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Association between postoperative haemoglobin concentrations and composite of non-fatal myocardial infarction and all-cause mortality in noncardiac surgical patients: *post hoc* analysis of the POISE-2 trial

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Abstract

Background: Myocardial infarction is the most common postoperative major vascular complication. Perioperative anaemia may contribute to cardiac supply–demand mismatch, and therefore myocardial injury. We therefore tested the hypothesis that the lowest in-hospital postoperative haemoglobin concentration is associated with a composite of non-fatal myocardial infarction and all-cause mortality within the first 30 days after noncardiac surgery.

Methods: We conducted a retrospective analysis of patients enrolled in the PeriOperative Ischemic Evaluation-2 (POISE-2) trial. We assessed the association between the lowest postoperative haemoglobin concentration during the initial hospitalisation and a composite of non-fatal myocardial infarction (Third Universal Definition) and all-cause mortality within 30 postoperative days, using a multivariable logistic regression model.

Results: We analysed 7227 patients from POISE-2, of whom 7.8% developed myocardial infarction; 1.5% died within 30 days. The composite primary outcome of non-fatal myocardial infarction and all-cause mortality occurred in 8.9% patients overall, ranging from 16% in patients with postoperative haemoglobin concentrations <88 g L^{-1} to 4.1% in patients with postoperative haemoglobin >113 g L^{-1}. After adjusting for baseline factors, in patients with a lowest postoperative haemoglobin concentration <110 g L^{-1}, each 10 g L^{-1} reduction in the lowest postoperative haemoglobin concentration was associated with a 1.46 (95% confidence interval: 1.37–1.56; $P<0.001$) fold increase in the odds of the composite outcome. In contrast, there was no significant relationship amongst patients with lowest postoperative haemoglobin concentration >110 g L^{-1}.

Conclusions: Postoperative anaemia may be a modifiable risk factor for non-fatal myocardial infarction and all-cause mortality.

Keywords: anaemia; anaesthesia; cardiovascular risk; haemoglobin; myocardial infarction; postoperative outcomes risk; surgery

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Editor's key points

- Perioperative anaemia may contribute to cardiac supply–demand mismatch, and therefore myocardial injury.
- The authors tested the hypothesis that the lowest in-hospital postoperative haemoglobin concentration is associated with a composite of non-fatal myocardial infarction and all-cause mortality within the first 30 days after noncardiac surgery, using data from the PeriOperative Ischemic Evaluation-2 (POISE-2) trial.
- The overall incidence of non-fatal myocardial infarction and all-cause mortality in 7227 patients ranged from 16% amongst patients with haemoglobin concentrations <88 g L^{-1} to 4.1% in those with haemoglobin >113 g L^{-1}.
- Using a multivariable logistic regression model, each 10 g L^{-1} reduction in the lowest haemoglobin concentration was associated with a 1.46 (95% confidence interval: 1.37–1.56) fold increase in the odds of the composite outcome.
- Postoperative anaemia may be a modifiable risk factor for non-fatal myocardial infarction and all-cause mortality.

Globally, more than 300 million patients have noncardiac surgery annually.[1] Mortality within 30 days of noncardiac inpatient surgery remains near 2%,[2–4] with cardiovascular events being the leading contributor.[3–6] In the UK, for example, the annual number of surgeries is around 5 million and 30-day mortality across both outpatient and inpatient operations is 1.1%.[7]

Myocardial infarction is the most common postoperative major vascular complication with an incidence of 6% during the first 30 postoperative days; infarctions at least triple 30-day mortality.[8,9] Myocardial infarctions after noncardiac surgery are probably mostly consequent to myocardial oxygen supply–demand mismatch.[10] Pre-existing cardiovascular disease is a strong predictor of myocardial infarction and death.[2,3] The only modifiable factor that is so far convincingly linked to myocardial injury or infarction after noncardiac surgery is hypotension.[11,12]

Perioperative anaemia is common and strongly associated with postoperative complications and mortality.[13,14] The lowest haemoglobin that individuals can tolerate depends largely on oxygen delivery to vital organs, which in turn depends on the oxygen-carrying capacity and regional perfusion.[15] The perioperative period presents special risk for organ oxygenation because patients have high metabolic demand as a result of surgical injury and consequent inflammation, and because cardiovascular function is often depressed by sedatives and analgesics. Tissue oxygenation is further reduced by anaemia consequent to surgical bleeding which reduces the oxygen-carrying capacity of blood.[15,16]

Current patient blood management guidelines advocate for a restrictive transfusion strategy with haemoglobin transfusion thresholds as low as 70 or 80 g L^{-1}, as there is no evidence that a liberal strategy reduces morbidity and mortality.[17,18] However, most postoperative myocardial infarctions are asymptomatic, meaning that most were probably missed in major anaemia threshold trials. It therefore remains plausible that low haemoglobin transfusion thresholds increase the incidence of acute coronary syndrome, mortality, or both in patients with cardiovascular disease.[16,19]

In our accompanying study,[20] we observed a strong association between postoperative anaemia and myocardial injury in noncardiac surgical patients at the Cleveland Clinic. Here, we report a similar analysis of patients who participated in the PeriOperative Ischemic Evaluation-2 (POISE-2) trial.[8,9] Specifically, we tested the primary hypothesis that the lowest in-hospital postoperative haemoglobin concentration was associated with a composite of non-fatal myocardial infarction and all-cause mortality within the first 30 days after noncardiac surgery.

Methods

Study participants

Our sub-study, based on de-identified data, was approved by the Cleveland Clinic Institutional Review Board with waived individual consent. Patients enrolled in the POISE-2 trial were considered for this *post hoc* observational analysis (ClinicalTrials NCT01082874).[8,9] A total of 10 010 noncardiac surgical patients from 23 countries, with or at risk for cardiovascular disease, were 2-by-2 factorially randomised to aspirin *vs* placebo and to clonidine *vs* placebo. Both study drugs were initiated before surgery (goal 2–4 h) and continued after surgery. The primary outcome was a composite of myocardial infarction and mortality within 30 postoperative days. Troponin measurements were done at 6 and 12 h after surgery and on postoperative days 1, 2, and 3. Patients were followed thorough their time in the hospital and contacted by phone at 30 days and 1 yr after randomisation. Patients, healthcare providers, data collectors, and outcome adjudicators were blinded to treatment allocation. Regular quality control checks were done to ensure data quality. The main results showed that aspirin did not reduce major cardiovascular outcomes, but significantly increased major bleeding from 3.7% to 4.6% {hazard ratio 1.2 (95% confidence interval [CI], 1.0–1.5); P=0.04}; aspirin had no direct effect on BP or HR.[8] Clonidine increased the risk of bradycardia and hypotension (1.32 [95% CI, 1.24–1.40]) but did not reduce the incidence of myocardial infarction.[9] There was no interaction between aspirin and clonidine.

Inclusion and exclusion criteria

All POISE-2 patients were included for analysis, other than those recruited from Cleveland Clinic sites as they were included in the companion analysis. We also excluded patients in whom postoperative haemoglobin concentrations were not recorded.[20]

Exposure of interest

The exposure of interest was the lowest haemoglobin concentration during the initial hospitalisation.

Primary outcome

The outcome was the same as for the main POISE-2 trial,[8,9] namely a collapsed composite of non-fatal myocardial infarction and all-cause mortality during the initial 30 days. The diagnosis of myocardial infarction was based on Third Universal Definition of Myocardial Infarction criteria

Table 1 Baseline characteristics stratified by quartiles of lowest haemoglobin groups during hospital stay (N=7227). Summary statistics are presented as mean (standard deviation), median [Q1, Q3], or median (minimum, maximum) for continuous variables, and N (%) for categorical variables. Intraoperative hypotension was defined as recorder of a systolic BP <100 mm Hg.

	<88 g L^{-1} (n=1831)	88–100 g L^{-1} (n=1791)	101–113 g L^{-1} (n=1757)	>113 g L^{-1} (n=1848)
Age (yr)	73 (45–102)	72 (45–97)	71 (45–95)	68 (45–93)
Body mass index (mg kg^{-2})	29 (7)	30 (8)	30 (7)	30 (7)
Female (%)	1040 (57)	961 (54)	863 (49)	605 (33)
Smoking history (%)	372 (20)	401 (22)	437 (25)	631 (34)
Coronary artery disease (%)	345 (19)	364 (20)	343 (20)	450 (24)
Treated diabetes (%)	644 (35)	667 (37)	674 (38)	696 (38)
Peripheral vascular disease (%)	164 (9)	174 (10)	155 (9)	187 (10)
Congestive heart failure (%)	66 (4)	62 (3)	36 (2)	52 (3)
Hypertension (%)	1601 (87)	1552 (87)	1519 (86)	1570 (85)
Stroke (%)	109 (6)	90 (5)	68 (4)	104 (6)
Ischemic attack (%)	71 (4)	69 (4)	68 (4)	72 (4)
Creatinine >175 μmol L^{-1} (%)	117 (6)	56 (3)	42 (2)	16 (0.9)
Baseline haemoglobin (g L^{-1})	121 [108, 132]	129 [117, 139]	135 [126, 144]	144 [134, 153]
Major vascular surgery (%)	107 (6)	104 (6)	116 (7)	129 (7)
Major surgery (%)	1575 (86)	1520 (85)	1458 (83)	1352 (73)
Urgent/emergency surgery (%)	143 (8)	118 (7)	98 (6)	133 (7)
Surgery duration (h)	2 [2, 4]	2 [1, 3]	2 [2, 3]	2 [1, 3]
Intraoperative hypotension (%)	1261 (69)	1152 (64)	1171 (67)	1117 (60)
Randomised treatment (%)				
Aspirin	465 (25)	437 (24)	455 (26)	445 (24)
Clonidine	429 (23)	416 (23)	454 (26)	494 (27)
Clonidine+aspirin	460 (25)	458 (26)	446 (25)	438 (24)
Placebo	477 (26)	480 (27)	402 (23)	471 (25)

(Supplementary Table S1),[21] and verified by central adjudication. The earliest clear diagnostic feature for myocardial infarction was considered to be the onset time. Mortality was defined as any death during the initial 30 days after noncardiac surgery, regardless of the apparent cause.

Statistical analysis

Analyses were based on an *a priori* detailed protocol and statistical analysis plan that was approved by our Institutional Review Board before data were accessed for this purpose. Patients were divided into quartiles based on lowest haemoglobin concentration for purposes of data presentation: <88 g L^{-1}, 88–100 g L^{-1}, >101–113 g L^{-1}, and >113 g L^{-1}.

We used a multivariable logistic regression model to assess the association between lowest haemoglobin during hospital stay as a continuous variable and the composite of myocardial infarction and all-cause mortality within 30 days of surgery. We adjusted for potential confounding variables recorded in the POISE-2 case report that may affect the primary outcome (Table 1) in all models. POISE-2 included patients with or at cardiovascular risk, thus we have information about cardiovascular risk factors (age, BMI, smoking, coronary artery disease, treated diabetes, peripheral vascular disease, congestive heart failure, hypertension, stroke and ischemic attack) creatinine, baseline haemoglobin, major surgery or major vascular surgery, and urgent/emergent surgery. We also added the duration of the surgery and the intraoperative hypotension defined as systolic BP<100 mm Hg. Unfortunately, blood loss was not available. Missing values of confounders, where missing rate is lower than 5%, were imputed from multivariate normal distribution. All analyses were based on this single imputation dataset.

Because the relationship between haemoglobin concentration and the probability of myocardial infarction and all-cause mortality could be non-linear, we first plotted the raw relationship between probability of myocardial infarction and all-cause mortality within the range of haemoglobin concentrations. We then added a cubic spline term with knots at the 10th, 50th, and 90th percentiles to the regression model. If we observed a non-linear trend, we would consider adding a spline term of lowest haemoglobin to improve the model fitting. Otherwise, we would fit a logistic regression model with haemoglobin as linear term.

Sensitivity analysis

As a sensitivity analysis, we performed the primary analysis but excluded the patients whose lowest haemoglobin was recorded after infarction. As a further sensitivity analysis, we also assessed the association between the change of haemoglobin, defined as minimum postoperative haemoglobin minus the preoperative haemoglobin, and the composite outcome.

Sample size estimation

Among 10010 patients randomised in POISE-2, we expected that about 8000 would meet inclusion criteria. We expected a composite incidence of about 7% during the initial 30 days after noncardiac surgery. This provided 80% power to detect an odds ratio of 1.1 or greater for 10 g L^{-1} change in haemoglobin concentration at the 0.05 significance level, assuming that the distribution of haemoglobin had a standard deviation of 20 g L^{-1}.

Results

Participants

Among 10010 patients enrolled in the POISE-2 trial, we excluded 993 who were recruited from Cleveland Clinic sites,

as they were included in the companion analysis. We further excluded 1790 patients in whom postoperative haemoglobin concentrations were not recorded (Fig. 1).

Among those 7227 patients included in the analysis, only 429 patients had haemoglobin concentrations exceeding 130 g L^{-1}, representing just 5.9% of the entire population. In contrast, 4029 (56%) of patients had haemoglobin concentrations less than 110 g L^{-1}, and 960 (13%) had concentrations less than 80 g L^{-1}. Clinical characteristics, including details on surgical procedures, were divided by quartiles of lowest postoperative haemoglobin for display purposes (Table 1).

Primary outcome

The overall incidence of non-fatal myocardial infarction and all-cause mortality was 8.9%. A total of 562 (7.8%) patients had a myocardial infarction; 107 (1.5%) died within 30 days of surgery. Amongst patients in the lowest quartile of haemoglobin concentrations (<88 g L^{-1}), the incidence of non-fatal myocardial infarction, all-cause mortality, or both was 301 (16%). The incidence of the composite outcome was 149 (8.3%) in patients whose lowest haemoglobin was 88–100 g L^{-1}, 103 (5.9%) in those with haemoglobin 101–113 g L^{-1}, and 76 (4.1%) in those with haemoglobin concentrations >113 g L^{-1} (Table 2). Patients with low minimum haemoglobin concentrations had higher probabilities of non-fatal myocardial infarction/all-cause mortality (Fig. 2).

Multivariable logistic regression analyses

The adjusted relation between lowest haemoglobin concentration and the composite of 30-day myocardial infarction and all-cause mortality was non-linear (Fig. 3). We therefore added a linear spline term at 110 g L^{-1} which allowed us to differentially quantify the relationship in patients with the lowest haemoglobin concentrations above and below 110 g L^{-1}. After adjusting for baseline factors presented in Table 1, each 10 g L^{-1} reduction in lowest haemoglobin concentration was associated with a 1.46 (95% CI: 1.37–1.56; $P<0.001$) increase in the odds of the composite outcome in patients with a lowest haemoglobin concentration <110 g L^{-1}. In contrast, there was no significant relationship amongst patients with a lowest haemoglobin concentration that exceeded 110 g L^{-1} (odds ratio [OR]=0.99, 95% CI: 0.91–1.09; $P=0.87$>) (Table 2).

Considering that linear relationships are more robust than piece-wise linear models, we assessed the overall linear association between haemoglobin and the outcome as an alternative method. A 10 g L^{-1} decrease was significantly associated with higher odds of the composite outcome (OR: 1.35 [95% CI: 1.27–1.43]; $P<0.001$). In *post hoc* analysis of each component, we found that lowest haemoglobin was significantly associated with both myocardial infarction and mortality in patients with a lowest haemoglobin concentration <110 g L^{-1}, but not in patients with the concentrations >110 g L^{-1} (Supplementary Table S2). The total transfusion-adjusted association was similar to the original analysis: odds ratio of myocardial infarction/mortality associated with 10 g L^{-1} decrease in haemoglobin was 1.31 (95% CI: 1.21–1.42; $P<0.001$) for Hb<110 g L^{-1} and 1.01 (95% CI: 0.89–1.13; $P=0.92$) for Hb>110 g L^{-1}. The interaction between haemoglobin and total transfusion was not significant ($P=0.92$) (Supplementary Table S3).

Sensitivity analysis

We excluded 243 patients in whom the lowest haemoglobin was measured after myocardial infarction. Low haemoglobin concentrations remained associated with higher risk for the composite of myocardial injury and all-cause mortality in patients with a lowest haemoglobin concentration less than 110 g L^{-1} (OR=1.37, 95% CI: 1.27–1.48; $P<0.001$), a relationship not observed for patients with higher haemoglobin concentrations (Supplementary Table S4). As a further sensitivity analysis, we assessed the association between the change of haemoglobin, defined as minimum postoperative haemoglobin minus the preoperative haemoglobin, and the composite outcome. As shown in Supplementary Figure S1, the adjusted relationship was similar to the one presented in Figure 3. The overall odds ratio of myocardial infarction/mortality associated with 10 g L^{-1} decrease in the change of haemoglobin is 1.17 (95% CI: 1.11–1.22; $P<0.001$), adjusted for variables listed in Table 1.

Discussion

We found that the association between lowest haemoglobin and the composite of 30-day myocardial infarction and all-cause mortality was non-linear, with a significant increase in the risk when haemoglobin concentrations were below 110 g L^{-1}, but no relationship at higher concentrations. Below the

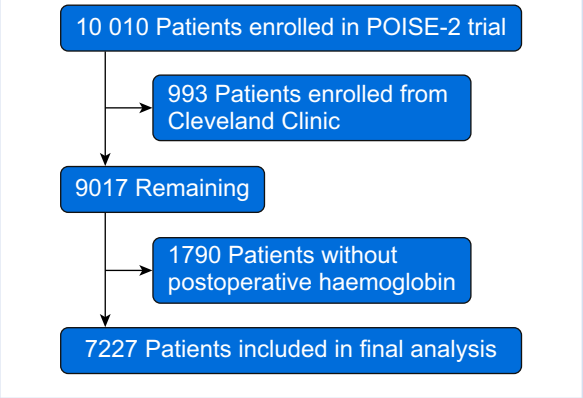

Fig 1. Study flow diagram. POISE-2, PeriOperative Ischemic Evaluation-2.

Table 2 Association between minimum postoperative haemoglobin concentration and myocardial infarction or death. *Odds ratio for 10 g L^{-1} decrease in minimum haemoglobin was estimated from a logistic regression model adjusted for variables listed in Table 1. Minimum haemoglobin was modelled as two-piece linear terms with a changing point at 110 g L^{-1}. CI, confidence interval; MI, myocardial infarction.

Minimum haemoglobin	Incidence of MI/death	Estimated odds ratio* (95% CI)	P
≤110 g L^{-1}	528/4989	1.46 (1.37–1.56)	<0.001
>110 g L^{-1}	101/2238	0.99 (0.91–1.09)	0.87

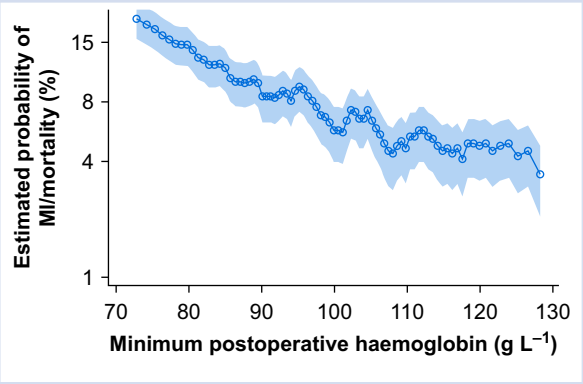

Fig 2. Adjusted probability of 30-day myocardial infarction (MI) or mortality estimated using the moving average method. Each bin contains 723 patients and is moved in 80-patient increments.

threshold of 110 g L^{-1}, there was a 46% increase in the combined odds of myocardial infarction and all-cause mortality for each 10 g L^{-1} decrease in haemoglobin. Cleveland Clinic data from an accompanying study showed a 29% hazard increase of myocardial injury after noncardiac surgery (MINS) for a 10 g L^{-1} decrease in haemoglobin concentration.[20] However, the curve was roughly linear throughout the entire range without a defined cut-off as observed in the POISE-2 data (compare Fig. 3 here with the acompanying article).

There is only scarce evidence about the cardiovascular risks of postoperative anaemia after noncardiac surgery. The largest trial, Carson and colleagues,[22] included 2000 patients who were randomised to be transfused when haemoglobin concentrations were less than 80 g L^{-1} or to transfusions as needed to keep haemoglobin at least 100 g L^{-1}. There were no

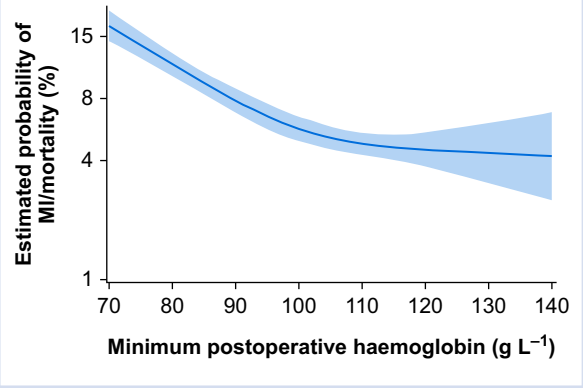

Fig 3. Adjusted relationship between lowest postoperative haemoglobin and a collapsed composite of 30-day myocardial infarction (MI) or mortality. The solid line represents predicted probability of the composite outcome, and the shaded area indicates the 95% confidence intervals around the prediction. The change in the slope shows that the relationship was non-linear: the risk of the composite was similar at haemoglobin concentrations exceeding 110 g L^{-1}, whereas risk of the composite increased at lower concentrations.

differences in mortality (primary outcome) or a composite of myocardial infarction, unstable angina, and death (secondary outcome). However, the observed incidence of composite of in-hospital myocardial infarction, unstable angina, or death was 4.3% *vs* 5.2% and the trial was not powered to detect the cardiovascular effects of this relatively small difference. More importantly, patients were randomised between postoperative days 1 and 3, although there is now strong evidence that nearly all myocardial injury occurs during the first two postoperative days.[3,4] Additionally, the composite of myocardial infarction, unstable angina, and death was censored to hospital discharge, whereas in POISE-2 >99% of trial data were obtained through 30 days after surgery.[8,9] Consequently, many mortality events—which occur at a median of 14 days after surgery—may have been missed by Carson and colleagues.[22]

There are also two small trials that assessed the effect of anaemia on patients with acute coronary syndrome, but their conclusions differed.[19,23] In a pilot trial of 110 patients, Carson and colleagues[19] found that restrictive transfusion strategies (haemoglobin <80 g L^{-1}) doubled the incidence of a composite of mortality, myocardial infarction, and unscheduled revascularisation from 11% to 26% compared with maintaining haemoglobin ≥100 g L^{-1}. In contrast, Cooper and colleagues[23] evaluated 45 patients who had postoperative myocardial infarctions and found that liberal transfusion increased the incidence of 30-day mortality, myocardial injury, and congestive heart failure.[23] The results of each of these studies are fragile because they included few patients who had few outcome events.[24,25]

Our conclusions from this analysis of POISE-2 data are consistent with our accompanying analysis of 4550 Cleveland Clinic noncardiac surgical inpatients. In that analysis, each 10 g L^{-1} decrease in the lowest postoperative haemoglobin concentration was associated with 29% higher risk of MINS, defined as at least one fourth-generation troponin T plasma concentration measurement ≥0.03 ng ml^{-1} during the hospital stay or within 3 days, whichever came first, judged to be of an ischaemic origin. The overall incidence of MINS was 3.9%, ranging from 0% among patients with minimal postoperative haemoglobin concentrations exceeding 130 g L^{-1} to 9.2% in patients with minimal haemoglobin concentrations <80 g L^{-1}. Important differences between the analyses include: (1) the POISE-2 dataset is substantially larger and represents 135 hospitals in 23 countries; (2) patients in the POISE-2 dataset reliably had troponin testing the day of surgery and on the first 3 postoperative days while patients remained hospitalised; (3) the Cleveland Clinic patients had haemoglobin recorded frequently (usually daily), whereas only the lowest postoperative haemoglobin was recorded for POISE-2 patients; and (4) the outcome in the Cleveland Clinic analysis was myocardial injury (troponin elevation with or without symptoms or signs of cardiac ischaemia) where in POISE-2 it was a composite of myocardial infarction (by Third Universal Definition[21] criteria) and death. The two studies therefore complement each other because exposure was better characterised in the Cleveland Clinic patients, whereas outcomes were better characterised in the POISE-2 patients. Analysis of both datasets therefore provides a more complete understanding of the relationship between anaemia and myocardial injury.

Postoperative anaemia may be especially harmful because surgery provokes an ongoing inflammatory response which increases metabolic demand. Additionally, some postoperative analgesics depress cardiorespiratory function.

Desaturation[26] and hypotension[27,28] after surgery are common, and frequently prolonged, yet are rarely detected with routine intermittent vital sign monitoring. Cardiac (and other organ) supply–demand mismatch may be further aggravated by concomitant anaemia. Hypotension or desaturation in anaemic patients is thus presumably more detrimental than either condition alone.

The major limitation of our analysis is that POISE-2 was a pragmatic trial in which only the date and value of the lowest postoperative haemoglobin concentration were recorded. However, results were similar in a sensitivity analysis that excluded patients whose lowest haemoglobin was recorded after myocardial infarction. Furthermore, changes in haemoglobin during the late postoperative period are usually small compared with the range of changes observed in the early postoperative period. Moreover, it is encouraging that results were similar in the accompanying analysis in which haemoglobin concentrations were better characterised.

As in any observational analysis, unobserved confounding may distort our results. We used a composite of myocardial infarction and all-cause mortality as the primary outcome because that was the primary outcome for the underlying POISE-2 trial.[29] However, analysis of each component separately was concordant with the primary analysis.

In summary, lowest haemoglobin and the composite of 30-day myocardial infarction and all-cause mortality were non-linearly associated, with a significant increase in the risk when the haemoglobin concentrations were below 110 g L^{-1}. Pre-existing cardiovascular risk factors[3] are the strongest predictors of myocardial infarction after noncardiac surgery, with perioperative hypotension being the best documented modifiable factor. Our results suggest that haemoglobin is an additional potentially modifiable risk for non-fatal myocardial infarction and all-cause mortality, especially in patients with or at risk of cardiovascular disease. As with hypotension, the extent to which the relationship is causal, and thus amenable to intervention, remains unknown.

Authors' contributions

Study design: AT, ER, MB, GM, BC
Data collection: AT, ER, PJD
Data interpretation, manuscript writing: all authors
Data analysis: GM, XP, KL
All the authors meet all of the following four conditions:

- Substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data;
- Drafting the article or revising it critically for important intellectual content;
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.08.054.

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