Bleeding Impacting Mortality after noncardiac Surgery: A protocol to establish diagnostic criteria, estimate prognostic importance, and develop and validate a prediction guide in an international prospective cohort study.

Journal:	*CMAJ Open*
Manuscript ID	CMAJOpen-2016-0106
Manuscript Type:	Protocol
Date Submitted by the Author:	11-Aug-2016
Complete List of Authors:	Roshanov, Pavel; London Health Sciences Centre London Kidney Clinical Research Unit; McMaster University, Clinical Epidemiology and Biostatistics Eikelboom, John; McMaster University, Medicine Crowther, Mark A.; McMaster University, Medicine Tandon, Vikas; McMaster University, Medicine Borges, Flavia; Population Health Research Institute; McMaster University, Medicine Kearon, Clive; McMaster University, Medicine Lamy, Andre; McMaster University, Surgery Whitlock, Richard; McMaster University, Biccard, Bruce; Groote Schuur Hospital, Anaesthesia and Perioperative Medicine Szczeklik, Wojciech; Uniwersytet Jagiellonski w Krakowie Collegium Medicum, Intensive Care and Perioperative Medicine Guyatt, Gordon; McMaster University, Clinical Epidemiology and Biostatistics Panju, Mohamed; McMaster University, Medicine Spence, Jessica; Population Health Research Institute; McMaster University, Anesthesia Garg, Amit X.; University of Western Ontario, Kidney Clinical Research Unit; McGillion, Michael ; McMaster University, School of Nursing VanHelder, Tomas; McMaster University, Anesthesia Kavsak, Pete; McMaster University, Pathology and Molecular Medicine DeBeer, Justin; McMaster University, Department of Surgery Winemaker, Mitchell; McMaster University, Sessler, Daniel; Cleveland Clinic, Department of Outcomes Research Le Manach, Yannick; McMaster University, Anesthesia; Population Health Research Institute Sheth, Tej; McMaster University, Medicine Pinthus, Jehonathan; McMaster University, Surgery Thabane, Lehana; McMaster University, Clinical Epidemiology and Biostatistics Simunovic, Marko R. I.; Juravinski Cancer Centre, Surgical Oncology; Mizera, Ryszard; McMaster University, Medicine Ribas, Sebastian; McMaster University, Medicine Devereaux, PJ; Population Health Research Institute, ; McMaster University, Departments of Clinical Epidemiology and Biostatistics and Medicine

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Keywords:	Anesthesia and analgesia, Surgery, Epidemiology
More Detailed Keywords:	bleeding, perioperative medicine, transfusion
Abstract:	Introduction: Perioperative studies have used varying definitions of bleeding without systematically assessing their independent association with outcomes important to patients. Here we define Bleeding Impacting Mortality after noncardiac Surgery (BIMS) as bleeding that is independently associated with death during or within 30 days after noncardiac surgery. We describe our protocol to 1) establish the diagnostic criteria for BIMS, 2) estimate the independent contribution of BIMS to 30-day mortality, and 3) develop and internally validate a clinical prediction guide to estimate patient-specific risk of BIMS. Methods: In the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) study (ClinicalTrials.gov NCT00512109), we prospectively collected bleeding data in 16,079 patients ≥45 years old who had inpatient noncardiac surgery between 2007 and 2011 at 12 centres in eight countries across 5 continents. We will include bleeding features independently associated with 30-day mortality in the diagnostic criteria for BIMS. Candidate features will include the need for reoperation due to bleeding, the number of units of red blood cells transfused, the lowest postoperative hemoglobin, and the absolute and relative decrements in hemoglobin from the preoperative value. We will estimate the incidence of BIMS and its independent association with 30-day mortality, and construct and internally validate a clinical prediction guide for BIMS. Interpretation: This study will address an important gap in our knowledge about perioperative bleeding with implications for the 300 million patients who undergo noncardiac surgery globally every year.

Bleeding **I**mpacting **M**ortality after noncardiac **S**urgery: A protocol to establish diagnostic criteria, estimate prognostic importance, and develop and validate a prediction guide in an international prospective cohort study.

Pavel S. Roshanov M.D. M.Sc.,[1§] John W. Eikelboom M.B.B.S.,[2,3] Mark Crowther M.D. M.Sc.,[4] Vikas Tandon M.D.,[2] Flavia K. Borges M.D. PhD.,[2,3] Clive Kearon M.D. Ph.D.,[2,5] Andre Lamy M.D. M.HSc.,[3,6,7] Richard Whitlock M.D. PhD.,[3,6] Bruce M. Biccard Ph.D.,[8] Wojciech Szczeklik M.D. Ph.D.,[9] Gordon H. Guyatt M.D. M.Sc.,[7] Mohamed Panju M.D. M.Sc.,[2] Jessica Spence M.D.,[3,10] Amit X. Garg M.D. Ph.D.,[1,11] Michael McGillion R.N. Ph.D.,[3,12,13] Tomas VanHelder M.D. Ph.D.,[10] Peter A. Kavsak Ph.D.,[4] Justin de Beer M.D.,[6] Mitchell Winemaker M.D.,[6] Daniel I. Sessler M.D.,[14] Yannick Le Manach M.D. Ph.D.,[3,7,10] Tej Sheth M.D.,[2] Jehonathan H. Pinthus M.D. Ph.D.,[6] Lehana Thabane Ph.D.,[7,15] Marko R. I. Simunovic M.D. M.P.H.,[6,7] Ryszard Mizera M.D.,[2] Sebastian Ribas M.D.,[2] P.J. Devereaux M.D. Ph.D.,[2,3,7] on behalf of the VISION Investigators

Affiliations
1. Lilibeth Caberto Kidney Clinical Research Unit, London Health Sciences Centre, London, ON, Canada
2. Department of Medicine, McMaster University, Hamilton, ON, Canada
3. Population Health Research Institute, Hamilton, ON, Canada
4. Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada
5. Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada
6. Department of Surgery, McMaster University, Hamilton, ON, Canada
7. Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada
8. Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital, Observatory, South Africa and University of Cape Town, South Africa
9. Department of Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Maloposka Province, Poland
10. Department of Anesthesia, McMaster University, Hamilton, ON, Canada
11. Institute for Clinical Evaluative Sciences at Western, London, ON, Canada
12. Faculty of Health and Life Sciences, Coventry University, Coventry, United Kingdom
13. School of Nursing, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada
14. Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio
15. Biostatistics Unit, St. Joseph's Healthcare, Hamilton, ON, Canada

[§]**Corresponding author:** Pavel S. Roshanov
Address: Lilibeth Caberto Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario, Canada N6A 4G5
Email: roshanp@mcmaster.ca
Tel: 519-685-8502
Fax: 519-685-8072

1

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Perioperative studies have used varying definitions of bleeding without systematically assessing their independent association with outcomes important to patients. Here we define **B**leeding **I**mpacting **M**ortality after noncardiac **S**urgery (BIMS) as bleeding that is independently associated with death during or within 30 days after noncardiac surgery. We describe our protocol to 1) establish the diagnostic criteria for BIMS, 2) estimate the independent contribution of BIMS to 30-day mortality, and 3) develop and internally validate a clinical prediction guide to estimate patient-specific risk of BIMS.

Methods: In the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) study (ClinicalTrials.gov NCT00512109), we prospectively collected bleeding data in 16,079 patients ≥45 years old who had inpatient noncardiac surgery between 2007 and 2011 at 12 centres in eight countries across 5 continents. We will include bleeding features independently associated with 30-day mortality in the diagnostic criteria for BIMS. Candidate features will include the need for reoperation due to bleeding, the number of units of red blood cells transfused, the lowest postoperative hemoglobin, and the absolute and relative decrements in hemoglobin from the preoperative value. We will estimate the incidence of BIMS and its independent association with 30-day mortality, and construct and internally validate a clinical prediction guide for BIMS.

Interpretation: This study will address an important gap in our knowledge about perioperative bleeding with implications for the 300 million patients who undergo noncardiac surgery globally every year.

2

Introduction

More than 300 million people undergo major surgery worldwide each year(1). Prior studies have associated perioperative bleeding with higher risk of postoperative death and complications, longer hospital stay, and higher healthcare costs(2–4). Studies use varying definitions of bleeding(5,6). Consensus definitions were developed without systematically assessing the diagnostic criteria for their independent association with poor patient outcomes(7).

There is value in establishing diagnostic criteria for **B**leeding **I**mpacting **M**ortality after noncardiac **S**urgery (BIMS). Our proposed definition of BIMS is bleeding that independently increases patients' 30-day probability of death and occurs either during or in the 30 days following noncardiac surgery. We propose methods to establish diagnostic criteria for BIMS in the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) cohort study to determine: 1) the diagnostic criteria for BIMS, 2) its incidence, prognostic impact and population attributable risk fraction with respect to 30-day mortality, and 3) to create a clinical prediction guide to estimate patient-specific risk of BIMS.

Methods

Figure 1 summarizes the flow of participants through the study. **Figure 2** summarizes the methods described in this protocol. We will use Stata MP version 13.1 (College Station, Texas) and R version 3.3 (R Development Core Team) with the *-rms-* package(8) for all analyses.

Study design

We will analyze data from the VISION study—a prospective international cohort study— that included 16,079 patients from 12 centres in eight countries (throughout North and South

America, Australia, Asia, and Europe) recruited from August 2007 to January 2011 (ClinicalTrials.gov NCT00512109). Previous reports have described VISION enrollment and data collection(9–11). Briefly, participants ≥45 years old who had inpatient noncardiac surgery (i.e., with planned overnight stay) were screened and, if eligible and consenting, answered a series of questions regarding their past medical, surgical, and social history. Study personnel reviewed medical charts for additional history. Throughout each patient's hospital stay, research personnel performed clinical evaluations, reviewed medical records, and noted outcome events. A follow-up telephone interview was conducted with the patient or their caregiver 30 days after surgery. If the patient interview indicated the occurrence of an outcome, their primary care physicians were contacted to obtain further documentation.

Data monitoring involved central data consistency checks, statistical monitoring, and on-site monitoring for all centres. For on-site monitoring, the central coordinator randomly selected participants with and without a perioperative complication and an on-site monitor then audited patient's medical records and all other supporting documents.

Sample size and completeness of study data

We completed 30-day follow-up for 99.7% of 16,079 patients; the other 53 patients (0.3%) did not die within 30-days of surgery and were censored at the time of hospital discharge.

The protocol is divided into three objectives. We have stated the sample size and missing data separately for each objective in **Figure 1**. Where specified, we will impute missing data using single stochastic conditional imputation with predictive mean matching(12) for continuous variables and augmented logistic regression(13) for binary variables, both with fully conditional specification(14). **Box 1** lists all variables to be included in the imputation model. Single stochastic imputation is much more practical for our analysis than multiple imputation and, with

4

little missing data, its drawback—slightly more narrow confidence intervals—will be negligible(15).

Objective 1: Establish the diagnostic criteria for BIMS.

We will restrict the analysis for Objective 1 to 5,476 patients who experienced a bleeding event captured in VISION to better protect against residual confounding and time-dependent biases (16). Among these patients 165 died within 30 days of surgery. VISION defined bleeding broadly to avoid missing prognostically important bleeding events. The definition included all bleeding that resulted in a drop in hemoglobin of at least 30 g/L, or led to a transfusion of blood products or reoperation, or were thought to be the immediate cause of death. If a patient experienced more than one bleeding episode throughout the first 30 days after surgery, we will evaluate only the first episode in all analyses.

The diagnostic criteria for BIMS should, among people who experience a bleed, identify as many patients as possible who will die as a consequence of the bleed within 30 days of surgery and exclude as many patients as possible who will not die within this period.

We will consider five candidate features for inclusion in the diagnostic criteria in the order listed: 1) reoperation for reasons of bleeding, 2) number of units of red blood cells transfused, 3) the lowest (nadir) postoperative hemoglobin, 4) the absolute drop in hemoglobin from the preoperative value, and 5) the relative drop in hemoglobin from the preoperative value. The features that are least subjective and easiest to ascertain will be tested first, to ensure that they have a greater chance to become part of the BIMS diagnostic criteria compared to less practical correlated candidate features that are similarly associated with mortality. Bleeding was suspected by the clinical team to be the direct cause of death in some patients; this feature will be included in the diagnostic criteria without statistical testing.

We will model the association between 30-day mortality and candidate BIMS criteria using shared (by study centre) frailty multivariable Cox proportional hazards regression models adjusted for preoperative patient characteristics, surgical factors (type and timing of surgery), and other postoperative complications (**Table 1**). We selected these adjustment variables on the basis of previous VISION work that has identified variables independently associated with mortality among all patients, with the assumption that the same factors are associated with mortality in patients who have experienced a VISION bleed(10).

We will also adjust for postoperative complications including sepsis, pulmonary embolism, stroke, and myocardial injury after noncardiac surgery (MINS) (10) that occurred on a day before the day of a bleeding event, but not those that occurred on the same day or in the days after the bleeding event because BIMS may cause these complications directly (e.g., MINS due to supply-demand mismatch from a low hemoglobin) or indirectly (e.g., pulmonary embolism due to BIMS that resulted in the withdrawal of an anticoagulant; sepsis through prolongation of hospital stay and exposure to additional interventions). Adjusting for complications that BIMS may have caused would underestimate the association between a candidate feature and mortality(17).

Figure 3 summarizes the criteria selection algorithm. This is an iterative process that begins with a baseline model in which the explanatory variables include only the adjustment variables. Candidate features are added to the baseline model, one at a time, in the order described in **Table 1**. We will test the statistical significance of this feature (adjusted for the other variables in the model) using a likelihood ratio test. If this test produces a $p \geq 0.05$, we will consider the candidate feature not to be an independent predictor of mortality and it will no longer be considered for inclusion in the BIMS criteria. The next candidate feature replaces it

6

and is tested in the same way. If, instead, this test produces a p<0.05, the candidate feature will

be considered to be a proven independent predictor of mortality and will be retained in the

model. When subsequent candidate features are tested, they will be compared to the model that

contains already-proven features and the adjustment variables.

To simplify integration of continuous variables into the diagnostic criteria (e.g. number of

red blood cell units transfused), they will be dichotomized at thresholds according to **Table 1** and

a dichotomous version representing each threshold will be tested in the model. The threshold

which returns the highest Chi-squared statistic from the likelihood ratio test will be selected for

inclusion in the diagnostic criteria, as long as p<0.05 for that threshold. If p≥0.05, the entire

variable will be rejected as it was not related to mortality at any dichotomization threshold. The

process will continue until all candidate features have been tested.

We will then join the retained features with a series of 'or' statements along with

'bleeding thought to be the cause of death' (which will not be subjected to the selection process).

This series will form the BIMS diagnostic criteria.

Objective 2: Estimate the incidence and prognostic value of BIMS.

We will perform this analysis in all 15,109 patients with available data for MINS. Among

these patients, 268 died within 30 days of surgery. We will categorize patients as having

experienced BIMS, non-BIMS bleeding, or no bleeding. We will estimate the association

between BIMS and mortality in a shared frailty Cox proportional hazards model. BIMS will

enter the model as a time-varying covariate. The model will be adjusted for the same adjustment

variables used in the candidate selection process, except that in this model we will also adjust (as

time-varying covariates) for MINS, sepsis, pulmonary embolism, and stroke. To aid in the

interpretation of the results, we will estimate the percentage of deaths potentially attributable to

BIMS and all other statistically significant variables (i.e. the population attributable risk fraction)

with corresponding 95% confidence intervals. We will repeat this analysis without adjustment

for MINS, sepsis, pulmonary embolism, or stroke because for many patients these complications

may be the direct result of BIMS or its management. Comparing population attributable risk

fractions adjusted and unadjusted for these complications will provide a minimum and maximum

estimate of BIMS' potential independent contribution to mortality.

Subgroup analyses for Objective 2

We will estimate the incidence and prognostic value of BIMS with respect to mortality in

subgroups defined by age <75 vs. ≥75 years, preoperative hemoglobin <120 vs. ≥120 g/L, men

vs. women, and known cardiovascular disease vs. no cardiovascular disease. We will interpret a

subgroup effect as significant if the effect BIMS is associated with mortality in one of the

subgroups but not the other and if a statistical test of interaction demonstrates a p <0.01. We use

this stringent p-value for interaction to protect against spurious findings in subgroups with few

events. We additionally require that BIMS is associated with mortality in one of the subgroups

but not the other because a weaker association of BIMS with mortality would still satisfy the

definitional requirement that BIMS is positively associated with mortality.

Objective 3: Develop and internally validate a clinical prediction guide to predict BIMS.

This analysis will be performed in all 16,079 patients. We will first construct a single

candidate logistic regression model that includes all preoperative and surgical variables listed in

Figure 1. We will substitute a preoperative estimated glomerular filtration rate (eGFR) value of

5 mL/min/1.73m^2 for any patients who were receiving dialysis preoperatively and have an eGFR

value > 5 mL/min/1.73m^2 by the CKD-EPI equation(18) after imputation of missing preoperative

serum creatinine data. Continuous variables will be modelled using restricted cubic spline

8

functions. Next, we will simplify the model through backward elimination with a p-value criterion for removal of p>0.10. In large samples with many events per variable tested, backward elimination produces models that can outperform competing methods(19). We expect there will be many BIMS events given that one third of patients experienced bleeding and 165 of them died. If there are not enough BIMS events to maintain at least 10 events per variable tested, we will combine types of surgery into larger categories (e.g. major orthopedic, major general).

We will repeat the modelling procedure in each of 1000 bootstrap samples and test each resultant version of the model on the original data, reporting model discrimination using c-statistic and calibration using a plot of observed versus predicted probabilities. We will report the full model as a risk estimating equation that can be integrated into software for use on handheld devices.

We will attempt to further simplify this model into a risk index consisting of no more than 5 equally-weighted risk factors, the sum of which can stratify patients into just a few risk categories. We will report the proportion of patients who experience BIMS across the categories of this risk index, along with its c-statistic to evaluate discrimination.

Discussion

While perioperative bleeding is common, the nature and characteristics of bleeding that increase the risk of perioperative death are unclear. We described our methods for establishing the diagnostic criteria for BIMS—bleeding impacting mortality after noncardiac surgery—and for estimating its incidence and prognostic importance. Recognition of BIMS can direct closer monitoring and supportive care and an estimate of the prognostic importance of BIMS can also serve as an estimate of the maximum potential benefit of interventions that prevent bleeding still to be developed and tested. We further described the methods for developing and testing a

9

statistical model to predict BIMS. Prediction of BIMS can be used to enrich clinical trials,

inform the timing and appropriateness of surgery, and can guide surgical technique and

perioperative care with emphasis on hemostasis and availability of blood products.

Although this is a large study, the number of deaths among people who experienced a

bleed limits the number of thresholds that we can assess for units of blood transfused,

hemoglobin nadir, and hemoglobin decrement. As we assess more thresholds, we risk

establishing diagnostic criteria of BIMS that are not, in truth, independently associated with

mortality but are merely the product of statistical overfitting. Simulation studies show that, for

causal inference, the risk of spurious findings is only marginally higher when we test 1 variable

for every 5 events than if we test 1 variable for every 10 or more events, but becomes more

concerning with 4 events per variable or less(20). Our sample size is also insufficient to reliably

identify diagnostic criteria for BIMS in specific types of noncardiac surgery. This will remain a

frontier for future research.

We considered the range of hemoglobin nadir values that one might reasonably expect to

contain the most discriminating threshold; this also informed the selection of thresholds for the

absolute and relative hemoglobin decrements. The Transfusion Trigger Trial for Functional

Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair demonstrated

that, in patients at high cardiovascular risk undergoing surgery for hip fracture, a liberal strategy

for blood transfusion (hemoglobin of 100 g/L) did not affect mortality or functional outcome

compared to a restrictive strategy (<80 g/L)(21). These results are highly consistent with a recent

meta-analysis of 23 trials including 8,321 patients and 1,144 deaths across surgical and

nonsurgical settings(22). If we assume that red cell transfusion itself does not appreciably

increase risk of mortality(23) but would decrease mortality if given at the appropriate

hemoglobin threshold, then these data would suggest that a perioperative bleed should result in hemoglobin lower than 80 g/L or perhaps 70 g/L before it increases the risk of mortality. This evidence may not be directly applicable to our study because transfusion protocols are often halted in acute bleeds, but they provide a reasonable starting point to direct the analysis. We will additionally examine the prognostic importance of BIMS in a subgroup of patients with known cardiovascular disease because a recent meta-analysis suggests that this subgroup may benefit from a more liberal transfusion threshold(24). These patients may be more sensitive to smaller hemoglobin decrements.

This study will address an important gap in our knowledge about perioperative bleeding with implications for the nearly 300 million patients who undergo noncardiac surgery globally every year.

Footnotes

Contributions

Study concept and design: PSR, JWE, MC VT, FKB, CK, AL, RW, BMB, WS, GHG, MP, JP, AXG, MM, TVH, PAK, JDB, MW, DIS, YLM, TS, JMP, LT, MRIS, RM, SR, and PJD.

Acquisition, analysis, or interpretation of data: PSR, JWE, MC VT, FKB, CK, AL, RW, BMB, WS, GHG, MP, JP, AXG, MM, TVH, PAK, JDB, MW, DIS, YLM, TS, JMP, LT, MRIS, RM, SR, and PJD.

Drafting of the manuscript: PSR, JWE, MC VT, FKB, CK, AL, RW, BMB, WS, GHG, MP, JP, AXG, MM, TVH, PAK, JDB, MW, DIS, YLM, TS, JMP, LT, MRIS, RM, SR, and PJD.

Critical revision of the manuscript for important intellectual content: PSR, JWE, MC VT, FKB, CK, AL, RW, BMB, WS, GHG, MP, JP, AXG, MM, TVH, PAK, JDB, MW, DIS, YLM, TS, JMP, LT, MRIS, RM, SR, and PJD.

Statistical analysis: PSR.

All authors approved the version to be published.

12

Role of the Sponsors

The VISION funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Ethics

The research ethics board at each site approved the protocol prior to patient recruitment.

Conflicts of interest

Roche-Diagnostics provided Troponin T assays and financial support for the study. Dr. Devereaux reports grants from Roche-Diagnostics and Abbott-Diagnostics during the conduct of

References

1. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet (London, England). 2015 Apr 27;385 Suppl:S11.

2. Wu W-C, Smith TS, Henderson WG, Eaton CB, Poses RM, Uttley G, et al. Operative Blood Loss, Blood Transfusion, and 30-Day Mortality in Older Patients After Major Noncardiac Surgery. Ann Surg. 2010;252(1):11–7.

3. Whitlock EL, Kim H, Auerbach AD. Harms associated with single unit perioperative transfusion: retrospective population based analysis. BMJ. 2015;350:h3037.

4. Weber EWG, Slappendel R, Prins MH, Van Der Schaaf DB, Durieux ME, Str??mper D. Perioperative blood transfusions and delayed wound healing after hip replacement surgery: Effects on duration of hospitalization. Anesth Analg. 2005;100(5):1416–21.

5. Dahl OE, Quinlan DJ, Bergqvist D, Eikelboom JW. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. J Thromb Haemost. 2010;8(9):1966–75.

6. Acedillo R, Shah M, Devereaux P, Li L, Iansavichus A, Walsh M, et al. The Risk of Perioperative Bleeding in Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis. Ann Surg. 2013;258(6):901–13.

7. Schulman S, Anger SU, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010 Jan;8(1):202–4.

8. Harrell FE. rms: Regression Modeling Strategies. R package; 2016.

9. Devereaux PJ, Chan MT V, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012 Jun 6;307(21):2295–304.

10. Botto F, Alonso-Coello P, Chan MT V, Villar JC, Xavier D, Srinathan S, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014 Mar;120(3):564–78.

11. Berwanger O, Le Manach Y, Suzumura EA, Biccard B, Srinathan SK, Szczeklik W, et al. Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION study. Eur Heart J. 2015;ehv456.

12. Landerman LR, Land KC, Pieper CF. An Empirical Evaluation of the Predictive Mean Matching Method for Imputing Missing Values. Sociol Methods Res. 1997 Aug 1;26(1):3–33.

13. White IR, Daniel R, Royston P. Avoiding bias due to perfect prediction in multiple imputation of incomplete categorical variables. Comput Stat Data Anal. Elsevier B.V.; 2010 Oct 1;54(10):2267–75.

14. Van Buuren S, Oudshoorn C. MICE: multivariate imputation by chained equations. J Stat Softw. Citeseer; 2010;VV(Ii).

15. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Statistics. New York, NY: Springer-Verlag New York; 2009.

16. Wolkewitz M, Allignol A, Harbarth S, De Angelis G, Schumacher M, Beyersmann J. Time-dependent study entries and exposures in cohort studies can easily be sources of
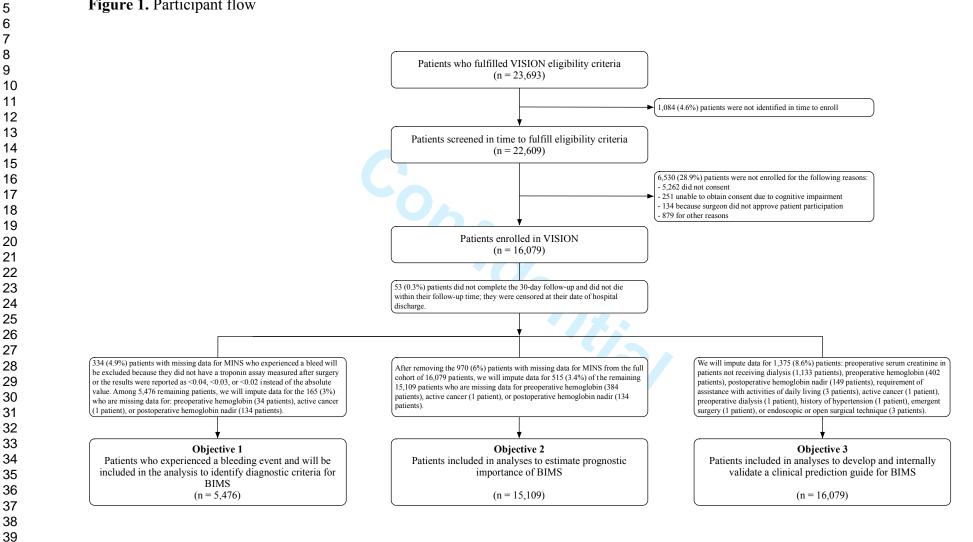
16

different and avoidable types of bias. J Clin Epidemiol. Elsevier Inc; 2012;65(11):1171–80.

17. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology. 2009;20(4):488–95.

18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604–12.

19. Ambler G, Brady AR, Royston P. Simplifying a prognostic model: a simulation study based on clinical data. Stat Med. 2002 Dec 30;21(24):3803–22.

20. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007 Mar;165(6):710–8.

21. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011 Dec 29;365(26):2453–62.

22. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ. England; 2015;350:h1354.

23. Carson JL, Sieber F, Cook DR, Hoover DR, Noveck H, Chaitman BR, et al. Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. Lancet. 2015;385(9974):1183–9.

24. Docherty AB, O'Donnell R, Brunskill S, Trivella M, Doree C, Holst LB, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. BMJ. 2016 Mar 29;i1351.

Figure 1. Participant flow

18

Figure 2. Summary of analysis plan.

Objective 1: In patients who experienced a bleed and have available MINS data

BIMS criteria selection with shared frailty Cox proportional hazards models	
Adjustment variables independelty associated with mortality in VISION	**BIMS candidate components**
Age, preoperative hemoglobin, recent high-risk CAD, history of stroke, history of PVD, active cancer, major general surgery, neurosurgery, urgent/emergency surgery, and postoperative sepsis, MINS, pulmonary embolism, and stroke that occured before the day of the bleeding episode.	Reoperation for reasons of bleeding RBC transfusion (# of units) Postoperative hemoglobin nadir (g/L) Absolute hemoglobin drop from preop Relative (%) hemoglobin drop from preop

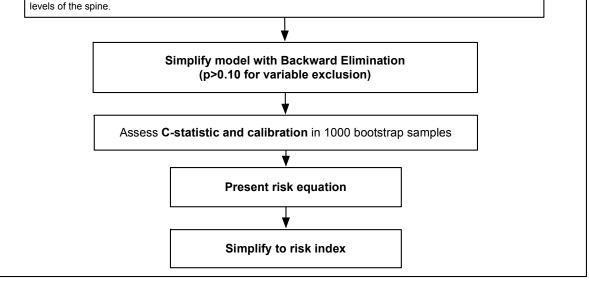### Objective 2: In all patients with available MINS data

Estimate prognostic value of BIMS relative to 30-day mortality in shared frailty Cox proportional hazards model.
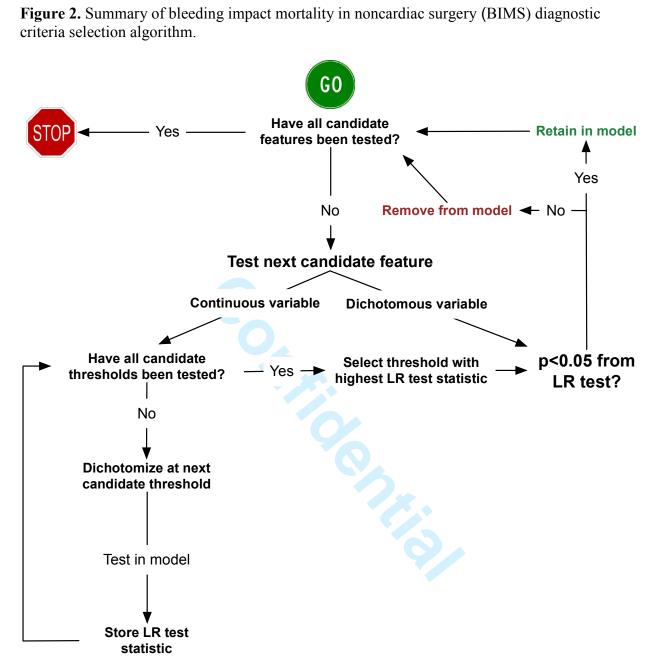
Objective 3: In all patients

Development and validation of a clinical prediction guide for BIMS

Fit full logistic regression model with all candidate predictors

Age, preoperative hemoglobin, eGFR, assistance with ADLs, recent high-risk CAD, history of CHF, history of stroke, history of PVD, history of COPD, active cancer, urgent/emergent surgery, thoracic aorta reconstructive vascular surgeries, aorto-iliac reconstructive vascular surgery, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery, endovascular abdominal aortic aneurysm repair, complex visceral resection general surgery, partial or total colectomy or stomach surgery, other intra-abdominal surgery, major head and neck resection for non-thyroid tumor, pneumonectomy, lobectomy, other thoracic surgeries, visceral urologic or gynecologic resection, cytoreductive surgery, hysterectomy, radical hysterectomy, radical prostatectomy, transurethral prostatectomy, major hip or pelvic surgery, internal fixation of femur, knee arthroplasty, above knee amputations, lower leg amputation (amputation below knee but above foot), craniotomy, major spine surgery involving multiple levels of the spine.

↓

Simplify model with Backward Elimination (p>0.10 for variable exclusion)

↓

Assess **C-statistic and calibration** in 1000 bootstrap samples

↓

Present risk equation

↓

Simplify to risk index

Abbreviations: BIMS, bleeding impact mortality in noncardiac surgery; eGFR, estimated glomerular filtration rate; ADL, activities of daily living; CAD; coronary artery disease; CHF, congestive heart failure; PVD, peripheral vascular disease; MINS, myocardial injury after noncardiac surgery; RBC, red blood cell.

19

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 2. Summary of bleeding impact mortality in noncardiac surgery (BIMS) diagnostic criteria selection algorithm.

Candidate features are tested for association with 30-day mortality in shared frailty Cox proportional hazards model, adjusted for potential pre, intra, and postoperative confounders. The threshold for retaining a candidate feature in the model is $p<0.05$ from a likelihood ratio (LR) test comparing the model with the feature to a model without it.

Table 1. Hierarchy for entry of candidate Bleeding Impact Mortality in noncardiac Surgery (BIMS) features into regression model.

Adjustment variables (always in model)	Candidate features	Position of entry into model	Rationale for position
1. Age, years 45-64, 65-74, 75+	Reoperation for reasons of bleeding	1st	Decision for reoperation is somewhat subjective but easy to ascertain
2. Preop. hemoglobin, g/L <100, 100-119, 120-139, 140+ 3. History of COPD	RBC transfusion ≥ 1 unit(s) vs 0 units ≥ 2 units vs <2 units ≥ 3 units vs <3 units	2nd	Decision regarding if and how much to transfuse is subjective but information is reliably ascertained
4. History of recent high-risk CAD 5. History of stroke 6. History of PVD	Hg nadir g/L <80 vs ≥80 <70 vs ≥70 <60 vs ≥60	4th	Nadir dependent on transfusions and time of measurement
7. Active cancer 8. Major general surgery 9. Major neurosurgery 10. Urgent/emergency surgery 11. Postop. sepsis before bleeding	Absolute drop in hemoglobin from preoperative value: preoperative Hg – nadir Hg g/L ≥40 vs <40 ≥50 vs <50 ≥60 vs <60	5th	Preoperative Hg may not be available, nadir dependent on transfusions and time of measurement, and drop requires a (simple) calculation
12. MINS before bleeding 13. Postop. pulmonary embolus before bleeding	Drop in Hg relative to preoperative value: (preoperative Hg – nadir Hg)/preoperative Hg *100% ≥30% vs <30% ≥40% vs <40%	6th	Preoperative Hg may not be available, nadir dependent on transfusions and time of measurement, and a relative drop represents a less practical calculation for clinicians
14. Postop. stroke before bleeding	Thought to be the cause of death	Not entered in model but will automatically become part of the diagnostic criteria after other candidate features have been tested	Judgement is subjective but has face validity and is very specific for mortality

Abbreviations: BIMS, bleeding impact mortality in noncardiac surgery; eGFR, estimated glomerular filtration rate; ADL, activities of daily living; COPD, chronic obstructive pulmonary disease; CAD; coronary artery disease; PVD, peripheral vascular disease; MINS, myocardial injury after noncardiac surgery; RBC, red blood cell; Hg, hemoglobin

21

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Box 1. Variables included in imputation model.

Age, gender, age-by-gender interaction, preoperative weight, height, preoperative serum creatinine, preoperative hemoglobin, active cancer, preoperative dialysis, patient requires assistance with activities of daily living preoperatively, endoscopic surgical technique, open surgical technique, duration of surgery, history of chronic obstructive pulmonary disease, history of coronary artery disease (not recent high-risk coronary artery disease), history of recent high-risk coronary artery disease, history of diabetes not requiring preoperative insulin, history of diabetes requiring preoperative insulin, history of congestive heart failure, history of transient ischemic attack, history of stroke, history of hypertension, peripheral vascular disease, major general surgery, thoracic surgery, orthopaedic surgery, major urologic or gynecologic surgery, neurosurgery, vascular surgery, duration of surgery, myocardial injury after noncardiac surgery, stroke within 30 days of surgery, pulmonary embolus within 30 days of surgery, sepsis within 30 days of surgery, death within 30 days of surgery, number of red blood cell units transfused, reoperation for reasons of bleeding, postoperative hemoglobin nadir, study centre, calendar year of surgery.

22

Variable definitions

Preoperative variables

Age: The patient's age in years, calculated as the difference between their birthdate and the date of surgery and rounded down to the nearest year.

Preoperative hemoglobin: Latest available routinely measured preoperative hemoglobin value.

Preoperative estimated glomerular filtration rate (eGFR): Calculated using CKD-Epi equation and latest available routinely measured preoperative serum creatinine value.

Requires assistance with Activities of Daily Living: Patient requires assistance from **another person** with **any** of the following activities: dressing, eating, ambulating, toileting, hygiene**.** If a patient has suffered an acute injury leading to the need for surgery (e.g., hip fracture) the assessment for requirement of help for ADLs was based upon their condition prior to their acute injury.

Congestive heart failure: A physician diagnosis of a current or prior episode of congestive heart failure or prior radiographic evidence of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema.

Recent high risk coronary artery disease: Diagnosis ≤ 6 months prior to non-cardiac surgery of: a myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society Class (CCSC) III angina or CCSC IV angina.
CCSC III angina – angina occurring with level walking of 1-2 blocks or climbing ≤ 1 flight of stairs at a normal pace
CCSC IV – inability to perform any physical activity without the development of angina

Cerebral vascular event: A physician diagnosis of stroke, CT or MRI evidence of a prior stroke, or physician diagnosis of a prior transient ischemic attack (TIA).

Peripheral vascular disease: A current or prior history of: physician diagnosed intermittent claudication, vascular surgery for atherosclerotic disease, an ankle/arm systolic blood pressure ratio ≤ 0.90 in either leg at rest, or angiographic or doppler study demonstrating ≥ 70% stenosis in a non-cardiac artery.

Chronic Obstructive Pulmonary Disease (COPD): If the chart or a physician has ever indicated that a patient has chronic bronchitis, we accepted this as a patient having COPD. If there is no mention of this but the patient reported they have had daily production of sputum for at least 3 months in 2 consecutive years then they were marked as having COPD. Likewise, if a physician has ever indicated that a patient has emphysema or if a patient's Pulmonary Function Tests (PFT) state fixed or irreversible airflow limitation and/or emphysema then they were marked as having COPD.

Active cancer: The patient has a current diagnosis of cancer or is undergoing surgery for cancer.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Surgical variables

If patient underwent more than one surgery, all performed surgeries were included.

Major Vascular Surgery
1. Thoracic aorta reconstructive vascular surgeries (thoracic aortic aneurysm repair, repair of supra-aortic trunks not requiring total cardiopulmonary bypass, thoracoabdominal aortic aneurism repair with or without aorto-femoral bypass)
2. Aorto-iliac reconstructive vascular surgery (open abdominal aortic aneurysm repair, aorto-femoral bypass, iliac-femoral bypass, renal artery revascularization, celiac artery revascularization, superior mesenteric artery revascularization)
3. Peripheral vascular reconstruction without aortic cross-clamping (axillo-femoral bypass, femoral-femoral bypass, femoro-infragenicular bypass, profundoplasty, or other angioplasties of the infrainguinal arteries)
4. Extracranial cerebrovascular surgery (carotid endarterectomy, carotid-subclavian bypass)
5. EVAR – endovascular abdominal aortic aneurysm repair

Major General Surgery
1. Complex visceral resection (surgery involving the liver, esophagus, pancreas, or multiple organs)
2. Partial or total colectomy or stomach surgery
3. Other intra-abdominal surgery (gallbladder, appendix, adrenals, spleen, regional lymph node dissection)
4. Major head and neck resection for non-thyroid tumor

Thoracic Surgery
1. Pneumonectomy
2. Lobectomy
3. Other thoracic surgeries (wedge resection of lung, resection of mediastinal tumor, major chest wall resection)

Major Urologic or Gynecologic Surgery
1. Visceral resection (nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration [i.e. radical procedure for cancer to remove pelvic organs])
2. Cytoreductive surgery "debulking" done when cancer has spread in the pelvic/abdominal area, to remove as much of the tumor as possible
3. Radical hysterectomy is surgery to remove the uterus, cervix and part of the vagina
4. Hysterectomy is surgery to remove the uterus and usually the cervix
5. Radical prostatectomy is surgery to remove entire prostate gland and surrounding tissue
6. Transurethral prostatectomy to remove overgrowth of prostate tissue

Major Orthopedic Surgery
1. Major hip or pelvic surgery (hemi or total hip arthroplasty, internal fixation of hip, pelvic arthroplasty)
2. Internal fixation of femur
3. Knee arthroplasty

24

4. Above knee amputations

5. Lower leg amputation (amputation below knee but above foot)

Major Neurosurgery
1. Craniotomy
2. Major spine surgery is surgery involving multiple levels of the spine

Urgent or emergency surgeries: surgeries performed within 72 hours of acute event that led to need for surgery.

Duration of surgery: The minutes elapsed between the time the surgeon began the procedure and the time the surgeon closed the wound.

Postoperative complications

Bleeding: Bleeding is defined as bleeding which results in a drop in hemoglobin of 30 g/L (3 g/dL), or leads to a transfusion, reoperation, or is thought to be the cause of death.

MINS (myocardial injury after noncardiac surgery): MINS was defined as any peak cardiac troponin T ≥ 0.03 ng/mL resulting from myocardial ischemia (i.e. without evidence of a non-ischemic etiology) that occurred with the first 30 days after surgery(10). We measured non-high sensitivity cardiac troponin T using a Roche fourth-generation Elecsys assay 6-12 h post-operatively and on the first 3 days after surgery to look for myocardial injury.

Stroke: new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours

Pulmonary embolus: The diagnosis of PE required any one of the following:
1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:
   A. Non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan
   B. Non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

Sepsis: Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms. Systemic inflammatory response requires 2 or more of the following factors: core temperature > 38° C or < 36° C; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count > 12 x 10^9/L or < 4 x 10^9/L.