Full Methods

VISION Cohort methods

The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION; clinicaltrials.gov identifier NCT00512109) is an international prospective cohort study evaluating major complications after noncardiac surgery. VISION recruited patients undergoing noncardiac surgery from 12 centres in 8 countries between August 2007 and December 2011. Participants were followed during their hospitalization and up to 30 days after surgery.

Participants

Participants in VISION were 45 years or older, were undergoing an operation that required a general or regional anesthetic and required at least an overnight hospital stay. Participants provided consent prior to surgery or, for those whom we could not obtain consent preoperatively due to emergency surgery, consent was obtained within the 24 hours following surgery. Further, 8 centres used a deferred consent process for patients unable to provide consent (e.g., patients sedated and mechanically ventilated) and no legal substitute decision maker was available. This allowed collection of cTnT measurements while awaiting patient's or legal substitute decision maker's consent. Patients were excluded if they had participated in VISION for a previous surgery. Potential participants were identified by screening daily patient lists in the preoperative assessment clinics, surgical wards, intensive care units, surgical lists and patients in preoperative holding areas. In centres where the surgical volume exceeded the research staff's capacity to enroll at least 80% of all cases, the centres were assigned random weeks for recruitment of all or randomly selected surgical services.

Outcomes and Exposures

The outcome of interest was mortality from any cause up to 30 days after surgery. Mortality was ascertained through hospital records, contacting the participant or the participant's family and/or the participant's primary care physician. The main exposures of interest were preoperative kidney function and postoperative cardiac troponin T concentrations. Preoperative kidney function was estimated using the serum creatinine concentration measured most recently prior to surgery as part of routine clinical care. The serum creatinine concentration was converted to an estimated glomerular filtration rate (eGFR) using the CKD-Epi equation.[20] Each participant's eGFR was then categorized as: ≥60, 45 to <60, 30 to <45, 15 to <30, and <15 ml/min/1.73m^2 or on dialysis. Therefore, in this study we further categorized low eGFRs compared to our prior study that categorized a low eGFR as <30 ml/min/1.73m^2 or on dialysis.

Cardiac troponin T was measured prospectively using the Roche 4th-generation Elecsys assay at 6 to 12 hours postoperatively then days 1, 2, and 3 postoperatively. Patients enrolled between 12 and 24 hours after surgery had a cTnT measured immediately and then daily up to the third postoperative day. All cTnT measurements were analyzed at the participating centre and were reported to the attending physicians. For our primary analysis, participants were classified by whether their cTnT was <0.02 or ≥0.02 ng/mL since this was the first threshold shown to have prognostic importance in our previous study.[6] In our exploratory analyses, participants were classified as having a cTnT either <0.03 or ≥0.03 ng/mL or as having a change in cTnT by at least 0.02 ng/mL over the course of the first three postoperative days. For the change in cTnT analysis patients with a lowest cTnT value of ≤0.01 ng/mL met the abnormal cTnT threshold if the highest cTnT value was at least 0.03 ng/mL while patients with a lowest value >0.01 ng/mL were required to have a value at least 0.02 ng/mL higher to be considered abnormal.

Other potential confounders were assessed prior to surgery or as soon as possible after surgery for patients enrolled using deferred consent (i.e. consented within 24 hours of surgery). A complete list of the potential confounders and their definitions is included Appendix 1.

Statistical Analysis

Patient characteristics are described as mean (SD) or median (25^{th} to 75^{th} percentile) as appropriate for continuous data and number (%) for frequency data. A two-sided p-value <0.05 was regarded as statistically significant for all analyses without adjustment for multiple comparisons.

For the primary objective, we performed Cox proportional hazards regression analysis in which the independent variables were the baseline characteristics determined to be of prognostic importance in our previous study.[6] These variables included: age (categorized as 45 to 65 [referent], >65 to 75, and >75 years), history of high risk coronary artery disease, history of peripheral vascular disease, history of stroke, chronic obstructive pulmonary disease, active cancer, urgent or emergent surgery (vs. other surgery), major general surgery, and major neurosurgery. The presence of an abnormal TnT (i.e. ≥0.02 ng/mL) was used as a dichotomous independent variable. As well, kidney function was included as an independent categorical variable with five levels (i.e., ≥60, 45 to <60, 30 to <45, 15 to <30, and <15 ml/min/1.73m^2 or on dialysis) using the ≥60 ml/min/1.73 m^2 category as the reference category. Included in the model were the interaction terms between abnormal cTnT and each kidney function category.

We calculated the effect estimates from the model calculated as an adjusted Hazard Ratio (aHR) with a corresponding 95% confidence interval computed by bootstrapping the model 500 times. The 2.5^{th} and 97.5^{th} percentile of the replicants defined the lower and upper bounds of the 95%

confidence interval. We tested the proportional hazards assumption using a global goodness of fit test of scaled Schoenfeld residuals utilizing rank based methods for both the overall model and each model variable at the same time. We assessed colinearity using the variance inflation factor (VIF) and considered reduction of model parameters for variables with a VIF >10, however, none of the variables had a VIF >10.

We assessed model predictive discrimination through evaluation of the NRI in patients with severely impaired kidney function (i.e. eGFR <30 ml/min/1.73 m^2).[21] The NRI is defined as the probability that an event is predicted with a 'new' model but not with an 'old' model. Our old model included all the predictors of 30 day postoperative mortality above (age, high risk coronary artery disease, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, active cancer, urgent/emergent surgery, and type of surgery) and the new model included the same predictors plus postoperative cTnT. For our analyses the old model was one based on preoperative clinical variables only (age, high risk coronary artery disease, peripheral vascular disease, stroke, chronic obstructive pulmonary disease, active cancer, urgent/emergent surgery, and type of surgery) and our new model included cTnT in addition to the preoperative clinical variables. To estimate the probability of survival at 30 days, we used proportional hazards regression (the same model used in the primary analysis) to obtain an estimate of the survival function over the first 30 days after surgery, using the BASELINE statement in the PROC PHREG procedure in SAS. One minus the estimate of the survival function at the last day of follow-up (30 days after surgery) was used as the estimated probability of death at 30 days. We categorized the predicted risk for each patient with each model as <1%, 1-5%, 5.1-10%, and >10%. The NRI represents the proportion of patients whose predicted risk more closely

approximates their actual 30 day event status when cTnT is used in addition to the preoperative clinical variables.

Exploratory analyses were conducted to determine if alternative definitions of an abnormal cTnT ameliorated any effect modification of eGFR. The alternative definitions of an abnormal cTnT included a peak cTnT of ≥0.03 ng/mL or a change in cTnT of ≥ 0.02 ng/mL as described above. These alternative definitions replaced the abnormal cTnT variable in the Cox model used for the primary analysis and the interaction terms between an abnormal cTnT and each strata of eGFR were recalculated.

All analyses were performed with SAS v9.2 (Cary, USA).

Supplemental Material

Appendix 1. Model covariate definitions.

1. Age – Patient age in years was recorded and subsequently categorized as 45-64 years of age, 65-74 years of age, and >75 years of age.

2. Sex – Male or female.

3. History of coronary artery disease – A current or prior history of any one of the following: i. angina; ii. myocardial infarction or acute coronary syndrome; iii. a segmental cardiac wall motion abnormality on echocardiography or a segmental fixed defect on radionuclide imaging; iv. a positive radionuclide exercise, echocardiographic exercise, or pharmacological cardiovascular stress test demonstrating cardiac ischemia; v. coronary angiographic or computer tomography (CT) coronary angiographic evidence of atherosclerotic stenosis ≥50% of the diameter of any coronary artery; vi. ECG with pathological Q waves in two contiguous leads.

4. Recent high-risk coronary artery disease – A physician diagnosis <6 months prior to noncardiac 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 angina - inability to carry on any physical activity without the development ofangina.

5. History of cardiac arrest – A patient with a prior history of a cardiac arrest.

6. History of 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.

7. History of peripheral vascular disease – A physician diagnosis of a current or prior history of: 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 noncardiac artery.

8. History of stroke – A physician diagnosis of a current or prior stroke, or CT or magnetic resonance (MR) evidence of a stroke.

9. History of a transient ischemic attack (TIA) – A physician diagnosis of a current or prior TIA.

10. History of deep venous thrombosis (DVT) or pulmonary embolus (PE) – A patient with a current or prior history of a DVT or PE.

11. Diabetes – Patient stated that they have a diagnosis of diabetes or a physician has previously recorded that the patient has diabetes. This included gestational diabetes at the time of noncardiac surgery, but not past gestational diabetes that had resolved.

12. Hypertension – A physician diagnosis of hypertension**.**

13. Current atrial fibrillation – A patient with a current history of atrial fibrillation.

14. Obstructive sleep apnea – A physician or sleep study diagnosis of obstructive sleep apnea.

15. Chronic obstructive pulmonary disease (COPD) – A physician current or prior diagnosis of chronic bronchitis, emphysema, or COPD, or a patient provided a history of daily production of sputum for at least 3 months in 2 consecutive years.

16. Active cancer – A patient was designated as having active cancer if they fulfilled any of the following criteria: i. undergoing surgery for cancer; ii. known metastatic disease; or iii. Patient had received active treatment for their cancer (e.g., chemotherapy, radiation, or surgery) within the 6 months prior to their surgery, but this did not apply to patients with non-melanoma skin cancers or surgery for a biopsy.

17. Urgent/Emergency surgery – Emergency surgery was surgery that occurred <24 hours after a patient developed an acute surgical condition, and urgent surgery was surgery that occurred 24-72 hours after a patient developed an acute surgical condition.

18. Major orthopedic surgery – A patient undergoing one or more of the following orthopedic surgeries: major hip or pelvis surgery, internal fixation of femur, knee arthroplasty, above knee amputations, or lower leg amputation (amputation below knee but above foot).

19. Major general surgery – A patient undergoing one or more of the following general surgeries: complex visceral resection, partial or total colectomy or stomach surgery, other intra-abdominal surgery, or major head and neck resection for non-thyroid tumor.

20. Major urology or gynecology surgery – A patient undergoing one or more of the following major urology or gynecology surgeries: nephrectomy, ureterectomy, bladder resection, retroperitoneal tumor resection, exenteration, cytoreduction surgery, hysterectomy, radical prostatectomy, or transurethral prostatectomy.

21. Major neurosurgery **–** A patient undergoing one or more of the following neurosurgeries: craniotomy or major spine surgery (i.e., surgery involving multiple levels of the spine).

22. Major vascular surgery – A patient undergoing one or more of the following vascular surgeries: thoracic aorta reconstructive vascular surgery, aorto-iliac reconstructive vascular surgery, peripheral vascular reconstruction without aortic cross-clamping, extracranial cerebrovascular surgery, or endovascular abdominal aortic aneurysm repair.

23. Major thoracic surgery – A patient undergoing one or more of the following thoracic surgeries: pneumonectomy, lobectomy, wedge resection of lung, resection of mediastinal tumor, or major chest wall resection.

24. Low-risk surgeries – A patient undergoing one or more of the following surgeries: parathyroid, thyroid, breast, hernia, local anorectal procedure, oopherectomy, salpingectomy, endometrial ablation, peripheral nerve surgery, ophthalmology, ears/nose/throat surgery, vertebral disc surgery, hand surgery, cosmetic surgery, arterio-venous access surgery for dialysis, or any other surgery not mentioned above.

Supplemental Table 1. Net reclassification improvement when cardiac Troponin T (cTnT) is added to clinical predictors of death at 30 days. Net reclassification is improved when, in patients who died, the risk level increases after adding cTnT to the model and, in patients who censored, the risk level decreases after adding cTnT to the model.

Table for patients who died

		Risk Level in Model with TnT			
		< 1%	1-5%	5.1 - 10%	> 10%
Risk Level in Model without TnT	< 1%	100.0	0.0	0.0	0.0
	1-5%	0.0	100.0	0.0	0.0
	5.1 - 10%	0.0	0.0	100.0	0.0
	> 10%	0.0	0.0	0.0	100.0

Table for patients who censored

		Risk Level in Model with TnT			
		< 1%	1-5%	5.1 - 10%	> 10%
Risk Level in Model without TnT	< 1%	96.3	3.7	0.0	0.0
	1-5%	3.0	91.9	5.1	0.0
	5.1 - 10%	0.0	18.1	78.3	3.6
	> 10%	0.0	0.0	3.7	96.3

Supplemental Table 2. Frequency of an abnormal cardiac Troponin T (cTnT) defined as ≥0.03 ng/mL and 30-day all-cause mortality by estimated glomerular filtration rate (eGFR) strata.

eGFR Strata (ml/min/1.73 m^2)	**cTnT value (ng/mL)**	**n (%)**	**% who died (95% CI)**	**aHR for Death (95% CI)**
≥60	<0.03	10682 (95%)	1.0 (0.8, 1.2)	
	≥0.03	584 (5%)	9.6 (7.5, 12.2)	5.14 (3.57, 7.1)
45 to <60	<0.03	1297 (87%)	1.2 (0.8, 2)	
	≥0.03	191 (13%)	9.9 (6.5, 15)	6.02 (3.21, 12.74)
30 to <45	<0.03	590 (77%)	1.5 (0.8, 2.9)	
	≥0.03	173 (23%)	13.9 (9.5, 19.8)	7.23 (3.61, 18.3)
15 to <30	<0.03	163 (59%)	5.5 (2.9, 10.2)	
	≥0.03	111 (41%)	10.8 (6.3, 18)	1.18 (0.44, 3.73)
<15 or on dialysis	<0.03	88 (36%)	4.5 (1.8, 11.1)	
	≥0.03	158 (64%)	8.9 (5.4, 14.3)	1.31 (0.47, 8.54)

eGFR = estimated glomerular filtration rate; cTnT = cardiac troponin T; n=number of patients with this value of cTnT; CI=confidence interval; aHR = adjusted hazard ratio

Supplemental Table 3. Frequency of an abnormal cardiac Troponin T (cTnT) defined as an absolute change of at least 0.02 ng/mL and 30-day all-cause mortality by estimated glomerular filtration rate (eGFR) strata.

eGFR Strata (ml/min/1.73 m^2)	**Change cTnT of at least 0.02 ng/mL**	**n (%)**	**% who died (95% CI)**	**Strata Specific Adjusted HR (95% CI)**
≥60	No	10882 (96.6%)	1.2% (1.0, 1.4)	
	Yes	384 (3.4%)	8.1% (5.8, 11.3)	3.19 (2.15, 4.76)
45 to <60	No	1361 (91.5%)	1.7% (1.1, 2.5)	
	Yes	127 (8.5%)	9.4% (5.5, 15.7)	3.91 (1.85, 7.92)
30 to <45	No	657 (86.1%)	2.9% (1.9, 4.5)	
	Yes	106 (13.9%)	13.2% (8.0, 20.9)	3.01 (1.37, 6.49)
15 to <30	No	210 (76.6%)	6.2% (3.7, 10.3)	
	Yes	64 (23.4%)	12.5% (6.5, 22.8)	1.03 (0.27, 2.72)
<15 or on dialysis	No	149 (60.6%)	8.1% (4.7, 13.6)	
	Yes	97 (39.4%)	6.2% (2.9, 12.9)	0.65 (0.18, 1.67)