Title

Risk of mortality following surgery in patients with a previous cerebrovascular accident or acute coronary syndrome: a 10-year database linkage between Hospital Episode Statistics, Myocardial Infarction National Audit Project, and Office for National Statistics

Sub-title

Mortality following surgery in patients with a previous cerebrovascular accident or acute coronary syndrome.

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KEY POINTS

Question

Is the time elapsed since a cardiovascular event associated with an increased risk of mortality in patients undergoing non-neurologic, non-cardiac surgery?

Findings

The increased risk of postoperative mortality after elective surgery decreased with increasing time since the cardiovascular event, with a plateau approximately 14 months after the event. A similar pattern was seen with emergency surgery, but it reached the plateau approximately seven months after the event.

Meaning

Clinicians should balance deferring the potential benefits of the surgery against the desire to avoid increased mortality from overly expeditious surgery after a recent cardiovascular event.

ABSTRACT

Importance: There is a lack of consensus regarding the interval of time-dependent postoperative mortality risk following an acute coronary syndrome or stroke.

Objective: To determine the magnitude and duration of risk associated with the time interval between a preoperative cardiovascular event and 30-day postoperative mortality.

Design: This is a longitudinal retrospective population-based cohort study.

Setting: This study linked data from the Hospital Episode Statistics for NHS England, Myocardial Ischaemia National Audit Project and Office for National Statistics mortality registry.

Participants: All adults undergoing a National Health Service-funded non-cardiac non-neurologic surgery in England between April 1, 2007, and March 31, 2018, registered in Hospital Episode Statistics Admitted Patient Care.

Exposure: The time interval between a previous cardiovascular event (acute coronary syndrome or stroke) and surgery.

Main outcomes and measures: The primary outcome was 30-day all-cause mortality. The secondary outcomes were postoperative mortality at 60, 90, and 365 days. Multivariable logistic regression models with restricted cubic splines were used to estimate adjusted odds ratios.

Results: There were 877,430 patients with, and 20,582,717 without, a prior cardiovascular event. Among patients with a previous cardiovascular event, the time interval associated with increased risk of postoperative mortality was surgery within 11.3 (95%CI 10.8-11.7) months, with subgroup risks of 14.2 (95%CI 13.3-15.3) months before elective surgery and 7.3 (95%CI 6.8-7.8) months for emergency surgery. Heterogeneity in these timings was noted across many surgical specialities. The time-dependent risk intervals following stroke and myocardial infarction were similar, but absolute risk was greater following a stroke. Regarding surgical urgency, the risk of 30-day mortality was higher in those with a prior cardiovascular event for emergency surgery (aHR = 1.35; 95%CI 1.34-1.37) and an elective procedure (aHR = 1.83; 95%CI 1.78-1.89) than those without a prior cardiovascular event.

Conclusion and relevance: Surgery within one year of an acute coronary syndrome or stroke is associated with increased postoperative mortality before reaching a new baseline, particularly for elective surgery. This information may help clinicians and patients balance deferring the potential benefits of the surgery against the desire to avoid increased mortality from overly expeditious surgery after a recent cardiovascular event.

KEYWORDS: adult anaesthesia, myocardial infarction, stroke, surgery, mortality

INTRODUCTION

Ischaemic heart disease (IHD) and stroke are the second and third most common causes of disability-adjusted life years worldwide, exceeded only by congenital diseases.(1) In the UK, over 5 million major NHS-funded operations are performed each year,(2) and it is recognised that pre-existing cardiovascular disease strongly contributes to the risk of adverse perioperative outcomes. (3) Despite improved and increased use of preventative and interventional treatments (4,5) the prevalence of cardiovascular disease in the surgical population continues to increase.(6) This results in surgery being offered to patients with co-morbidities previously felt to be significantly high risk or preclude surgery completely.(7,8) It is also not well-known which characteristics of the preoperative cardiovascular event or which treatments received at the time may predict a future adverse perioperative outcome other than that the very nature of requiring intervention is a risk factor.(9)

Surgery can cause haemodynamic, endocrine, and inflammatory disturbances, leading to an increased mortality risk compared to those not having surgery. These alterations are especially important for perioperative risks among patients with established cardiovascular disease.(10) The optimal time for surgery after an event is a complex interplay of the changing relative risks of adverse events associated with cardiovascular events, the risks of delaying surgery (disease progression, functional decline etc.), absolute risks and the patient's appetite for risk. Currently, there is limited evidence on the interactions between time, patient and surgical characteristics and the risk of postoperative adverse events. (11–13) The most recent large electronic health record studies have demonstrated a lack of consensus concerning the time-dependent risk interval. (12,14) The 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery make limited recommendations concerning the timing of non-cardiac surgery in patients with a history of acute coronary syndrome.(15)

Using individual patient-level data, we aim to describe the nature of the time-dependent association between preoperative cardiovascular events and postoperative mortality in an extensive and unselected cohort of patients undergoing non-cardiac, non-neurosurgical operations with NHS funding between 2007 and 2018 in hospitals in England to support shared decision-making.

METHODS

Study design and population

This is a longitudinal retrospective population-based cohort study of all adult patients (≥18 years) undergoing an NHS-funded surgery between April 1, 2007, and March 31, 2018, registered in Hospital Episode Statistics Admitted Patient Care (Figure 1). The first surgical episode within the study window using the *Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, 4th revision* (OPCS-4) codes was identified and acted as the index surgical event. Patients whose most recent cardiovascular event (acute coronary syndrome or stroke) was in the ten years preceding their index surgery were identified using the International Classification of Diseases, Tenth revision codes. Linking Hospital Episode Statistics records to the Myocardial Infarction National Audit Project; additional acute coronary syndrome cases were identified using MINAP-specific codes. More details about the study design, cardiovascular events, and surgery codes can be found in the prospectively published protocol.(16) A completed STROBE checklist is included as a supplement.

Setting

This study used Hospital Episode Statistics for NHS England linked to Myocardial Ischaemia National Audit Project and Office for National Statistics mortality data. Hospital Episode Statistics Admitted Patient Care is a national registry database containing details of all admissions to NHS hospitals in England and has been available since 1989.(17) Data from 1997 to 2018 were extracted. The Myocardial Infarction National Audit Project is a national cardiac clinical audit that collects information to measure the process and care outcomes of every patient diagnosed with myocardial infarction; data from 2003 (registry inception) to 2018 were extracted.(18) The Office for National Statistics mortality data were extracted between 2007 and 2019. Ethical approval was obtained from East Midlands – Nottingham 1 Research Ethics Committee (18/EM/0403) and Health Research Authority Confidential Advisory Group (19/CAG/0013).

NHS Digital is responsible for the collection, quality assurance and governance of HES APC and ONS data. The data in HES APC undergoes extensive cleaning prior to linkage.[1] After the linkage of NHS Digital's HES APC and ONS to the MINAP data set, the data were further cleaned to identify duplicates, lack of agreement, and potentially erroneously linked patient episodes. NHS Digital (HES) and the ONS openly publish how their databases are regularly checked to ensure the accuracy of the recorded data and their methods of data cleaning and quality assurance. (19,20)

The National Institute for Cardiovascular Outcomes Research (NICOR) is the data processor for MINAP. They are responsible for the data collection and quality assurance, performing annual audits which demonstrating high case ascertainment rates.(21) The Healthcare Quality Improvement Partnership is the data controller.

Classification of surgery

To stratify the effects of increasing operative severity, a classification based on OPCS-4 codes taking a minor, moderate, and major interpretation of the surgical invasiveness was used as already described by others.(2) Specifically, all OPCS-4 codes for hospital procedures were reviewed, and non-operative codes were removed (e.g., radiotherapy, diagnostic imaging, or oxygen therapy). The remaining codes were stratified according to the three categories of surgical invasiveness. The 'minor' category comprised all procedures that might be considered surgery, including minor surgery such as superficial skin procedures, interventional radiology procedures and diagnostic endoscopies, but excluding non-invasive diagnostic procedures (e.g., diagnostic imaging). The 'moderate' category included procedures routinely undertaken in an operating theatre and/or under general or regional anaesthesia. The 'major' category included major procedures that may often result in significant tissue injury due to duration or complexity. We also pre-specified common operations by surgical speciality such as major lower limb joint replacement, vascular, gastrointestinal, gynaecological, urological, ear nose and throat (ENT), ophthalmological and breast surgery. Finally, the surgical urgency was assessed according to the admission method (elective or emergency) recorded in HES.

We excluded the following surgical categories a priori: cardiac, neurosurgical, carotid endarterectomy, obstetrics, tracheostomy, and percutaneous gastrostomy.(16) The decision to exclude cardiac surgery was based on a pre-existing subspecialty-specific risk prediction tool EuroSCORE II, thus reducing the need to investigate this population. The lack of specificity within ICD-10 codes also means it is impossible to identify type III-V myocardial infarctions. Therefore, the results may be unreliable in this specific patient population. Neurosurgery and carotid endarterectomy were excluded based on the recognised high stroke risk specific to these surgeries. Both percutaneous gastrostomy insertion and tracheostomy formation were excluded due to significant confounding with post-stroke bulbar dysfunction. Obstetric surgical procedures were outside the scope of this study.

Outcomes

The primary outcome was 30-day all-cause postoperative mortality. The secondary outcomes were postoperative mortality at 60, 90, and 365 days.

(16)

Statistical analysis

The primary exposure was the time interval between the most recent pre-operative cardiovascular event and index surgery. The potential confounders in all patients from HES APC that were included as covariates in the modelling were: age (continuous), sex, index of multiple deprivation, comorbidities (hypertension, atrial fibrillation, stable angina, peripheral vascular disease, valvular heart disease, congestive heart failure, respiratory failure, diabetes mellitus, renal failure, cancer, liver disease, and dementia). The Charlson comorbidity index was also calculated.(16) For people with

MINAP data, additional information on comorbidities was extracted. All patients included in the analyses were unique individuals.

Multivariable logistic regression models were constructed for the association between the time interval from the most recent preoperative cardiovascular event to index surgery and postoperative mortality modelling time as a categorical variable to provide clinically interpretable thresholds, using 0-2, 3-6, 7-12, 12-24, and ≥24 months. Splines of the association of time elapsed between a cardiovascular event and 30-day mortality were created by restricted cubic spline functions.(22) Knots were placed at the 10th, 25th, 50th, 75th, and 90th percentile, with the 50th (median) as the reference. Because patients without a cardiovascular event did not have "time", restricted cubic splines and logistic regression analyses were restricted to patients with previous cardiovascular events. Multivariable logistic regression models were fitted for 30-day mortality among patients with a cardiovascular event with the following factors: cardiac arrest, left ventricle ejection fraction, infarction site, QRS, reperfusion treatment, and Killip class.

Incidence rates of postoperative mortality were calculated by dividing the deaths by follow-up person-years. Hazard ratio (HR) estimates, and 95% confidence intervals (CI) were calculated using Cox regression analysis, comparing the mortality risk between those with and without a cardiovascular event before surgery. The Cox model assumption was tested using Schoenfeld residuals.

Subgroup analyses were also performed for common operations by surgical speciality. Sensitivity analysis was also performed by taking the patient's last operation (instead of the first). Missing values for the index of multiple deprivation were retained by assigning a new category for them. Any missing data derived from the MINAP dataset were also assigned to a new category. All statistical analyses were performed using R, version 4.1.2.(23) The statistical threshold for significance was set at p = 0.05 for a 2-tailed test.

RESULTS

Baseline characteristics

The study population included 21,460,147 patients from 316 hospitals in England undergoing surgery between 2007 and 2018 (Table 1) after excluding 186,038 patients aged <18 years and 10,715 patients with unknown sex. 877,430 (4.1%) procedures were performed in patients with a history of cardiovascular events. On average, patients with a prior cardiovascular event were 19.3 years older, were more often men, and had a higher prevalence of comorbidities ($p < 0.0001$). Elective surgery accounted for 83% of the overall surgical workload. Emergency surgery was more frequent in patients with a prior cardiovascular event than in those without a prior event (29% vs 16%, $p < 0.0001$). The majority of patients in both groups underwent an operation of moderate risk.

The association of time elapsed from cardiovascular event and surgery with mortality

In patients with a prior cardiovascular event, there was a stepwise decline in odds associated with 30-day mortality for longer time periods between the event and operation, even after adjustment for known confounders (Table 2). The time-dependent association between the cardiovascular event and any surgery with the secondary outcomes is presented in eTables 3 to 5. The odds of 30-day all-cause mortality levelled off after 11.3 (95%CI 10.8-11.7) months, irrespective of surgical invasiveness (Figure 2). This plateau was 14.2 (95%CI 13.3-15.3) months for elective surgery and 7.3 (95%CI 6.8-7.8) months after a cardiovascular event for emergency surgery (Figure 2). There are qualitative differences in the time to plateau for different surgical specialities (eTable 7 to 34, eFigures 1 to 22). For example, the increased risk was observed 8 months after the event for elective vascular surgery (eFigure 13), 12 months for urological surgery (eFigure 1), 9 months for major gastrointestinal surgery (eFigure 18) and 6 months for gynaecological surgery (eFigure 3). The time-dependency following stroke and myocardial events were similar, but absolute risks were greater with stroke (Figure 1). The sensitivity analysis taking patients' last operation between 2007 and 2018 demonstrated similar results (eTable 36 & eFigure 35). The estimates reported when analysing only patients from the more specialised MINAP dataset were the same as those from the HES dataset (eTables 38 to 41 & eFigures 36 to 40).

Mortality comparing those with and without a prior cardiovascular event

Comparing those with a prior cardiovascular event at any time-point to those with no prior event, the 30-day crude mortality was greater across all types and urgency of surgery (minor 3.4% vs 0.8%; moderate 4.8% vs 0.8%; major 7.2% vs 1.1%; elective 0.9% vs 0.2%; emergency 14% vs 4.4%; all $p < 0.0001$) (eTable 1 & 2). Mortality rates were higher in patients with a cardiovascular event before surgery than those without (Table 3). Following adjustment, the highest risk of 30-day mortality was in those with prior cardiovascular events undergoing major surgery (aHR = 1.75; 95%CI 1.71 to 1.79). Elective procedures had the greater risk (aHR = 1.83; 95%CI 1.78 to 1.89) for those cardiovascular diagnoses than emergency surgery (aHR = 1.35; 95%CI 1.34 to 1.37).

Perioperative Risk Factors

Deprivation was associated with postoperative mortality, with the greatest risk for the most deprived patients compared with the least deprived, regardless of surgical categorization (aOR = 1.15 95%CI 1.07 to 1.21 – minor; aOR = 1.17 95%CI 1.08 to 1.21 – moderate; aOR = 1.15 95%CI 1.08 to 1.13 – major; aOR = 1.11 95%CI 1.01 to 1.20 - elective) (eTable 6). However, deprivation was less important with regard to emergency surgery (most vs. least deprived; aOR = 1.04; 95%CI 0.99 to 1.07). Using the MINAP-linked data, impaired cardiac contractility (left ventricular ejection fraction, LVEF) at the time of the cardiac event was associated with increased odds of 30-day postoperative mortality across all severities of surgical invasiveness (Table 4). Considering elective surgery, poor LVEF following myocardial event (aOR = 1.51; 95%CI 1.15 to 1.98) but not moderate LVEF impairment was associated with increased odds of mortality (aOR = 1.23; 95%CI 1.00 to 1.53). Moderate and poor LVEF were significantly associated with increased odds of postoperative mortality following emergency surgery (aOR = 1.17; 95%CI 1.05 to 1.30 and aOR = 1.78; 95%CI 1.57 to 2.02, respectively). Any infarction site (indeterminant, anterior, lateral) carried a higher mortality risk than the inferior territory. Of note, those who had primary PCI had lower odds of 30-day post-operative mortality after a minor (aOR = 0.77; 95%CI 0.65 to 0.91) or elective (aOR = 0.78; 95%CI 0.63 to 0.97) surgery as compared with no reperfusion therapy following an acute coronary syndrome.

DISCUSSION

Our study of 21.4 million patients undergoing surgery in England between 2007 and 2018 demonstrated that a prior cardiovascular event, irrespective of the time between the event and surgery, was associated with an increased mortality risk compared with patients without a prior cardiovascular event. We also report a strong time-dependent relationship between prior cardiovascular events and postoperative mortality, with risk plateauing after 14 months for elective surgery. The risk levelled off for emergency surgery at 7 months after the preoperative event.

Our findings about 30-day mortality in those with a prior stroke or acute coronary syndrome are consistent with previously published UK national registry analysis of postoperative mortality.(24) Fowler et al. reported that 90-day postoperative mortality in those with previous stroke and myocardial infarction was 10.7% and 5.7% compared with 9.9% and 6.5%, respectively, in our study (eTable 35).

Modelling the time from the event until surgery against 30-day postoperative mortality, the risk decreased non-linearly as the time interval increased. This time-dependent association between the preoperative event and postoperative mortality is comparable to the study by Jørgensen et al.(12) They demonstrated that elective surgery within 2 months after stroke carried the highest risk. This agrees with our findings, where the odds of death were over 9-fold greater for patients with surgery within two months of an event. Making specific observations about the previous stroke, they identified 9 months as their cut-off for elective surgery compared to our 14-month timeframe. Sanders et al. also conducted a UK registry study of the association between time elapsed before surgery following acute coronary syndrome or stroke and subsequent postoperative mortality.(13) Although their focus was only on elective joint replacement and AAA repair, they also found surgery within one year of acute coronary syndrome was associated with increased postoperative mortality. In contrast, whilst they did not find an association between the timing of previous stroke and mortality after elective joint replacement, the authors also acknowledged that their study lacked sufficient power to test this.

The existing evidence regarding perioperative risk in patients with a preoperative cardiovascular event has led to recommendations of at least a 6-month deferment of surgery where possible,(25) preferably 12 months.(11,26–28) In our study, 225,944 patients had surgery within this 12-month window of their preoperative cardiovascular event, of which 9.8% died within 30 days of surgery. Our data strongly support the recommendation that perioperative mortality risk is high during the first year after a cardiovascular event.(29) This is at variance with previous registry research, which suggested a potentially shorter 6-month interval for elective surgery (25) and the 2022 ESC guidelines on non-cardiac surgery, which suggest a minimum delay of only 3 months where possible.(15)

Whilst postoperative mortality risk reaches a plateau at 12 months across most surgical specialities, several exceptions were seen in the subgroup analysis. For instance, in the context of emergency vascular surgery, recent cardiovascular events are only associated with increased mortality risk for surgery within 3 months of an event. This is most likely due to other predominating risk factors, such as the underlying reason for surgery. In contrast, for elective orthopaedic operations such as primary hip arthroplasty, the risk was elevated for 18 months after a cardiovascular event, wherein the relative contribution to risk from cardiovascular disease can be reasonably expected to be large compared to the surgery itself.

It is well recognized that emergency surgery is associated with increased perioperative risk compared to elective surgery in general, even for the same procedure. This is due to the unplanned nature, including out-of-hours operating, lack of time for physiologic optimization, and potentially more serious underlying pathology. With these things in mind, the magnitude of the deleterious effect of operating shortly after a cardiovascular event is largely lost compared with these other drivers of postoperative mortality. In other words, the circumstances and underlying reason for surgery in the emergency setting are such that no matter what the baseline patient condition at presentation, the risks are predominantly from the former, which is why the risk associated with a previous cardiovascular event does not manifest for very long.

Postoperative mortality rates were similar between ischaemic stroke, haemorrhagic stroke, and myocardial infarction (NSTEMI and STEMI), although we found that preoperative TIA and unstable angina were associated with lower postoperative mortality rates (eTable 35). This would support placing comparable emphasis on understanding the time-dependent risk of preoperative stroke and myocardial infarction, justifying our aggregate reporting. It is important to emphasize that the risk curves for stroke and myocardial infarction indicated similar plateaus were reached at 12 months. Linking the MINAP data, we could show that patients with a history of ACS had favourable postoperative mortality rates when their ACS had been treated with a pPCI revascularization strategy (Table 4).

The demographic findings that a history of previous cardiovascular events is more common in older males with multiple other comorbidities are already well-established.(30) Importantly, we were also able to demonstrate that in this surgical population, increasing levels of socio-economic deprivation were more common in those with a previous cardiovascular event, in agreement with existing findings in the general population.(31,32) In broad agreement with previous population-level mortality data from the UK, we found liver disease, renal failure, and congestive heart failure were the three co-morbidities associated with the greatest fold increase in 30-day mortality, followed by peripheral vascular disease, dementia, and cardiac arrhythmias.(13,24)

To our knowledge, this is the largest and most detailed study of the time-dependent nature of postoperative mortality in patients with a prior cardiovascular event. One of the key strengths of our study is the size of our study population – the whole adult population of England having non-cardiac, non-neurologic, and non-obstetric surgery between 2007 and 2018. The next largest study of the time-dependent nature of a preoperative cardiovascular risk factor was by Jorgensen in 2014.(12) They studied 7,137 people undergoing surgery after a previous stroke, with 145 postoperative deaths within 30 days of surgery. In contrast, we report 877,430 people undergoing surgery after stroke or acute coronary syndrome, with 40,999 deaths within 30 days of surgery. Whilst the primary outcome assessed 30-day mortality and allows comparability with existing surgical literature,(33) we were also able to report 60-day, 90-day and 1-year mortality modelled against time elapsed since the preoperative cardiovascular event. In particular, this will allow future comparison as surgical research and clinical practice move from assessing 30-day to 90-day postoperative mortality.(34–36) The demographics of our study are comparable with that of large North American (37) and other Western European surgical populations,(12) and broad inclusion criteria, maximising the generalisability of our findings. Due to the magnitude of our study population and the 30-day mortality event rate, we could control for many confounders and provide reliable estimates for subgroup analyses, allowing clinicians to refer to their specific surgical speciality.

Our study has several limitations. It is observational and retrospective in nature; therefore, caution must be exercised in drawing inferences about causality between the timing of surgery and postoperative outcome. Some time-dependent changes in mortality will be unrelated to surgery at all – mortality hazards decay with time after stroke and myocardial infarction. This, in turn, will probably lead to a degree of unavoidable survivor bias – those who are fit enough (or alive) to have surgery over one-year post event may represent a fitter cohort than those having surgery earlier. However, the data are specifically presented to inform patients and their peri-operative care team about the temporal nature of preoperative cardiovascular risk factors as part of a shared decision-making process, not to dictate when nor whether an individual patient is offered surgery. Registry coding inaccuracies risk leading to the under-representation of comorbidity diagnoses. However, by linking data between HES and MINAP, we have corroborated our findings across different registries and indicated the association between increasing time since the cardiovascular event and decreasing postoperative mortality remains present. Some patients will have undergone unavoidable high-risk surgery irrespective of a recent cardiovascular event with the potential to skew mortality findings, but we have presented the data by surgical severity and urgency to minimize this effect. Some patients can have undergone surgery without their history of the cardiovascular event being known. However, this is unlikely to be in large numbers and reflects clinical practice where, unfortunately, patient medical histories are sometimes incomplete. As these are routinely collected inpatient data, we did not have information on lifestyle factors more commonly recorded in primary care datasets, such as smoking or alcohol consumption.

In conclusion, clinicians must balance deferring the potential benefits of the surgery (e.g., relief of pain, avoidance of disease progression) against the desire to avoid increased mortality from overly expeditious surgery after a recent cardiovascular event. As part of shared decision-making, this will require integrating individual patients' values about these competing aspects of their health. This study specifically demonstrates that elective surgery within one year of an acute coronary syndrome or stroke is associated with increased postoperative mortality.

CONTRIBUTORS

C.V.C & M.S.L had full access to all the study data and take full responsibility for the integrity of the data and the accuracy of the data analysis. C.V.C and M.S.L contributed equally to this paper. Conception and design: R.S, T.M.M & I.M.; acquisition of data: M.S.L, WL, I.M; analysis of data: C.V.C & M.S.L; interpretation of data: C.V.C, M.S.L, R.S, T.M.M, I.M.; drafting the article: C.V.C & M.S.L.; revision for important intellectual content and approval of the version to be published: All authors.

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ROLE OF FUNDER

The funder was not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICTS OF INTEREST

None to declare.

DATA SHARING STAMENT

The authors are not permitted to share the data publicly. Research ethics committee approval is required to access the data, including an application to the HRA Confidentiality Advisory Group with respect to Section 251 (4) of the NHS Act 2006.

ETHICS

Ethical approval for this observational study has been obtained from East Midlands—Nottingham 1 Research Ethics Committee; REC reference: 18/EM0403.

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Tables

Table 1. Baseline characteristics of all patients undergoing surgery between 2007 and 2017.

	Overall (N=21,460,147)	Without prior event (N=20,582,717)	With prior event (N=877,430)	Absolute difference (95%CI)
Age yrs., mean (SD)	53.4 (19.4)	52.6 (19.2)	71.9 (12.7)	-19.3 ()
Sex				
Female	11,577,157 (54)	11,220,826 (55)	356,331 (41)	14 (13.8 to 14.2)
Male	9,882,990 (46)	9,361,891 (45)	521,099 (59)	-14 (-14.1 to -13.9)
Ethnicity				
Asian	3,217,494 (15)	3,150,564 (15)	66,930 (7.6)	7.4 (7.2 to 7.6)
Black	929,443 (4.3)	891,350 (4.3)	38,093 (4.3)	0 (-0.2 to 0.2)
Others	475,541 (2.2)	464,016 (2.3)	11,525 (1.3)	1 (0.9 to 1.3)
White	16,367,832 (76)	15,617,378 (76)	750,454 (86)	-10 (-10.1 to -9.9)
Unknown	469,837 (2.2)	459,409 (2.2)	10,428 (1.2)	1 (0.8 to 1.2)
Index of multiple deprivation				
Least deprived	4,029,196 (19)	3,877,746 (19)	151,450 (17)	2 (1.8 to 2.2)
-	4,202,019 (20)	4,030,286 (20)	171,733 (20)	0 (-0.2 to 0.2)
-	4,197,716 (20)	4,016,653 (20)	181,063 (21)	-1 (-1.2 to -0.8)
-	4,154,682 (19)	3,975,900 (19)	178,782 (20)	-1 (-1.2 to -0.8)
Most deprived	4,176,252 (19)	3,988,656 (19)	187,596 (21)	-2 (-2.2 to -1.8)
Unknown	700,282 (3)	693,476 (3)	6,806 (1)	2 (1.8 to 2.2)
Charlson comorbidity index				
0	16,401,423 (76)	15,936,777 (77)	464,646 (53)	24 (23.8 to 24.2)
1	3,936,433 (18)	3,673,547 (18)	262,886 (30)	-12 (-12.2 to -11.8)
2	889,944 (4)	782,878 (4)	107,066 (12)	-8 (-8.2 to -7.8)
≥3	232,347 (1)	189,515 (1)	42,832 (5)	-4 (-4.2 to -3.8)
Comorbidities				
Hypertension	3,804,608 (18)	3,389,416 (16)	415,192 (47)	-31 (-31.1 to -30.8)
Atrial fibrillation	594,199 (2.8)	480,216 (2.3)	113,983 (13)	-10.7 (-10.9 to -10.5)
Stable angina	50,786 (0.2)	4,016 (<0.1)	46,770 (5.3)	-5.2 (-5.4 to -5)
Dementia	242,844 (1.1)	193,834 (0.9)	49,010 (5.6)	-4.7 (-4.9 to -4.5)
Peripheral Vascular Disease	108,255 (0.5)	89,306 (0.4)	18,949 (2.2)	-1.8 (-2 to -1.6)
Valvular Heart Disease	212,441 (1.0)	151,632 (0.7)	60,809 (6.9)	-6.2 (-6.4 to -6)
Heart failure	1,920,406 (8.9)	1,796,263 (8.7)	124,143 (14)	-5.3 (-5.5 to -5.1)
Respiratory disease	1,455,402 (6.8)	1,295,413 (6.3)	159,989 (18)	-11.7 (-11.9 to -11.5)
Diabetes mellitus	420,301 (2.0)	353,673 (1.7)	66,628 (7.6)	-5.9 (-6.1 to -5.7)
Chronic kidney disease	1,153,917 (5.4)	1,091,083 (5.3)	62,834 (7.2)	-1.9 (-2.1 to -1.78)
Active malignancy	199,401 (0.9)	189,443 (0.9)	9,958 (1.1)	-0.2 (-0.4 to 0.001)
Chronic liver disease	208,294 (1.0)	174,318 (0.8)	33,976 (3.9)	-3.1 (-3.3 to -2.9)
Surgical invasiveness				

Commented [ML1]: Christos - should there be data between these brackets?

Minor	7,493,661 (35)	7,142,867 (35)	350,794 (40)	-5 (-5.2 to -4.8)
Moderate	9,413,447 (44)	9,056,811 (44)	356,636 (41)	3 (2.8 to 3.2)
Major	4,553,039 (21)	4,383,039 (21)	170,000 (19)	2 (1.8 to 2.2)
Surgical urgency				
Elective	17,833,826 (83)	17,208,304 (84%)	625,522 (71)	13 (12.8 to 13.2)
Emergency	3,626,321 (17)	3,374,413 (16%)	251,908 (29)	-13 (-13.2 to -12.8)

Data are expressed as absolute numbers and (percentages, %) unless otherwise stated.

Table 2. The effect of timing from a cardiovascular event to a surgery on 30-day all-cause mortality.

	With prior event (N = 877,430)			
	30-d all-cause mortality			
Time elapsed from recent event	**Alive (%)**	**Dead (%)**	**Unadjusted OR (95%CI)**	**Adjusted[a] OR (95%CI)**
Minor surgery				
0 to 2-months	30521 (87.9)	4218 (12.1)	5.85 (5.61-6.10)	3.76 (3.59-3.94)
3 to 6-months	25985 (96.8)	858 (3.2)	1.40 (1.30-1.50)	1.27 (1.18-1.37)
7 to 12-months	30414 (97.7)	721 (2.3)	1.00 (0.93-1.09)	1.00 (0.92-1.08)
12 to 24-months	45439 (97.6)	1130 (2.4)	1.05 (0.99-1.12)	1.06 (0.99-1.13)
>24 months	206358 (97.7)	4865 (2.3)	Reference	Reference
Moderate surgery				
0 to 2-months	29081 (79.3)	7589 (20.7)	9.57 (9.24-9.92)	6.22 (5.98-6.49)
3 to 6-months	18554 (94.4)	1097 (5.6)	2.17 (2.03-2.32)	1.70 (1.59-1.83)
7 to 12-months	27732 (96.6)	968 (3.4)	1.28 (1.18-1.37)	1.14 (1.06-1.22)
12 to 24-months	46241 (97.1)	1384 (2.9)	1.08 (1.03-1.16)	1.05 (0.99-1.12)
>24 months	217861 (97.3)	5959 (2.7)	Reference	Reference
Major surgery				
0 to 2-months	21107 (79.7)	5386 (20.3)	5.39 (5.17-5.62)	4.16 (3.97-4.35)
3 to 6-months	8357 (92.7)	654 (7.3)	1.65 (1.52-1.80)	1.39 (1.27-1.52)
7 to 12-months	11534 (95)	609 (5)	1.11 (1.02-1.22)	1.02 (0.94-1.12)
12 to 24-months	20790 (95.4)	1003 (4.6)	1.02 (0.95-1.09)	1.00 (0.93-1.07)
>24 months	101001 (95.5)	4783 (4.5)	Reference	Reference
Elective surgery				
0 to 2-months	25925 (93.2)	1897 (6.8)	13.6 (12.7-14.4)	9.57 (8.94-10.2)
3 to 6-months	36544 (98.9)	416 (1.1)	2.11 (1.90-2.34)	1.88 (1.69-2.09)
7 to 12-months	53143 (99.3)	366 (0.7)	1.28 (1.14-1.42)	1.22 (1.09-1.36)
12 to 24-months	88497 (99.4)	546 (0.6)	1.14 (1.04-1.25)	1.13 (1.03-1.24)
>24 months	415647 (99.5)	2234 (0.5)	Reference	Reference
Emergency surgery				
0 to 2-months	54784 (78.2)	15296 (21.8)	2.23 (2.17-2.28)	2.23 (2.17-2.29)

3 to 6-months	16352 (88.2)	2193 (11.8)	1.07 (1.11-1.22)	1.05 (1.00-1.10)
7 to 12-months	16537 (89.5)	1932 (10.5)	0.93 (0.88-0.98)	0.93 (0.87-0.98)
12 to 24-months	23973 (89)	2971 (11)	0.99 (0.95-1.03)	0.99 (0.95-1.04)
>24 months	104512 (88.9)	13105 (11.1)	Reference	Reference

[a] *Adjusted for age, sex, index of multiple deprivation, hypertension, atrial fibrillation, stable angina, peripheral vascular disease, valvular heart disease, congestive heart failure, respiratory diseases, diabetes mellitus, renal failure, cancer, liver disease, and dementia.*

Table 3. Hazard ratios of mortality after a surgical event comparing patients with a cardiovascular event prior the surgery and those without any cardiovascular event.

	With prior event		**Without prior event**			
All-cause mortality	**Events**	**Incidence per 1,000 p-yrs.**	**Events**	**Incidence per 1,000 p-yrs.**	**Unadjusted HR (95%CI)**	**Adjusted HR[a,b] (95%CI)**
Minor surgery		**(N=350,794)**		**(N=7,142,867)**		
30-d	11,806	417.5 (410.0-425.1)	59,622	102.1 (101.3-102.9)	4.09 (4.01-4.17)	1.44 (1.41-1.47)
31 to 60-d	7,068	127.6 (124.6-7-130.6)	41,447	35.7 (35.3-36.0)	3.59 (3.50-3.68)	1.36 (1.32-1.40)
61 to 90-d	5,190	63.6 (61.9-65.4)	32,535	18.8 (18.6-19.0)	3.40 (3.30-3.50)	1.31 (1.27-1.35)
91 to 1-year	27,108	86.0 (85.0-87.0)	177,463	25.6 (25.5-25.7)	3.38 (3.33-3.42)	1.34 (1.32-1.36)
Within 1-year	51,172	161.1 (159.7-162.5)	311,067	44.8 (44.6-44.9)	3.55 (3.52-3.58)	1.36 (1.35-1.37)
Moderate surgery		**(N=356,636)**		**(N=9,056,811)**		
30-d	17,011	599.7 (590.7-608.7)	71,484	96.6 (95.9-97.3)	6.17 (6.07-6.27)	1.71 (1.68-1.74)
31 to 60-d	5,424	97.6 (95.0-100.3)	27,860	18.9 (18.7-19.1)	5.19 (5.04-5.34)	1.59 (1.54-1.64)
61 to 90-d	3,672	44.7 (43.252-46.1)	20,589	9.3 (9.2-9.5)	4.80 (4.64-4.97)	1.52 (1.46-1.57)
91 to 1-year	22,085	68.7 (67.8-69.6)	132,317	14.9 (14.8-15.0)	4.64 (4.57-4.70)	1.53 (1.51-1.56)
Within 1-year	48,192	149.1 (147.7-150.4)	252,250	28.4 (28.3-28.5)	5.16 (5.11-5.21)	1.59 (1.58-1.61)
Major surgery		**(N=170,000)**		**(N=4,383,039)**		
30-d	12,182	914.8 (898.7-931.2)	47,441	132.7(131.5-133.9)	6.83 (6.70-6.97)	1.75 (1.71-1.79)
31 to 60-d	4,684	182.1 (177.0-189.4)	22,963	32.3 (31.9-32.7)	5.67 (5.50-5.86)	1.58 (1.52-1.63)
61 to 90-d	3,076	81.8 (79.0-84.7)	16,468	15.5 (15.3-15.7)	5.30 (5.10-5.51)	1.54 (1.48-1.61)
91 to 1-year	12,373	85.5 (84.0-87.1)	81,295	19.1 (19.0-19.2)	4.51 (4.42-4.59)	1.49 (1.46-1.52)
Within 1-year	32,315	221.0 (218.6-223.4)	168,167	39.4 (39.2-39.6)	5.44 (5.38-5.51)	1.59 (1.57-1.61)
Elective surgery		**(N=625,522)**		**(N=17,208,304)**		
30-d	5,462	106.8 (104.0-109.7)	29,407	20.8 (20.6-21.1)	5.13 (4.98-5.28)	1.83 (1.78-1.89)
31 to 60-d	4,428	43.5 (42.3-44-9)	33,364	11.8 (11.7-12.0)	3.69 (3.57-3.80)	1.49 (1.44-1.54)
61 to 90-d	4,031	26.6 (25.8-27.4)	31,898	7.6 (7.5-7.6)	3.53 (3.41-3.65)	1.42 (1.37-1.47)
91 to 1-year	30,839	51.5 (50.9-52.0)	239,573	14.1 (14.0-14.1)	3.67 (3.63-3.71)	1.49 (1.47-1.51)
Within 1-year	44,760	74.5 (43.8-75.2)	334,242	19.6 (19.6-19.7)	3.79 (3.75-3.83)	1.52 (1.50-1.53)
Emergency surgery		**(N=251,908)**		**(N=3,374,413)**		

30-d	35,537	1887.2 (1867.7-1906.9)	149,140	553.6 (550.8-556.4)	3.36 (3.32-3.40)	1.35 (1.34-1.37)
31 to 60-d	12,748	364.3 (358.0-370.7)	58,906	111.7 (110.8-112.6)	3.29 (3.23-3.36)	1.30 (1.28-1.33)
61 to 90-d	7,907	158.6 (155.2-162.2)	37,694	48.4 (47.9-48.9)	3.31 (3.23-3.39)	1.28 (1.25-1.32)
91 to 1-year	30,727	168.7 (166.9-170.6)	151,502	49.5 (49.3-49.8)	3.44 (3.40-3.48)	1.29 (1.27-1.30)
Within 1-year	86,919	466.5 (463.4-469.6))	397,242	129.0 (128.6-129.4)	3.37 (3.35-3.40)	1.31 (1.30-1.33)

[a] *Adjusted for age, sex, index of multiple deprivation, hypertension, atrial fibrillation, stable angina, peripheral vascular disease, valvular heart disease, congestive heart failure, respiratory diseases, diabetes mellitus, renal failure, cancer, liver disease, and dementia.*

[b] *All p-values < 0.0001*

Table 24. Effect of preoperative predictors on 30-days all-cause mortality by surgical invasiveness and urgency using HES linked MINAP data.

30-days all-cause mortality										
	Surgical invasiveness						**Surgical urgency**			
	Minor		**Moderate**		**Major**		**Elective**		**Emergency**	
Predictors	**aOR[a] (95%CI)**	**p-value**	**aOR[a] (95%CI)**	**p-value**	**aOR[a] (95%CI)**	**p-value**	**aOR[a] (95%CI)**	**p-value**	**aOR[a] (95%CI)**	**p-value**
Cardiac arrest	3.17 (2.66-3.78)	<.0001	3.15 (2.76-3.59)	<.0001	2.96 (2.46-3.57)	<.0001	2.28 (1.80-2.90)	<.0001	3.35 (3.02-3.7)	<.0001
Left ventricle ejection fraction										
Good	Reference		Reference		Reference		Reference		Reference	
Moderate	1.07 (0.90-1.28)	.457	1.26 (1.09-1.45)	0.002	1.21 (1.01-1.47)	0.037	1.23 (1.00-1.53)	.053	1.17 (1.05-1.30)	.003
Poor	1.85 (1.50-2.27)	<.0001	1.67 (1.42-1.97)	<.0001	1.62 (1.27-2.05)	<.0001	1.51 (1.15-1.98)	.003	1.78 (1.57-2.02)	<.0001
Unassessed	1.42 (1.22-1.65)	<.0001	1.61 (1.42-1.83)	<.0001	1.48 (1.26-1.73)	<.0001	1.21 (1.00-1.47)	.045	1.60 (1.46-1.75)	<.0001
Unknown	1.32 (1.15-1.52)	<.0001	1.42 (1.26-1.59)	<.0001	1.41 (1.22-1.63)	<.0001	1.24 (1.05-1.48)	.01	1.44 (1.33-1.57)	<.0001
Infarction site										
Inferior	Reference		Reference		Reference		Reference		Reference	
Indeterminant	1.44 (1.15-1.81)	.002	1.27 (1.07-1.44)	.007	1.36 (1.09-1.70)	.007	1.44 (1.10-1.87)	.008	1.24 (1.08-1.41)	.002
Anterior	1.40 (1.14-1.73)	.001	1.23 (1.05-1.51)	.01	1.10 (0.89-1.37)	.379	1.30 (1.02-1.66)	.036	1.17 (1.03-1.32)	.015
Lateral	1.51 (1.11-2.05)	.009	1.27 (1.00-1.60)	.048	1.54 (1.15-2.06)	.004	1.31 (0.91-1.90)	.145	1.37 (1.15-1.63)	.<001
Posterior	1.36 (0.79-2.32)	.268	0.99 (0.61-1.62)	.977	0.87 (0.46-1.66)	.677	0.80 (0.37-1.77)	.587	1.07 (0.75-1.52)	.708
Unknown	1.23 (1.04-1.46)	.014	0.99 (0.87-1.13)	.915	1.07 (0.91-1.27)	.413	0.97 (0.80-1.18)	.772	1.09 (0.98-1.20)	.098
QRS										
Normal	Reference		Reference		Reference		Reference		Reference	
Prolonged	0.97 (0.80-1.18)	.795	1.16 (1.00-1.34)	.043	0.98 (0.81-1.20)	.855	1.05 (0.82-1.34)	.701	1.09 (0.98-1.22)	0.105
Unknown	1.18 (1.06-1.31)	.002	1.10 (1.01-1.20)	.030	1.22 (1.09-1.36)	<.001	1.22 (1.06-1.39)	.004	1.11 (1.05-1.19)	<.001
Reperfusion treatment										
None	Reference		Reference		Reference		Reference		Reference	
pPCI	0.77 (0.65-0.91)	.002	1.04 (0.91-1.18)	.604	0.94 (0.78-1.14)	.545	0.78 (0.63-0.97)	.022	0.92 (0.83-1.02)	.119
Thrombolysis	1.05 (0.84-1.31)	.671	0.93 (0.76-1.12)	.440	1.27 (1.01-1.61)	.043	1.05 (0.80-1.38)	.736	1.03 (0.90-1.19)	.658
Unknown	0.88 (0.77-0.99)	.035	0.98 (0.88-1.08)	.637	1.11 (0.98-1.26)	.094	0.78 (0.67-0.92)	.003	1.02 (0.94-1.10)	.648
Killip class										
I	Reference		Reference		Reference		Reference		Reference	

II	1.14 (0.89-1.45)	.308	1.24 (1.02-1.51)	.03	1.32 (1.02-1.70)	.034	1.74 (1.27-2.38)	<.001	1.19 (1.03-1.37)	.015
III	1.48 (1.09-2)	.012	1.01 (0.79-1.29)	.943	0.80 (0.54-1.19)	.278	1.51 (0.97-2.36)	.068	1.10 (0.92-1.32)	.29
IV	2.71 (1.41-5.19)	.003	3.04 (2.12-4.37)	<.0001	3.44 (1.57-7.52)	.002	4.23 (2.14-8.34)	<.0001	3.05 (2.25-4.13)	<.0001
Unknown	1.33 (1.16-1.53)	<.001	1.54 (1.37-1.73)	<.0001	1.46 (1.27-1.69)	<.0001	1.65 (1.37-1.98)	<.0001	1.42 (1.30-1.54)	<.0001

[a] *Adjusted for age, sex, index of multiple deprivation, hypertension, atrial fibrillation, unstable angina, peripheral vascular disease, valvular heart disease, congestive heart failure, respiratory diseases, diabetes mellitus, renal failure, cancer, liver disease, and dementia.*

Figure legend

Figure 1. Study flowchart.

Figure 2. Restricted cubic splines for risk of 30-day all-cause mortality by the time between the most recent cardiovascular event (top) and myocardial infarction (middle) and ischaemic stroke (bottom) by surgery invasiveness and urgency. The spline was adjusted for age, sex, index of multiple deprivation, hypertension, atrial fibrillation, stable angina, peripheral vascular disease, valvular heart disease, congestive heart failure, respiratory diseases, diabetes mellitus, renal failure, cancer, liver disease, and dementia.