ANESTHESIOLOGY

One-year Outcomes after Discharge from Noncardiac Surgery and Association between Predischarge Complications and Death after Discharge: Analysis of the VISION Prospective Cohort Study

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ABSTRACT

Background: In previous analyses, myocardial injury after noncardiac surgery, major bleeding, and sepsis were independently associated with most deaths in the 30 days after noncardiac surgery, but most of these deaths occurred during the index hospitalization for surgery. The authors set out to describe outcomes after discharge from hospital up to 1 yr after inpatient noncardiac surgery and associations between predischarge complications and postdischarge death up to 1 yr after surgery.

Methods: This study was an analysis of patients discharged after inpatient noncardiac surgery in a large international prospective cohort study across 28 centers from 2007 to 2013 of patients aged 45 yr or older followed to 1 yr after surgery. The study estimated (1) the cumulative postdischarge incidence of death and other outcomes up to a year after surgery and (2) the adjusted time-varying associations between postdischarge death and predischarge complications including myocardial injury after noncardiac surgery, major bleeding, sepsis, infection without sepsis, stroke, congestive heart failure, clinically important atrial fibrillation or flutter, amputation, venous thromboembolism, and acute kidney injury managed with dialysis.

Results: Among 38,898 patients discharged after surgery, the cumulative 1-yr incidence was 5.8% (95% CI, 5.5 to 6.0%) for all-cause death and 24.7% (95% CI, 24.2 to 25.1%) for all-cause hospital readmission. Predischarge complications were associated with 33.7% (95% CI, 27.2 to 40.2%) of deaths up to 30 days after discharge and 15.0% (95% CI, 12.0 to 17.9%) up to 1 yr. Most of the association with death was due to myocardial injury after noncardiac surgery (15.6% [95% CI, 9.3 to 21.9%] of deaths within 30 days, 6.4% [95% CI, 4.1 to 8.7%] within 1 yr), major bleeding (15.0% [95% CI, 8.3 to 21.7%] within 30 days, 4.7% [95% CI, 2.2 to 7.2%] within 1 yr), and sepsis (5.4% [95% CI, 2.2 to 8.6%] within 30 days, 2.1% [95% CI, 1.0 to 3.1%] within 1 yr).

Conclusions: One in 18 patients 45 yr old or older discharged after inpatient noncardiac surgery died within 1 yr, and one quarter were readmitted to the hospital. The risk of death associated with predischarge perioperative complications persists for weeks to months after discharge.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Previous literature demonstrates that myocardial injury after noncardiac surgery, major bleeding, and sepsis are independently associated with most deaths in the 30 days after noncardiac surgery, but most of these deaths typically occur during the index hospitalization for surgery
- It is unclear to what extent complications during the index hospitalization are associated with postdischarge death up to 1 yr after surgery

What This Article Tells Us That Is New

- In a secondary analysis of a prospective cohort study of 38,898 patients across 28 hospitals aged 45 yr or older who had inpatient noncardiac surgery between 2007 and 2013 and survived to hospital discharge, 2,165 (5.6%; cumulative incidence, 5.8%) patients died within 1 yr after surgery
- Complications during the index hospitalization were associated with 33.7% (95% CI, 27.2 to 40.2%) of deaths up to 30 days after discharge and 15.0% (95% CI, 12.0 to 17.9%) of deaths up to 1 yr after discharge
- Myocardial injury (6.4%), major bleeding (4.7%), and sepsis (2.1%) were associated with the most deaths within 1 yr

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Advances in surgical technique, intraoperative monitoring, anesthesia, and early postoperative care have improved surgical safety in the hospital,[1] but most patients are not at their baseline health at the time of discharge to home. Discharge requires that clinicians consolidate the events of the hospital stay and plan outpatient care. This includes making decisions about the timing of follow-up visits, utility and urgency of additional investigations, and medication prescribing. Some patients may benefit from enrollment in transition care programs. These decisions can be informed by the likelihood of complications postdischarge.

Our group has found that myocardial injury after noncardiac surgery, major bleeding, and sepsis occurring in the first 30 days after major noncardiac surgery were

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independently associated with most deaths occurring up to 30 days after surgery.[2] The majority of these complications and the majority of deaths occurred during the index hospital stay after surgery.[2] Other studies have found that early perioperative complications are associated with mortality in the longer term,[3–11] but they have been small, had important methodologic limitations, or have not focused explicitly on risk after discharge. Further, studies have not characterized the proportion of longer-term deaths that are associated with early postoperative complications and have not adequately examined changes in risk over time.

The objectives of this study were to describe outcomes after discharge from hospital up to 1 yr after inpatient noncardiac surgery and to study the associations over time between predischarge complications and death up to 1 yr after surgery.

Materials and Methods

We report this study according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[12]

Study Procedures

We have previously reported the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study design and methods.[13,14] VISION was a prospective international cohort study that enrolled patients 45 yr old or older who had inpatient noncardiac surgery between August 2007 and October 2013 at 28 centers in 14 countries (ClinicalTrials.gov NCT00512109). The ethics review board at each participating center approved the VISION study protocol.

Study personnel identified potential participants during the day and night and on weekdays and on weekends through daily screening of patient lists in preoperative assessment clinics, surgical lists from the same and the previous day, lists on surgical wards and in intensive care units, and in preoperative holding areas. At some centers, the ratio of recruitment staff to potential patients exceeded the ability to recruit consecutive patients. At those centers, personnel recruited patients based on a statistician-generated schedule of randomly selected weeks or randomly selected surgical services proportional to the prevalence of the types of surgery at each center. At the end of each week, research personnel reviewed the surgical logbook and reported the number of patients who were eligible but not enrolled.

Eligible consenting patients answered a series of questions about their past medical and social history. Research personnel reviewed medical charts for further background history, noted outcome events throughout the hospital stay, and conducted a follow-up telephone interview with the patient or their next of kin 30 days after surgery and again 1 yr after surgery. Research staff obtained further documentation—including dates of events—if the interview indicated the occurrence of an outcome event. At the time of consent, patients provided contact details for two next of kin or close friends who did not reside together or with the patient. If the patient, their next of kin, or close friends could not be reached, research staff contacted family physicians, searched medical records, and consulted obituaries to obtain study outcomes. Researchers in Peru and Brazil also used national registries to identify deaths.

Study personnel followed patients prospectively while in the hospital, collecting data from patients and their charts. After hospital discharge, study personnel contacted patients or their next of kin at 30 days and 1 yr after surgery. Outcome definitions and ascertainment criteria were specified a priori. Cardiac troponin T measurements were to be done in all patients 6 to 12 h postoperatively and on days 1, 2, and 3 after the day of surgery, or until discharge (whichever was sooner). Patients enrolled between 12 and 24 h after surgery had blood drawn for troponin T measurement immediately; subsequent measurements followed the usual schedule. During the later phase of the study, high-sensitivity troponin T measurement was also performed before surgery. Research staff checked daily that measurements were done as scheduled. Clinical teams were encouraged to obtain electrocardiograms for several days after troponin T concentrations were elevated above the manufacturer's reference limit or if patients experienced an ischemic symptom. Troponin T thresholds for myocardial injury after noncardiac surgery were subsequently derived from their associations with 30-day postoperative death and adjudicated centrally by physicians to exclude events potentially explained by nonischemic causes (*e.g.*, sepsis, pulmonary embolism, atrial fibrillation, chronic elevation) as described previously.[13–15] Physician adjudicators also evaluated all reported cases of myocardial infarction, stroke, venous thromboembolism, and new clinically important atrial fibrillation to ensure that they met study criteria. Supplemental Digital Content 1 (https://links.lww.com/ALN/D307) provides definitions of study outcomes.

Investigators reviewed and approved data at each site. Research personnel submitted case report forms and supporting documentation directly to the coordinating center. Data monitoring involved central data consistency checks, statistical monitoring, and on-site monitoring for all centers. For on-site monitoring, the central coordinator randomly selected participants with and without a perioperative complication for audit by independent monitors.

We limited our analyses to patients who survived to discharge from the hospital after surgery. Some patients were transferred from the hospital at which the index surgery was performed to another acute care hospital; for these analyses, we only included these patients if they were discharged alive from the acute care hospital to which they were transferred. We included patients discharged to a rehabilitation facility.

Outcomes

The primary outcome was death from any cause occurring between discharge from acute hospital care after surgery up to 1 yr after surgery. We also describe the cumulative incidence of death from vascular causes (*i.e.*, believed to be due to myocardial infarction, asystole, ventricular fibrillation, pulseless electrical activity, other sudden or arrhythmic death, sustained ventricular tachycardia, cardiogenic shock, congestive heart failure, other cardiac causes, stroke, peripheral vascular disease, aortic dissection/rupture, pulmonary embolus, bleeding, other vascular cause, or unknown cause), death from nonvascular causes (*i.e.*, believed to be due to sepsis, pneumonia or other infection, renal failure, cancer, or other nonvascular causes), rehospitalization, myocardial infarction, congestive heart failure, stroke, amputation, venous thromboembolism, nonfatal cardiac arrest, coronary revascularization, new diagnosis of dementia, new diagnosis of diabetes, new cancer, and recurrent cancer.

Exposures

The exposures of interest were perioperative complications that occurred before discharge from acute hospital care for the index surgery. Complications of primary interest were sepsis, infection without sepsis, myocardial injury after noncardiac surgery that met the criteria for myocardial infarction, myocardial injury after noncardiac surgery that represented an isolated ischemic myocardial injury (*i.e.*, an elevated cardiac troponin T measurement of presumed ischemic origin that did not meet criteria for myocardial infarction), and major bleeding that met diagnostic criteria we previously developed for bleeding independently associated with mortality after noncardiac surgery (*i.e.*, bleeding during and up to 30 days after noncardiac surgery that resulted in hemoglobin less than 70 g/l or any red cell transfusion, or that was imminently fatal [although, this analysis excluded patients with fatal predischarge bleeds]).[16] Complications of secondary interest were stroke, new clinically important atrial fibrillation, venous thromboembolism, acute congestive heart failure, amputation, and acute kidney injury managed with dialysis. These complications affected a smaller number of patients; their associations with mortality were treated as exploratory.

Statistical Analyses

We developed a statistical analysis plan before conducting the analyses and briefly summarize the methods here. The analysis plan was written after data were accessed to determine feasibility (*e.g.*, by assessing number of primary outcome events, number of patients with various predischarge complications). We used R version 4.1.0 (R Core Team, 2021; Austria) and Stata version 17.0 (StataCorp, 2021; USA) for the analyses.

Missing Data. Data regarding one or more variables were missing in 12.9% of patients, mostly preoperative estimated glomerular filtration rate (6.7%), preoperative hemoglobin (6.5%), and postoperative troponin measurements (5.5%). We imputed these data using multiple imputation across 20 imputed datasets for the association analysis.[17] We present adjusted hazard ratios and percentages of associated deaths based on a single imputed dataset with model coefficients that closely approximated those pooled across the 20 imputed datasets.

Cumulative Incidence of Complications after Discharge. We calculated the cumulative incidence of events that occurred after discharge from the index surgical hospitalization up to 1 yr after surgery. For outcomes other than all-cause death, we accounted for competing risk of death, and we treated patients who did not experience the outcome as censored at the time of death or last known vital status. We used the cumulative incidence function instead of the complement of the Kaplan–Meier survival function to estimate the crude incidence of outcomes because the complement of the Kaplan–Meier function overestimates incidence in the presence of competing events.[18] We performed all analyses based on the time to the first event after discharge.

Analyses of the Association between Predischarge Complications and Mortality after Discharge. We fit a flexible parametric survival model with a smooth transformation of the log cumulative hazard function using restricted cubic splines.[19] We included as independent variables those listed in table 1, including predischarge complications, preoperative patient characteristics, type of the index surgery (major vascular, major general, major thoracic, major urologic or gynecologic, major neurosurgery, major orthopedic), surgical approach (*i.e.*, open *versus* endoscopic), and the urgency of surgery. We also adjusted for the study center. We did not include nonfatal cardiac arrest in the model because only two patients who had this complication before discharge died after discharge. We report detailed surgical procedure type (*e.g.*, lobectomy *versus* pneumonectomy) for transparency, but modeling included the broader categories of index surgery mentioned above (*e.g.*, major thoracic surgery). We modeled continuous variables using restricted cubic splines. We presented adjusted hazard ratios and corresponding 95% CIs describing the association between each in-hospital complication and time to death after discharge. We performed direct adjustment by regression standardization averaged over the distribution of covariates to estimate standardized survival functions. This method averages all patient-specific survival curves estimated at each time point across the year of follow-up from all patients in the study, with each survival curve adjusted for that patient's characteristics under hypothetical conditions under which they did and did not have each predischarge complication of interest.[20] We allowed the effects of predischarge complications, type and urgency of surgery, and surgical approach to vary with time because we expected *a priori* that their contribution to the hazard of mortality would decline over time. We treated the association of venous thromboembolism and acute kidney injury managed with dialysis as

Table 1. Description of Patients Discharged from Hospital after Surgery

Preoperative Characteristics	Overall* (N = 38,898)	Dead at 1 yr (N = 2,165)	Alive at 1 yr (N = 36,773)
Age, yr	63 (54–72)	69 (60–78)	62 (54–71)
Men	19,507 (50.1)	1,229 (56.8)	18,278 (49.8)
Women	19,391 (49.9)	936 (43.2)	18,455 (50.2)
Estimated glomerular filtration rate, ml/min per 1.73 m^2	84 (67–97)	78 (55–94)	84 (68–97)
Hemoglobin, g/l	132 (120–143)	118 (103–133)	133 (120–144)
Requires help with activities of daily living	1,945 (5.0)	298 (13.9)	1,647 (4.5)
History of hypertension	19,581 (50.4)	1,197 (55.6)	18,384 (50.1)
History of coronary artery disease	5,010 (12.9)	421 (19.6)	4,589 (12.5)
History of stroke or transient ischemic attack	2,471 (6.4)	243 (11.2)	2,228 (6.1)
History of peripheral arterial disease	3,057 (7.9)	285 (13.2)	2,772 (7.5)
History of congestive heart failure	1,329 (3.4)	166 (7.7)	1,163 (3.2)
In atrial fibrillation before surgery	1,052 (2.7)	148 (6.9)	904 (2.5)
Diabetes			
No diabetes	30,815 (79.3)	1,553 (72.2)	29,262 (79.7)
Diabetes not treated with insulin	4,326 (11.1)	239 (11.1)	4,087 (11.1)
Diabetes treated with insulin	3,707 (9.5)	360 (16.7)	3,347 (9.1)
History of chronic obstructive pulmonary disease	3,024 (7.8)	299 (13.8)	2,725 (7.4)
Active cancer	9,492 (24.4)	1,260 (58.2)	8,232 (22.4)
Metastatic disease	2,211 (5.7)	607 (28.0)	1,604 (4.4)
Type of surgery			
Major general surgery	7,632 (19.6)	627 (29.0)	7,005 (19.1)
Complex visceral resection	1,105 (2.8)	144 (6.7)	961 (2.6)
Partial or total colectomy or stomach surgery		205 (9.5)	1,898 (5.2)
Other abdominal surgery	4,051 (10.4)	246 (11.4)	3,805 (10.4)
Major head and neck resection of non-thyroid tumor	625 (1.6)	70 (3.2)	555 (1.5)
Major orthopedic surgery	6,839 (17.6)	327 (15.1)	6,512 (17.7)
Major hip or pelvic surgery	2,846 (7.3)	144 (6.7)	2,702 (7.4)
Surgery for hip fracture	885 (2.3)	108 (5.0)	777 (2.1)
Internal fixation of femur	722 (1.9)	89 (4.1)	633 (1.7)
Knee arthroplasty	2,861 (7.4)	22 (1.0)	2,839 (7.7)
Above-knee amputation	189 (0.5)	46 (2.1)	143 (0.4)
Below-knee amputation	236 (0.6)	31 (1.4)	205 (0.6)
Major urology/gynecology surgery	4,749 (12.2)	185 (8.5)	4,564 (12.4)
Visceral resection	1,063 (2.7)	70 (3.2)	993 (2.7)
Cytoreductive surgery	287 (0.7)	37 (1.7)	250 (0.7)
Hysterectomy	1,372 (3.5)	32 (1.5)	1,340 (3.6)
Radical hysterectomy	456 (1.2)	18 (0.8)	438 (1.2)
Transurethral prostatectomy	1,000 (2.6)	38 (1.8)	962 (2.6)
Radical prostatectomy	730 (1.9)	10 (0.5)	720 (2.0)
Major neurosurgery	2,560 (6.6)	158 (7.3)	2,402 (6.5)
Craniotomy	851 (2.2)	111 (5.1)	740 (2.0)
Major spine surgery	1,383 (3.6)	48 (2.2)	1,335 (3.6)
Major vascular surgery	2,234 (5.7)	159 (7.3)	2,075 (5.6)
Peripheral vascular reconstruction without aortic cross-clamping	1,175 (3.0)	91 (4.2)	1,084 (3.0)
Aorto-iliac reconstruction	609 (1.6)	29 (1.3)	580 (1.6)
Extracranial cerebrovascular surgery	430 (1.1)	18 (0.8)	412 (1.1)
Endovascular aneurysm repair	294 (0.8)	14 (0.6)	280 (0.8)
Thoracic aorta reconstruction	75 (0.2)	7 (0.3)	68 (0.2)
Major thoracic surgery	1,138 (2.9)	152 (7.0)	986 (2.7)
Lobectomy	462 (1.2)	43 (2.0)	419 (1.1)
Pneumonectomy	44 (0.1)	7 (0.3)	37 (0.1)
Other thoracic surgery	660 (1.7)	104 (4.8)	556 (1.5)
Other (only low-risk) surgery	14,024 (36.1)	579 (26.7)	13,445 (36.6)
Open surgery	30,333 (78.0)	1,751 (81.0)	28,582 (77.9)
Urgent/emergency surgery	3,908 (10.0)	333 (15.4)	3,575 (9.7)
Complications before discharge			
Major bleeding	5,535 (14.2)	640 (29.6)	4,895 (13.3)
Myocardial injury after noncardiac surgery: isolated ischemic myocardial injury	3,828 (10.4)	444 (21.8)	3,384 (9.7)
Myocardial injury after noncardiac surgery: myocardial infarction	1,219 (3.1)	166 (7.7)	1,053 (2.9)
Sepsis	1,191 (3.1)	190 (8.8)	1,001 (2.7)
Infection without sepsis	1,231 (3.2)	152 (7.0)	1,079 (2.9)
Congestive heart failure	285 (0.7)	61 (2.8)	224 (0.6)

(Continued)

Table 1. (Continued)

Preoperative Characteristics	Overall* (N = 38,898)	Dead at 1 yr (N = 2,165)	Alive at 1 yr (N = 36,773)
New clinically important atrial fibrillation or flutter	304 (0.8)	42 (1.9)	262 (0.7)
Venous thromboembolism	220 (0.6)	25 (1.2)	195 (0.5)
Amputation	165 (0.4)	32 (1.5)	133 (0.4)
Acute kidney injury managed with dialysis	51 (0.1)	10 (0.5)	41 (0.1)
Stroke	76 (0.2)	11 (0.5)	65 (0.2)
Nonfatal cardiac arrest†	20 (< 0.1)	2 (< 0.1)	18 (< 0.1)

Statistics presented for continuous variables were median (25th percentile, 75th percentile); for categorical variables, n (%). Statistics are based on complete data (not imputed). Denominators used for calculation of percentages differ by number of patients with missing data. Patients were missing data on the following variables: preoperative estimated glomerular filtration rate (2,621 patients), preoperative hemoglobin (1,346 patients), history of coronary artery disease (81 patients), hypertension (37 patients), diabetes (50 patients), history of congestive heart failure (61 patients), requiring assistance with activities of daily living (64 patients), in atrial fibrillation before surgery (57 patients), surgical approach (57 patients), and myocardial injury after noncardiac surgery that was isolated ischemic myocardial injury (2,154 patients).

*Follow-up completed for 37,544 patients (96.5%); the rest were censored on the day that their vital status was last known. †We did not include nonfatal cardiac arrest in the model associating predischarge complications with postdischarge death because only two patients who had this complication before discharge died after discharge.

constant over time due to problems with model convergence at the time of analysis because few patients had these complications before discharge, and few of them died after discharge.

We also compared the adjusted association with postdischarge mortality for myocardial injury after noncardiac surgery that met criteria for myocardial infarction to that of myocardial injury after noncardiac surgery that represented an isolated ischemic myocardial injury against the null hypothesis that their coefficients in the model were equal.

To help with interpretation of the time-dependent adjusted hazard ratios, we estimated average absolute adjusted differences in the risk of postdischarge mortality associated with each predischarge complication over time.

Hypothesis Testing. The test for statistical significance of the association between each complication and time to postdischarge death within 1 yr after surgery was an F test adapted for multiple imputation.[21] We calculated a single global P value for each the association between each predischarge complication and postdischarge death. All hypothesis tests were two-sided without multiplicity adjustments; $P < 0.05$ denoted statistical significance.

Percentage of Postdischarge Deaths Associated with Predischarge Complications. We calculated the percentages of deaths that occurred between discharge and 1 yr after surgery that were potentially attributable to each predischarge complication and with all predischarge complications combined (*i.e.*, attributable fractions).[22] We also estimated attributable hazard fractions that represent the percentage of the instantaneous hazard of death associated with predischarge complications at each day throughout the year after discharge.[22] Because three of the predischarge complications were associated with a disproportionately large percentage of the postdischarge deaths, we then grouped them together to communicate their prominence.

Prespecified Sensitivity Analyses. In the first sensitivity analysis, we changed the censoring times when calculating cumulative incidence of times to event outcomes other than death from the time of death or last known vital status (the primary analysis) to the time of last study contact when the patient was known not to have the event. The method used in the primary analysis might underestimate the cumulative incidence, while this sensitivity analysis might overestimate the cumulative incidence.[23] In the second sensitivity analysis, we repeated the association analyses in patients without missing data.

Post Hoc Analyses in Response to Reviewer Comments. We examined with logistic regression the relationship between the occurrence of censoring on day 30 after surgery (the day on which 94% of censoring occurred) and the independent variables included in our model for postdischarge death (*i.e.*, predischarge complications, preoperative patient characteristics, type and timing of surgery, surgical approach, and the study center). We provided an estimate of the cumulative incidence of postdischarge death due to cardiac causes. This *post hoc* definition in response to a reviewer comment included deaths due to myocardial infarction, due to cardiac arrest, or after coronary revascularization, but excluded death due to congestive heart failure.[24] We also presented the associations between adjustment variables and postdischarge death. Finally, we provided estimates of the cumulative incidence of postdischarge outcomes by study center.

Sample Size. The model to evaluate adjusted associations between in-hospital perioperative complications and mortality after discharge involved 101 parameters including the intercept, coefficients for each variable, and segments of restricted cubic splines and their interactions with variables that have time-dependent effects. Simulation studies suggest that, depending on the conditions, between 5 and 20 events per parameter are adequate to minimize bias in the estimates of association across a variety of scenarios.[25] We exceeded these requirements.

Results

Figure 1 summarizes the flow of participants through the study. VISION included 40,004 patients between 2007 and 2013. We excluded 1,106 patients (2.8% of the total 40,004) from these analyses, including 684 (1.7% of the total 40,004) because they died before hospital discharge. Table 1 describes the characteristics of the 38,898 patients included in these analyses. Their median age was 63 yr, 49.9% were women, 5.0% required help with activities of daily living, 12.9% had a history of coronary

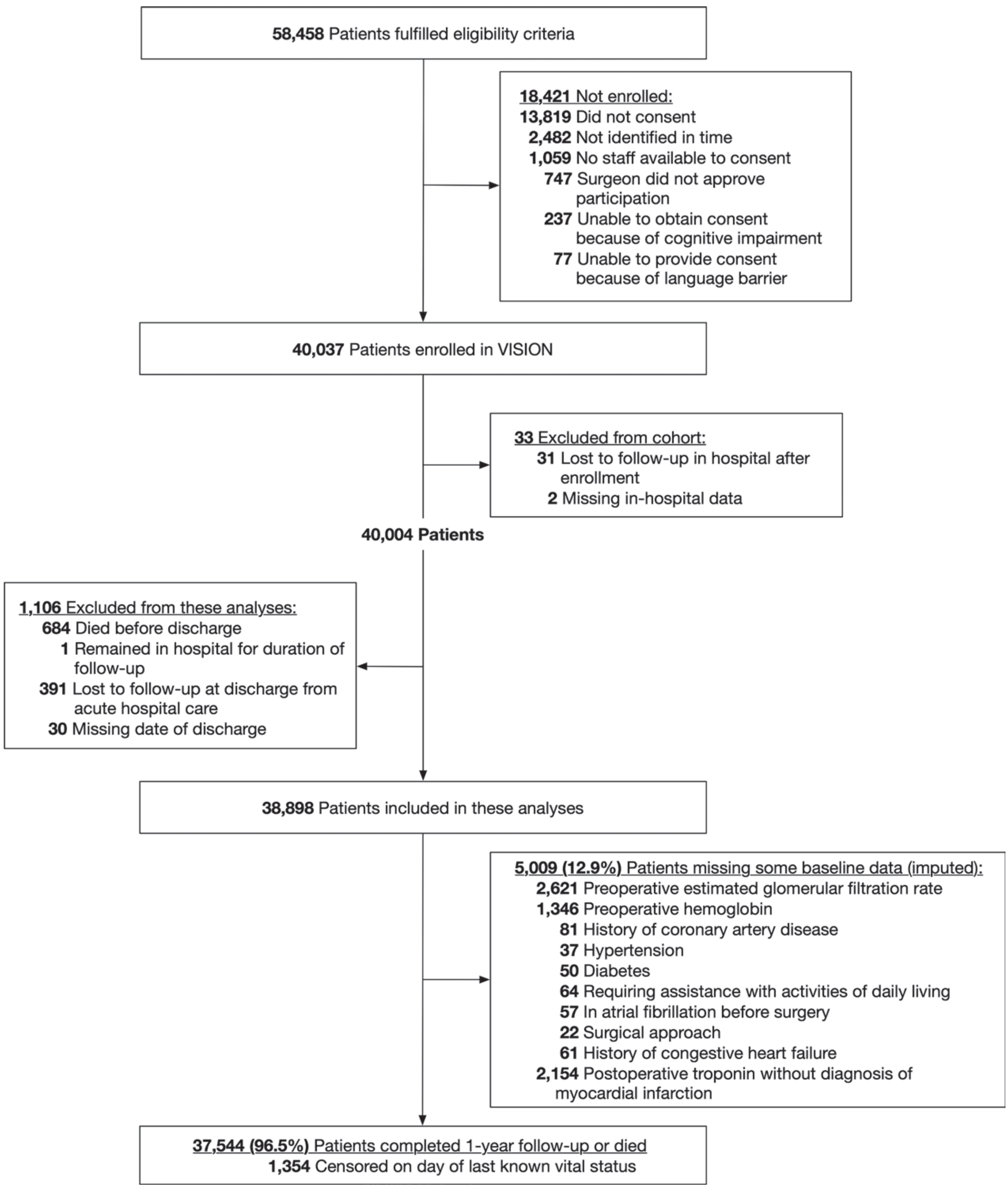

Fig. 1. Participant eligibility flow diagram. VISION, Vascular Events in Noncardiac Surgery Patients Cohort Evaluation.

artery disease, 24.4% had active cancer, 10.0% had urgent or emergency surgery, 19.6% had major general surgery, 17.6% had major orthopedic surgery, and 5.7% had major vascular surgery. Patients were followed for a median of 362 days after hospital discharge. Of these patients, 96.5% (37,544) completed follow-up at 1 yr after surgery or died before this time. Of the remaining 1,354 patients (who were censored on the day that their vital status was last known), 1,275 (94.1%) were censored at day 30 after surgery, and 72 (5.3%) were censored between days 345 and 364 after surgery.

Among the 2,165 patients (5.6%) who died between hospital discharge after surgery and 1 yr after surgery, the median (25th, 75th percentiles) time to death after discharge from acute hospital care after surgery was 141 days (60, 240) and after the index surgery was 154 days (75, 252).

Complications before Discharge

The median length of the index acute care hospital stay after surgery was 5 days (25th percentile, 2 days; 75th percentile, 9 days). Before hospital discharge, 14.2% of patients had major bleeding, 3.1% developed sepsis, 3.2% developed infection without sepsis, 3.1% had myocardial injury after noncardiac surgery that met criteria for myocardial infarction, and 10.4% had myocardial injury after noncardiac surgery that represented an isolated ischemic myocardial injury. Each of the other predischarge complications occurred in fewer than 1% of patients who were ultimately discharged from the hospital.

Outcomes after Discharge

The 1-yr cumulative incidence of postdischarge death was 5.8% (95% CI, 5.5 to 6.0%) from any cause, 2.0% (95% CI, 1.9 to 2.2%) from vascular causes, and 3.8% (95% CI, 3.6 to 4.0%) from nonvascular causes (fig. 2A). The cumulative incidence of first hospital readmission was 24.7% (95% CI, 24.2 to 25.1%); it increased most quickly in the first 45 days (fig. 2B). The cumulative incidences of new diabetes, dementia, new cancer, and recurrent cancer increased at a near constant rate over time (Figure S1, Supplemental Digital Content 1, https://links.lww.com/ALN/D307). The cumulative incidence of most vascular events increased faster in the first 60 to 120 days (Supplemental Figure S1, https://links.lww.com/ALN/D307) and was less than 1% for each. Table 2 summarizes the incidence of first events, and Supplemental Figure S2 (https://links.lww.com/ALN/D307) shows their distributions over time.

Association between Predischarge Complications and Mortality after Discharge. Figure 3 shows the adjusted associations between predischarge complications and postdischarge mortality over time. Although statistically significant for the 1-yr period overall, the adjusted hazard ratios associating several predischarge complications with death after discharge declined with time from discharge: myocardial infarction (30 days, 1.70 [95% CI, 1.32 to 2.18]; 180 days, 1.15 [95% CI, 0.95 to 1.40]; 365 days, 1.00 [95% CI, 0.75 to 1.32]; overall $P < 0.001$), sepsis (30 days, 1.62 [95% CI, 1.28 to 2.05]; 180 days, 1.28 [95% CI, 1.06 to 1.54]; 365 days, 1.16 [95% CI, 0.89 to 1.53]; overall $P < 0.001$), and major bleeding (30 days, 1.53 [95% CI, 1.30 to 1.81]; 180

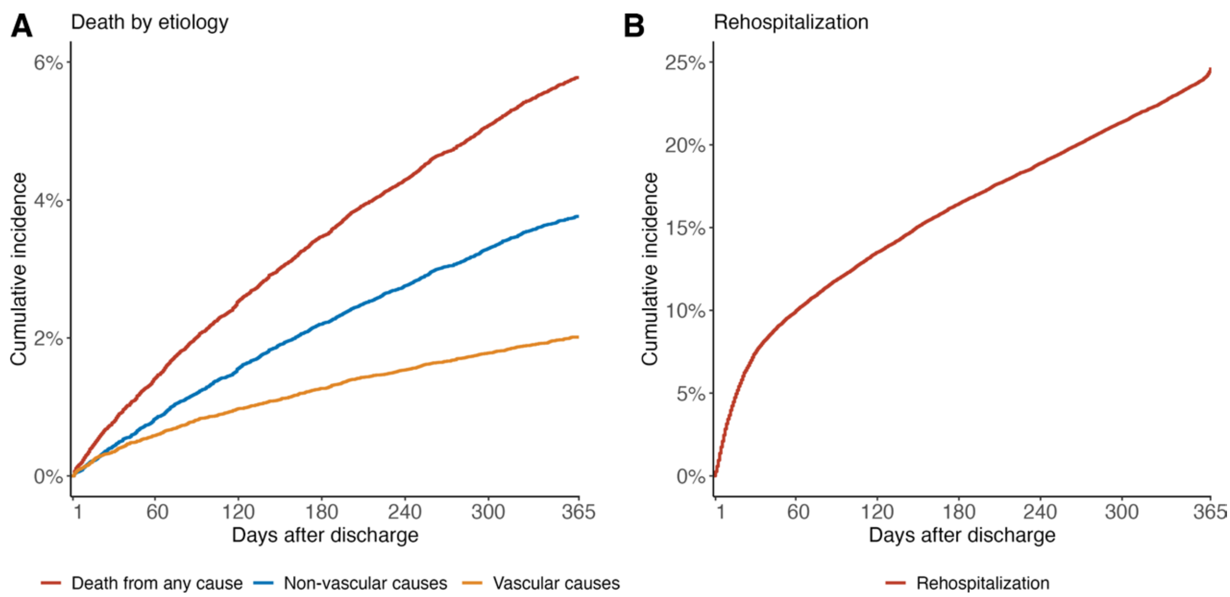

Fig. 2. Cumulative incidences of death and rehospitalization after hospital discharge from surgery. Competing risk of death was accounted for by the cumulative incidence function.

Table 2. One-year Postdischarge Outcomes

Outcomes after Discharge	Number of Patients with Outcome/ Number Contributing Data	Percent Cumulative 1-yr Incidence (95% CI)
Death from any cause	2,165/38,898	5.8 (5.5–6.0)
Death from nonvascular causes	1,409/38,898	3.8 (3.6–4.0)
Death from vascular causes	756/38,898	2.0 (1.9–2.2)
Death from cardiac causes*	129/38,898	0.34 (0.28–0.40)
Myocardial infarction	203/38,898	0.54 (0.46–0.61)
Congestive heart failure	220/38,898	0.59 (0.51–0.66)
Stroke	141/38,898	0.37 (0.31–0.44)
Nonfatal cardiac arrest	37/38,898	0.1 (0.07–0.13)
Amputation	249/38,898	0.66 (0.58–0.74)
Venous thromboembolism	268/38,898	0.71 (0.63–0.8)
Coronary revascularization	166/38,898	0.45 (0.38–0.52)
Rehospitalization	9,157/38,862	24.7 (24.2–25.1)
New diagnosis of cancer	353/33,903	1.1 (0.97–1.2)
New diagnosis of recurrent cancer	501/33,931	1.5 (1.4–1.6)
New diagnosis of dementia†	55/21,380	0.26 (0.19–0.33)
New diagnosis of diabetes	201/34,748	0.62 (0.53–0.72)
Living in a nursing home but not before surgery‡	924/33,051	2.8 (2.6–3.0)
Receiving dialysis but not before surgery‡	58/35,620	0.16 (0.13–0.21)

Due to differences in follow-up time between patients, cumulative incidence can differ from percentage of patients who experienced an event.

**Post hoc* outcome in response to reviewer comments: includes death due to myocardial infarction, due to cardiac arrest, or after coronary revascularization procedure. †Data collection for dementia began in 2011. ‡Percentages at 1 yr are reported instead of cumulative incidences.

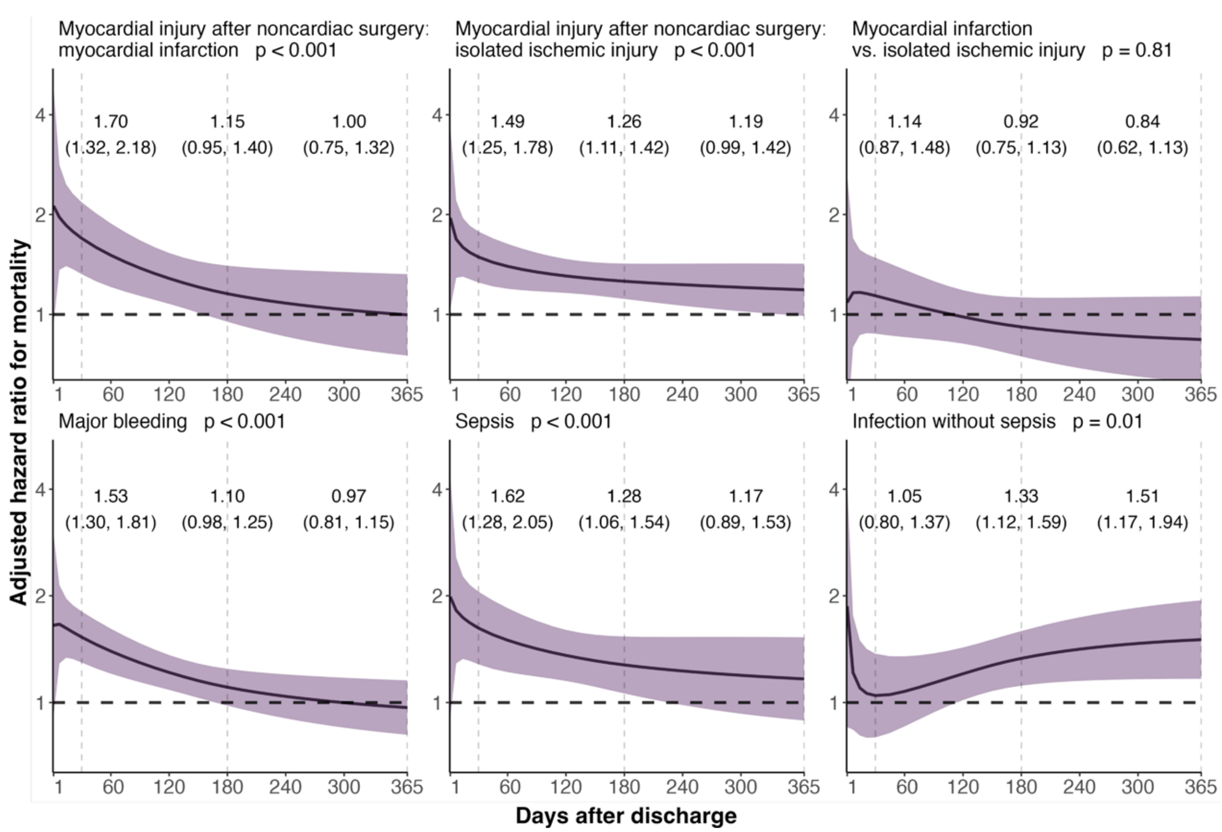

Fig. 3. Associations between predischarge perioperative complications of primary interest and mortality up to 1 yr after discharge from noncardiac surgery. Adjusted hazard ratios are presented; parentheses contain their 95% CIs. *P* values are from global tests for association between each predischarge complication and postdischarge mortality over the entire follow-up period.

days, 1.10 [95% CI, 0.98 to 1.25]; 365 days, 0.97 [95% CI, 0.81 to 1.15]; overall $P < 0.001$). The adjusted hazard ratio for isolated ischemic myocardial injury showed a similar trend but decreased more slowly (30 days, 1.49 [95% CI, 1.25 to 1.78]; 180 days, 1.26 [95% CI, 1.11 to 1.42]; 365 days, 1.19 [95% CI, 0.99 to 1.42]; overall $P < 0.001$) compared to myocardial infarction. Although the comparison is imprecise, there was no significant difference in the risk of death after discharge when comparing myocardial injury after noncardiac surgery that met the criteria for myocardial infarction to that which represented an isolated ischemic myocardial injury among patients who survived to hospital discharge (30 days, 1.14 [95% CI, 0.87 to 1.48]; 180 days, 0.92 [95% CI, 0.75 to 1.13]; 365 days, 0.84 [95% CI, 0.62 to 1.13]; overall $P = 0.81$). The hazard ratio for infection without sepsis was negligible early after discharge but increased over time (30 days, 1.05 [95% CI, 0.80 to 1.37]; 180 days, 1.33 [95% CI, 1.12 to 1.59]; 365 days, 1.51 [95% CI, 1.17 to 1.94]; overall $P = 0.01$).

To aid in the interpretation of these changing hazard ratios, Figure S3 in Supplemental Digital Content 1 (https://links.lww.com/ALN/D307) shows changes over time after discharge in the average differences in the absolute adjusted cumulative risk of mortality associated with each predischarge complication. As the hazard ratios decrease over time, differences in the cumulative risks of mortality increase more slowly over time. For example, the average adjusted absolute increase in the cumulative risk of mortality associated with myocardial infarction that occurred before discharge was 0.55% (95% CI, 0.21 to 0.88%) at 30 days after discharge and increased to 1.45% (95% CI, 0.68 to 2.23%) at 180 days after discharge, but only increased to 1.56% (95% CI, 0.51 to 2.6%) by 365 days after discharge. These absolute differences in the risk of mortality illustrate an average effect for patients in our study and may be higher or lower for any one patient depending on their baseline risk.

Among the predischarge complications of secondary interest, congestive heart failure and amputation were significantly associated with death after discharge (Supplemental Figure S4, https://links.lww.com/ALN/D307) but were uncommon and associated with a small percentage of deaths (Figure S5 in Supplemental Digital Content 1, https://links.lww.com/ALN/D307). Estimates of association were too imprecise to determine if new clinically important atrial fibrillation, venous thromboembolism, stroke, or acute kidney injury managed with dialysis that occurred before discharge were associated with death after discharge.

Considered together, the studied predischarge complications had an attributable fraction of 33.7% (95% CI, 27.2 to 40.2%) for deaths occurring between hospital discharge and 30 days after discharge, 20.7% (95% CI, 17.2 to 24.2%) for deaths between hospital discharge and 180 days after discharge, and 15.0% (95% CI, 12.0 to 17.9%) of all deaths up to 1 yr after discharge (fig. 4). Myocardial injury after noncardiac surgery (either myocardial infarction or isolated ischemic myocardial injury), sepsis, and major bleeding accounted for most postdischarge deaths associated with predischarge complications and for most of the instantaneous hazard of death associated with predischarge complications at any time after discharge (fig. 4). Isolated ischemic myocardial injury was more common than myocardial infarction and was independently associated with a greater percentage of deaths after discharge (Figure S5 in Supplemental Digital Content 1, https://links.lww.com/ALN/D307) and a greater percentage of the hazard of death at any time after discharge (Figure S6 in Supplemental Digital Content 1, https://links.lww.com/ALN/D307).

Results of Prespecified Sensitivity Analysis. Table S1 in Supplemental Digital Content 1 (https://links.lww.com/ALN/D307) reports results of the first sensitivity analysis where cumulative incidences for events other than death were calculated such that patients who did not have an event were censored at the time of last contact instead of at the time of death or last known vital status. Cumulative incidences calculated this way were similar to the primary analysis. Figures S7 and S8 in Supplemental Digital Content 1 (https://links.lww.com/ALN/D307) show association results from the complete case analysis; these were similar to the primary analyses with imputed data.

Results of Post Hoc Analyses. In the *post hoc* analysis to identify predictors of censoring, we found that study center was the strongest predictor (Supplemental Digital Content 1, Table S2, https://links.lww.com/ALN/D307). Additionally, the odds of censoring were modestly higher with older age, lower preoperative hemoglobin, and open surgery; the odds were lower with orthopedic surgery. All of these variables were already included in the model estimating the association between predischarge complications with postdischarge mortality. None of the postoperative predischarge complications studied were associated with censoring.

The cumulative incidence of postdischarge death from cardiac causes was 0.34% (95% CI, 0.28 to 0.40%) per year.

Table S3 in Supplemental Digital Content 1 (https://links.lww.com/ALN/D307) presents the associations between adjustment variables and postdischarge death. Some associations are in general as would be expected: older patients and those with various chronic diseases are more likely to die after discharge. Patients with active cancer before surgery had the highest hazard ratio with mortality. However, there was no association between postdischarge mortality and preoperative history of coronary disease, stroke or transient ischemic attack, or congestive heart failure. The risk of death was lower for patients with a history of hypertension than in those without. Men were

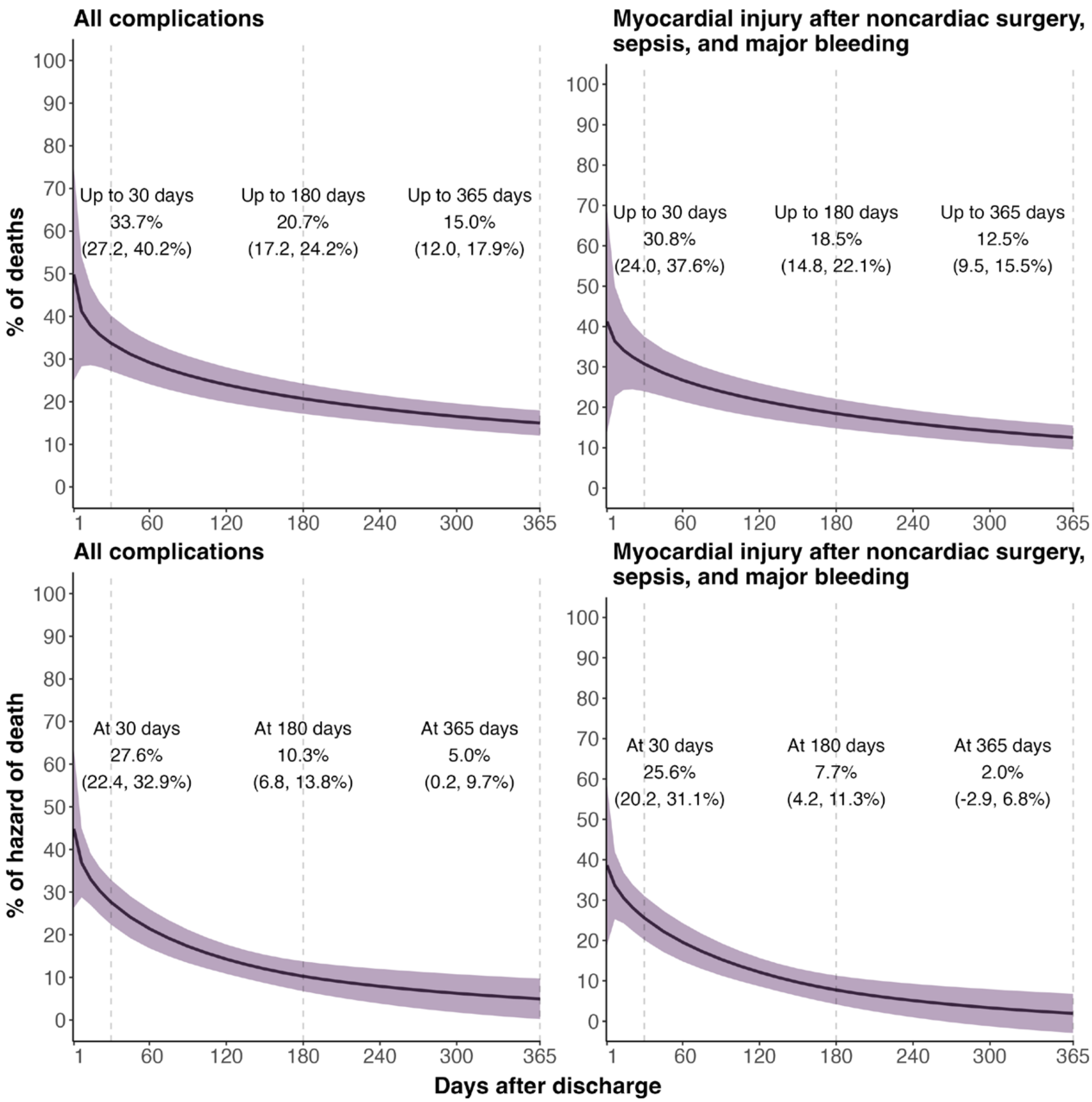

Fig. 4. Percentage of postdischarge deaths and of the hazard of death independently associated with predischarge complications up to 1 yr after discharge from noncardiac surgery. In the *top* panels, calculations are for events that occurred from the day of hospital discharge up to the specified time after discharge. For example, the calculation at 365 days considered all deaths that occurred during the follow-up period, while the calculation at 30 days considered only deaths that occurred in the first 30 days after discharge. In the *bottom* panels, calculations are for the instantaneous hazard of death on specific days; they pertain to deaths predicted to occur on those days. Predischarge complications included myocardial injury after noncardiac surgery, major bleeding, sepsis, infection without sepsis, acute congestive heart failure, amputation, new clinically important atrial fibrillation, acute kidney injury managed with dialysis, stroke, and venous thromboembolism. Parentheses contain 95% CIs.

more likely than women to die in the year after discharge. We caution that these associations were not the focus of our study and are fraught with risk of bias.[26,27]

Table S4 in Supplemental Digital Content 1 (https://links.lww.com/ALN/D307) presents cumulative incidences of postdischarge outcomes at each study center.

Discussion

In this large, international, prospective cohort study, approximately 1 in 18 patients aged 45 yr or older who were discharged from the hospital after inpatient noncardiac surgery died at 1 yr follow-up compared to 1 in 58 who died during the index surgical hospitalization. One in three deaths up to 30 days after discharge and one in five deaths up to 6 months after discharge were independently associated with perioperative complications that occurred before discharge. Predischarge myocardial injury after noncardiac surgery, sepsis, and major bleeding were the complications associated with the largest proportion of postdischarge deaths.

Numerous studies broadly corroborate our finding that early perioperative complications are associated with mortality in the longer term, but our study adds significantly more information about these associations and uniquely focuses on information available to healthcare providers at the transition from hospital to home. A study of patients who had predominantly orthopedic surgery at one United Kingdom center found increased long-term mortality associated with postoperative complications but lacked granularity with respect to the type of complications.[3] A larger sample from the Veterans Administration Surgical Quality Improvement Program showed associations between the number of postoperative complications and long-term mortality but ignored deaths occurring in the first 90 days after surgery[4]—a period when deaths were most strongly associated with predischarge complications in our study. In a prospective cohort study of 2018 patients having noncardiac surgery, myocardial injury after noncardiac surgery was associated with death occurring up to 30 days after surgery (adjusted hazard ratio, 2.28; 95% CI, 1.19 to 4.36) and up to 1 yr after surgery (adjusted hazard ratio, 1.48; 95% CI, 1.07 to 2.06).[5] That study also found other early postoperative complications (*i.e.*, sepsis, stroke, and pneumonia) to be associated with death up to 1 yr after surgery. An observational analysis of a large randomized trial found that postoperative anemia is associated with death or disability up to 90 days after major abdominal surgery.[6] Recent analysis of 9,733 patients pooled from two cohort studies found an association between complications occurring in the first 30 days after surgery and mortality up to 1 yr after surgery.[7] These included complications that occurred during the index postoperative hospitalization. Evolution of the association between complications and mortality was only crudely characterized as hazard ratios before and after postoperative day 20, and attributable fractions were not estimated.

Among patients who survived to discharge, the association between myocardial injury after noncardiac surgery and mortality was similar when the event met the diagnostic criteria for myocardial infarction and when it did not (*i.e.*, isolated ischemic myocardial injury). It is likely that isolated ischemic myocardial injury did not prompt the same secondary prevention measures as myocardial infarction. This highlights the importance of systematic postoperative troponin measurement because most patients with myocardial injury after noncardiac surgery have no other evidence of ischemia,[13,14] and because observational and randomized trial evidence suggests that treating patients with myocardial injury after noncardiac surgery can reduce long-term vascular risk.[28,29] Persistent inflammation may partially explain the time-dependent association between predischarge sepsis and the risk of death after discharge. Increased risk of death associated with perioperative infectious complications has been found to persist for months after cardiac surgery.[30] Major bleeding may confer risk beyond hospitalization through dysregulation of coagulation and thrombosis, through withholding of antithrombotic and antiplatelet therapy, or because persistent anemia after discharge potentiates cardiovascular risk.

Prevention of predischarge complications and increased awareness that they confer persistent mortality risk in the weeks to months after discharge are an opportunity to help prevent postdischarge deaths that may have previously appeared unrelated to the early postoperative course. However, because most deaths after discharge were not associated with in-hospital complications, research focused on postdischarge care is warranted to identify opportunities to prevent more deaths.

This was a large, representative, multicenter, multicountry, prospective cohort study with careful characterization and adjudication of perioperative complications with little loss to follow-up at 1 yr after surgery. We adjusted for preoperative characteristics, the type and urgency of surgery, and several perioperative complications. Unlike most survival analyses, we did not assume proportional hazards but instead allowed the association between covariates and postdischarge mortality to vary over time.

The study had potential limitations. Residual confounding remains a concern despite adjustment. Some of the time-dependent change in hazard ratios may be due to differential depletion of susceptible patients, but this bias is negligible under our study conditions when the outcome occurs in a low proportion of patients.[31] Our study may have underestimated the incidence of nonfatal postdischarge outcomes due to limitations of recall between 30 days and 1 yr after surgery. A sensitivity analysis that prevented attributing event-free time after the day of last study contact provided estimates similar to the primary analysis. Regional variation in healthcare contact after discharge may have also led us to underestimate the incidence of nonfatal postdischarge outcomes at some centers. This may explain some of the differences we observed between centers (Table S4 in Supplemental Digital Content 1, https://links.lww.com/ALN/D307), but differences in case mix and chance operating on low event rates can also exaggerate apparent differences in incidence.

We did not adjudicate some complications (*i.e.*, major bleeding, sepsis, infection without sepsis, congestive heart failure, and acute kidney injury managed with dialysis), and this may have influenced the association between some of these complications and mortality.

Generalizability of absolute estimates of risk to any specific patient, surgical approach, or type of surgery is limited by the broad eligibility criteria in our study. Nevertheless, absolute risk estimates in broad populations remain useful for policy makers, administrators, and researchers to understand what outcomes have the most potential for impact if focused upon. The magnitudes of association between predischarge complications and postdischarge mortality are less likely to differ meaningfully across patient characteristics, surgical approaches, and types of surgery, and identifying differences in magnitude with certainty beyond chance would require a much larger and more costly study with a much greater burden of data collection. It is likely, however, that sepsis, myocardial injury, and major bleeding remain the main prognostically important complications with temporal risk patterns maintained across most patient groups.

We completed follow-up on vital status for 96.5% of participants up to 1 yr after surgery. Nearly all patients lost to follow-up were censored at 30 days after surgery. Medical records, obituaries, and—in one country—a national registry provided data for the occurrence and date of death, but we relied on next of kin for some participants. It is unlikely that reliance on next of kin had any meaningful effect on the estimate of mortality or in the estimate of its association with predischarge complications, and if there was an effect, it would most likely be to modestly underestimate both. Propensity for loss to follow-up was strongly dependent on study center and to a small extent on some preoperative characteristics. Our analyses adjusted for these variables and for study center, thereby minimizing risk of bias from the small proportion of patients lost to follow-up.

Although encouraged to do so, clinical teams did not obtain electrocardiograms in some patients with elevated troponin. As a result, some myocardial infarctions may have been misclassified as isolated ischemic myocardial injury. This would falsely increase the similarity in prognosis between the two myocardial injury categories. However, only a small proportion of patients who had an electrocardiogram after an elevated troponin measurement had ischemic changes. We would expect ischemic changes to be even less common among patients who did not have an electrocardiogram. Such misclassification is likely to be more common in practice, and this further highlights the need to take notice of myocardial injury after noncardiac surgery that is isolated ischemic myocardial injury. Similarly, we may have missed atrial fibrillation as a cause of myocardial injury in patients without electrocardiograms, but myocardial injury due to atrial fibrillation tends to occur with rapid ventricular response that typically prompts investigation. Not all patients with troponin elevation had imaging to rule out pulmonary embolism, but we expect most pulmonary emboli that cause myocardial necrosis to have other features that would prompt investigation.

We imputed a small amount of missing preoperative estimated glomerular filtration rate, preoperative hemoglobin, and myocardial injury status due to missing postoperative troponin for our primary association analyses to avoid loss of sample size from casewise deletion and to avoid bias. Sensitivity analyses without imputation found very similar results.

Conclusions

Approximately 1 in 18 patients 45 yr and older who are discharged from hospital after inpatient noncardiac surgery died within 1 yr after surgery. One quarter of patients were readmitted to the hospital. One third of the deaths that occurred in the first 30 days after discharge and one fifth that occurred in the first 6 months were independently associated with myocardial injury after noncardiac surgery, sepsis, and major bleeding that occurred before hospital discharge.

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Competing Interests

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Supplemental Digital Content

Supplemental Appendix, https://links.lww.com/ALN/D307

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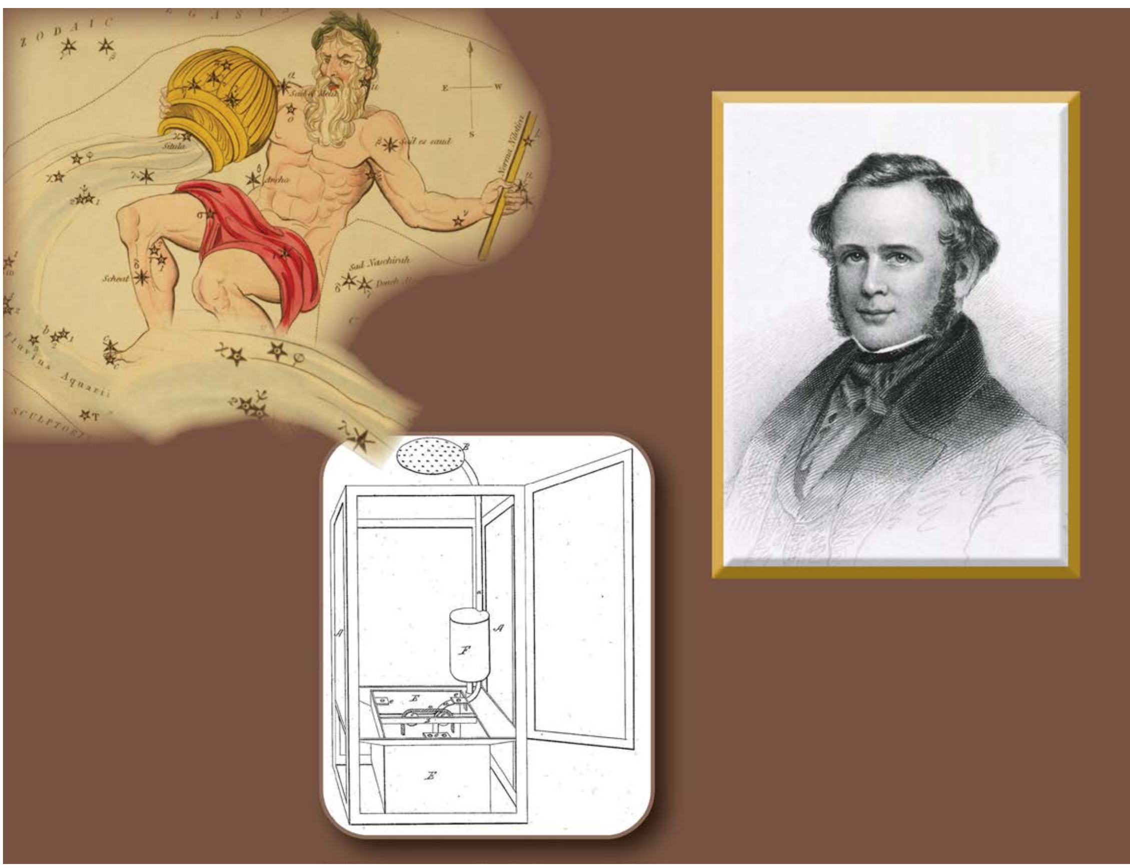
Horace Wells: Showering the World in Aquarian Starlight



Now reserved for entertainment in many cultures, astrology was inseparable from astronomy in ancient times. By following bright stars through seasons in the night sky, scholars hoped to divine celestial influence on human destiny. Midwinter brought the greatest monthly rainfall to Mesopotamia, so a succession of constellations, from Babylon's Gula (Great One) to Greece's Hydrochóos and Rome's Aquarius (*upper*, *left*), all depict the pouring of water. More than 2,000 years later, a future dentist-anesthetist, Horace Wells (1815 to 1848, *right*), was born under Aquarius. Awash in his sign's humanitarian qualities, Wells progressively advocated for preventative dental care and famously explored nitrous oxide to alleviate the pain of dental extractions. Although his public trial of painless dentistry was sentenced to an eternal "Humbug" in 1845, the disappointment did not halt a flood of intellectual pursuits, including a patent for a foot-powered shower (*lower*, *center*) a year later. Unfortunately, his temperament ebbed and flowed, perhaps between hypomania and depression. Rough waters consumed Wells and his former mentee, William T. G. Morton, as their conflict over primacy in discovering anesthesia pushed Wells to his emotional brink. Alas, Aquarian Wells met his tragic end after an impassioned outpouring led to his incarceration and subsequent suicide. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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