial fibrillation on first ECG, n (%)	268 (2.2%)	20 (4.1%)	<0.001
Region, n (%):			<0.001
North America	1455 (12.1%)	84 (17.2%)	
Western Europe	2365 (19.6%)	75 (15.3%)	
Eastern Europe	4185 (34.7%)	107 (21.9%)	
Asia	1054 (8.7%)	49 (10%)	
Other	2999 (24.9%)	174 (35.6%)	
Medical History, n (%):			
Coronary artery disease	4856 (40.3%)	238 (48.7%)	<0.001
Myocardial infarction	2324 (19.3%)	108 (22.1%)	0.124
Coronary artery bypass graft (CABG)	802 (6.7%)	48 (9.8%)	0.006
Percutaneous coronary intervention (PCI)	442 (3.7%)	19 (3.9%)	0.799
Stroke/TIA	617 (5.1%)	44 (9%)	<0.001
Peripheral arterial disease	556 (4.6%)	44 (9%)	<0.001
Carotid endarteriectomy/stenting	113 (0.9%)	9 (1.8%)	0.045
Congestive heart failure	609 (5.1%)	57 (11.7%)	<0.001
Hypertension	8499 (70.5%)	408 (83.4%)	<0.001
Hypercholesterolemia	6392 (53%)	271 (55.4%)	0.295
Diabetes mellitus	3315 (27.5%)	194 (39.7%)	<0.001
Current smoker	4098 (34%)	121 (24.7%)	<0.001
Family history of coronary artery disease (CAD)	3882 (32.2%)	153 (31.3%)	0.674
Alcohol habits: n (%):			<0.001
Never	6789 (56.4%)	337 (68.9%)	
At least monthly	2153 (17.9%)	67 (13.7%)	
At least weekly	1976 (16.4%)	50 (10.2%)	
At least daily	35 (7.2%)	35 (7.2%)	

Inclusion criteria, n (%):			
Biomarker elevation	10608 (88%)	434 (88.8%)	0.603
ECG changes	4836 (40.1%)	240 (49.1%)	0.003
GRACE risk score at baseline, n (%):			<0.001
<96	1675 (14.9%)	37 (7.9%)	
96 - 112	1989 (17.7%)	47 (10%)	
113 - 133	2996 (26.7%)	100 (21.2%)	
>133	4556 (40.6%)	287 (60.9%)	
TIMI risk score at baseline, n (%):			<0.001
0-2	3845 (31.9%)	97 (19.8%)	
3-4	5754 (47.7%)	258 (52.8%)	
5-7	2459 (20.4%)	134 (27.4%)	
Creatinine clearance, median (std), mL/min:	94.85 (36.61)	77.06 (35.74)	<0.0001
Anticoagulation during the PCI, n (%):			0.012
Unfractionnated Heparin + eptifibatide	5001 (41.5%)	170 (34.8%)	
Otamixaban 0.100	2414 (20%)	107 (21.9%)	
Otamixaban 0.140	4643 (38.5%)	212 (43.4%)	
Antiplatelet therapy received between randomization and discharge, n (%):			
Aspirin	11834 (98.1%)	462 (94.5%)	<0.001
Oral ADP receptor antagonist:			
Clopidogrel	10559 (87.6%)	371 (75.9%)	<0.001
Prasugrel	608 (5%)	10 (2%)	0.002
Ticagrelor	416 (3.4%)	14 (2.9%)	0.484
Other medications between randomization and discharge, n (%):			
Statins	11187 (92.8%)	450 (92%)	0.529
ACEI	9453 (78.4%)	367 (75.1%)	0.078
betablockers	9997 (82.9%)	426 (87.1%)	0.014
Mangement during the index admission, n (%):			
Percutaneous coronary intervention (PCI)	8474 (70.3%)	182 (37.2%)	<0.001
Neither PCI nor CABG	3584 (29.7%)	307 (62.8%)	<0.001
Duration of the index hospitalization, mean (sd) days	5.38 (3.38)	9.16 (7.88)	<0.001

GRACE: Global Registry of Acute Coronary Events; TIMI: Thrombolysis in Myocardial Infarction; ECG: electrocardiogram; ACEI: *angiotensin-converting-enzyme* inhibitor