Invited Commentary

Trends in Perioperative Cardiovascular Events
Mostly Sunny, With Showers

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The past decade and a half has witnessed a culture change in perioperative cardiovascular evaluation and management. On the basis of landmark studies such as the Coronary Artery Revascularization Project (CARP)[1] and the PeriOperative ISchemic Evaluation (POISE) trial,[2] we have learned that practices such as routine preoperative coronary angiography and one-size-fits-all β-blockade are not beneficial (and, in the latter case, appear to be harmful). The most recent iteration of the American College of Cardiology/American Heart Association (ACC/AHA) perioperative guidelines advocates a relatively parsimonious approach to preoperative stress testing and advises caution with regard to initiating and titrating β-blockers.[3]

Now that the "less is more" approach has grown deeper roots in the clinical cardiology community, it seems that this is a fitting time to take stock of perioperative outcomes on a national scale. Smilowitz and colleagues[4] have used the National Inpatient Sample to review trends in major adverse cardiovascular and cerebrovascular events (MACCE) from 2004 to 2013. The overall frequency of MACCE declined significantly over the study period, as did perioperative death and acute myocardial infarction (AMI). These findings are encouraging, as they suggest that patients have not been harmed (and perhaps have avoided harm) because of contemporary preoperative evaluation practices. However, the perioperative stroke rate increased over this time period. This held true after adjustment for a multitude of variables, although the trend was attenuated somewhat in patients undergoing nonvascular surgery.

In an era when stroke incidence is decreasing nationwide, and stroke mortality is also declining,[5] albeit at a slower rate than in the past,[6] it is concerning that perioperative stroke does not appear to be following suit. What might be unique about the perioperative population that could increase their risk? Patients subjected to anesthesia and fluid shifts may be prone to hypoperfusion-related strokes, or so-called watershed infarcts, more commonly than the general population. Smilowitz and colleagues[4] suggest that an increase in perioperative β-blocker use may have contributed to the stroke rate increase, though the curve does not appear to level off at 2008 or 2009 as one might expect, given the publication of POISE at the time.[2] Is it likely that perioperative β-blockade is still overprescribed? Unfortunately, medication data was not available in the data set used by Smilowitz and colleagues, and this is perhaps the most significant limitation of the study. In addition to β-blockers, it would have been very useful to know how many of these patients were taking statins and aspirin. Given the recent expansion of indications for statins in primary prevention, as per the 2013 ACC/AHA lipid guidelines,[7] it will be interesting to see if perioperative stroke rates decline in future studies.

In an administrative data set like the National Inpatient Sample, there is no clinical narrative, or even a timeline, for any given admission. Therefore, it was not possible for the authors to determine with certainty how many of the reported MACCE were truly perioperative events, despite the sensitivity analyses that were performed. Introduction of a new *International Classification of Diseases, Ninth Revision (ICD-9)* code for prior stroke or transient ischemic attack in 2007 may have somehow increased recognition of cerebrovascular events. Conversely, perioperative AMI rates may have appeared to decrease because clinicians obtained fewer routine postoperative electrocardiograms and cardiac biomarkers over time. While many trials and cohort studies in cardiovascular medicine include heart failure admissions or heart failure with clinical worsening under the umbrella of MACCE, heart failure was not included in this study, likely because heart failure exacerbations or incident heart failure would have been difficult to distinguish from chronic heart failure based on *ICD-9* codes alone. With our aging population, it will be especially important to understand the relationship between perioperative care and acute on chronic heart failure, and the relative specificity of *ICD-10* codes may help with this in the future.

Smilowitz and colleagues[4] showed that the downward trend in overall perioperative MACCE and upward trend in stroke was consistent between sexes and across racial groups. There were strikingly higher perioperative death and stroke rates among non-Hispanic black patients than among other groups. Although the gaps appear to have narrowed slightly over time, these findings suggest that further concerted efforts to identify and reduce disparities in care are badly needed.

It is also important to note that despite adjustment for many identifiable risk factors, 3 types of surgery—vascular, thoracic, and transplant—were associated with higher risks of all types of MACCE. This may be a reflection in part of procedural complexity, but more likely, a consequence of multiple comorbidities in these patient populations. While major vascular surgery and thoracic surgery have long been considered higher risk than most other general surgical procedures, as recognized by the Revised Cardiac Risk Index,[3] the current results imply that solid organ transplant surgery should be given equal consideration in perioperative risk assessment. However, it remains somewhat unclear how these patients should be risk stratified and treated to prevent perioperative MACCE effectively. Many liver and kidney transplant programs in this country mandate annual stress testing for patients to maintain actively listed status, but

there is no compelling evidence to suggest that this practice improves outcomes. On the basis of idiosyncratic presurgical testing protocols, which vary greatly among centers, patients with no clinical cardiovascular disease may be denied life-saving organs, while others with extensive disease may be cleared for transplant and go on to have postoperative cardiovascular events. Multidisciplinary teams, including cardiologists who are invested in caring for organ transplant recipients both preoperatively and postoperatively, should evaluate and follow these patients. Ultimately, multicenter studies will be needed to help define best practices in this population.

While the work by Smilowitz and colleagues[4] is hypothesis generating, we are in need of prospectively collected, clinically relevant data to confirm and elaborate upon the findings. The apparent increase in perioperative stroke is disconcerting, but until the specific causes of this phenomenon are clear, we cannot develop useful countermeasures. Multicenter, multiregional collaboration will be essential to accomplish these goals.

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JAMA Cardiology | Original Investigation

Perioperative Major Adverse Cardiovascular and Cerebrovascular Events Associated With Noncardiac Surgery

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IMPORTANCE Major adverse cardiovascular and cerebrovascular events (MACCE) are a significant source of perioperative morbidity and mortality following noncardiac surgery.

OBJECTIVE To evaluate national trends in perioperative cardiovascular outcomes and mortality after major noncardiac surgery and to identify surgical subtypes associated with cardiovascular events using a large administrative database of United States hospital admissions.

DESIGN, SETTING, PARTICIPANTS Patients who underwent major noncardiac surgery from January 2004 to December 2013 were identified using the National Inpatient Sample.

MAIN OUTCOMES AND MEASURES Perioperative MACCE (primary outcome), defined as in-hospital, all-cause death, acute myocardial infarction (AMI), or acute ischemic stroke, were evaluated over time.

RESULTS Among 10 581 621 hospitalizations (mean [SD] patient age, 65.74 [12.32] years; 5 975 798 female patients 56.60%]) for major noncardiac surgery, perioperative MACCE occurred in 317 479 hospitalizations (3.0%), corresponding to an annual incidence of approximately 150 000 events after applying sample weights. Major adverse cardiovascular and cerebrovascular events occurred most frequently in patients undergoing vascular (7.7%), thoracic (6.5%), and transplant surgery (6.3%). Between 2004 and 2013, the frequency of MACCE declined from 3.1% to 2.6% (*P* for trend <.001; adjusted odds ratio [aOR], 0.95; 95% CI, 0.94-0.97) driven by a decline in frequency of perioperative death (aOR, 0.79; 95% CI, 0.77-0.81) and AMI (aOR, 0.87; 95% CI, 0.84-0.89) but an increase in perioperative ischemic stroke from 0.52% in 2004 to 0.77% in 2013 (*P* for trend <.001; aOR 1.79; CI 1.73-1.86).

CONCLUSIONS AND RELEVANCE Perioperative MACCE occurs in 1 of every 33 hospitalizations for noncardiac surgery. Despite reductions in the rate of death and AMI among patients undergoing major noncardiac surgery in the United States, perioperative ischemic stroke increased over time. Additional efforts are necessary to improve cardiovascular care in the perioperative period of patients undergoing noncardiac surgery.

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Worldwide, more than 300 million noncardiac surgeries are performed each year.[1] Major adverse cardiovascular and cerebrovascular events (MACCE), including myocardial infarction and ischemic stroke, are a significant source of perioperative morbidity and mortality.[2,3] Cardiovascular complications prolong inpatient hospitalization, increase medical costs, and are the leading cause of perioperative death.[4,5] Over the past decades, there have been improvements in perioperative risk stratification, advances in surgical and anesthetic technique, and ongoing efforts to improve perioperative cardiovascular care with large therapeutic trials in the perioperative period.[6-10] At the same time, the rising burden of cardiovascular risk factors in the population undergoing noncardiac surgery may attenuate improvements in perioperative outcomes over time.[11]

Despite the significant burden perioperative events place on the national health care system, trends in perioperative MACCE among patients hospitalized for major noncardiac surgery have not been reported in the contemporary era.[5] We sought to evaluate national trends in perioperative cardiovascular outcomes and mortality after noncardiac surgery and to identify surgical predictors of in-hospital perioperative cardiovascular events using a large administrative database of hospital admissions from the United States.

Key Points

Question What are the trends in perioperative major adverse cardiovascular events (MACCE) after noncardiac surgery in the United States?

Finding In this analysis of patients undergoing in-hospital major noncardiac surgery from 2004 to 2013, the frequency of MACCE declined from 3.1% to 2.6% driven by a decline in frequency of perioperative death and acute myocardial infarction but an increase in perioperative ischemic stroke from 0.52% in 2004 to 0.77% in 2013.

Meaning Perioperative MACCE occurs in 1 of every 33 hospitalizations for noncardiac surgery; despite reductions in the rate of death and acute myocardial infarction among patients undergoing major noncardiac surgery in the United States, perioperative ischemic stroke increased over time.

Methods

Study Population

Patients age 45 years or older requiring major noncardiac surgery between January 2004 and December 2013 were included in this analysis. Patients were identified using the Healthcare Cost and Utilization Project's (HCUP) National Inpatient Sample (NIS), a large administrative database of discharge-level data from a 20% stratified sample of all hospitals in the United States with deidentified data from approximately 8 million hospitalizations per year.[12] Patients were included if they had a principal Clinical Classifications Software (CCS) procedure code representing a major therapeutic operating room procedure (HCUP Procedure Class 4). Principal CCS procedure codes represent an aggregate of relevant primary *International Classification of Diseases, Ninth Revision* (*ICD-9*) procedure codes by surgical subtype. Patients who underwent cardiac procedures (n = 1 655 567), cardiac surgery and cardiac transplantation (n = 582 726), bone marrow transplantation (n = 18 151), ophthalmologic surgery (n = 13 342), radiation therapy (n = 9817), dental surgery (n = 1779), and nonoperating room procedures (n = 386) as a principal in-hospital procedure were excluded. Major noncardiac surgery CCS procedure codes were clustered into 13 major surgical subtypes: breast, endocrine, otolaryngology, general, genitourinary, gynecologic, neurosurgery, obstetrics, orthopedic, skin and burn, thoracic, noncardiac transplant, and vascular surgery.

Outcomes

The primary outcome was major adverse cardiovascular and cerebrovascular events (MACCE), defined as in-hospital all-cause death, acute myocardial infarction (AMI), or ischemic stroke; AMI was identified using CCS diagnosis code 100. Acute ischemic stroke was identified using *ICD-9* diagnosis codes 433.x1, 434.x1, 436, and 437.1.[13] Other outcomes evaluated were complete heart block using *ICD-9* diagnosis code 426.0, cardiogenic shock using *ICD-9* diagnosis code 785.51, and cardiac arrest using *ICD-9* diagnosis code 427.5.

Statistical Analysis

Continuous variables were reported as mean (SD) and compared using the *t* test and analysis of variance tests for multiple comparisons. Categorical variables were reported as percentages and compared by χ^2 tests. Analyses of proportions over time were performed using the Cochran-Armitage test for trend. Multivariable logistic regression models were generated to estimate odds of perioperative cardiovascular events, adjusted for patient demographics, cardiovascular risk factors, and relevant comorbidities. Models included age, sex, race/ethnicity, obesity, tobacco use, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, end stage renal disease, coronary artery disease, prior revascularization with either percutaneous coronary intervention or coronary artery bypass surgery, peripheral artery disease, valvular heart disease, congestive heart failure, prior venous thromboembolism, chronic lung disease, alcohol abuse, malignancy, anemia, elective or urgent hospitalization, surgery type and year of hospitalization as covariates. To facilitate data presentation, patient characteristics and adverse-event rates were reported in 2-year intervals: 2004 to 2005, 2006 to 2007, 2008 to 2009, 2010 to 2011, and 2012 to 2013. Sampling weights were applied to calculate rates for trend analyses and to determine national incidence estimates.[14] Unweighted data were used in all other analyses, unless otherwise specified. Statistical analyses were performed using SPSS 20 (IBM SPSS Statistics). Statistical tests are 2-sided and *P* values less than .05 were considered statistically significant.

Sensitivity Analyses

Several sensitivity analyses were performed to validate the study findings. To confirm established associations between

validated risk factors and perioperative MACCE in this national data set, the incidence of perioperative MACCE was determined for subgroups by modified Revised Cardiac Risk Index (RCRI) score using *ICD-9* codes for ischemic heart disease, heart failure, prior transient ischemic attack or stroke, chronic kidney disease, diabetes, and high-risk surgery.[7] Due to the introduction of an *ICD-9* diagnosis code for prior stroke or transient ischemic attack in mid-2007, modified RCRI scores were calculated from 2008 to 2013 data. To exclude cases in which MACCE may have preceded the primary noncardiac surgery, a sensitivity analysis was performed excluding patients who were hospitalized urgently or emergently. Similarly, a sensitivity analysis was performed in the cohort of patients who underwent noncardiac surgery within the first 72 hours of hospital admission. Finally, due to the established risks of perioperative stroke in patients undergoing major vascular surgery,[15] a sensitivity analysis was performed excluding this high-risk cohort.

Results

Study Population

From January 2004 to December 2013, 12 863 389 hospitalizations for major surgery were identified among patients 45 years and older. After excluding patients undergoing cardiac surgery, low-risk and nonoperative procedures, the final study sample consisted of 10 581 621 hospitalizations for major noncardiac surgery (eFigure 1 in the Supplement). This corresponds to an estimated 50 558 529 surgical hospitalizations in the United States during this time period, after applying sampling weights.

Major Adverse Cardiovascular and Cerebrovascular Events

Major adverse cardiovascular and cerebrovascular events occurred in 317 479 major noncardiac surgeries (3000 events per 100 000 [3.0%]), corresponding to an estimated 1 510 694 perioperative events in the United States during this time period, after applying sampling weights. Nonfatal AMI occurred in the perioperative period of 80 076 surgeries (757 events per 100 000 [0.76%]), nonfatal stroke occurred in 57 350 (542 events per 100 000 [0.54%]), both nonfatal AMI and nonfatal stroke occurred in 3094 (29 events per 100 000 [0.03%]), and death occurred in 176 959 (1672 events per 100 000 [1.67%]) patients. Demographics and baseline characteristics of patients with and without perioperative MACCE are shown in **Table 1**. Patients who had a MACCE were older, more likely to be male, and more likely to have cardiovascular risk factors when compared with those who did not experience a MACCE (Table 1). As expected, patients with the highest RCRI scores were most likely to have perioperative MACCE compared with patients with the lowest RCRI scores (10 829 vs 1261 events per 100 000 surgeries; $P < .001$) (eFigure 2 in the Supplement).

Among all patients undergoing noncardiac surgery, complete heart block was identified in 8264 cases (78 events per 100 000 surgeries [0.08%]), cardiogenic shock occurred in 10 789 cases (102 events per 100 000 surgeries [0.10%]) and cardiac arrest occurred in 34 345 cases (325 events per 100 000 surgeries [0.32%]).

Trends in Major Adverse Cardiovascular and Cerebrovascular Events

Between January 2004 and December 2013, the number of perioperative MACCE per 100 000 surgeries declined by 580 (95% CI, 559-602), from 3181 to 2601 (P for trend <.001; adjusted odds ratio [aOR], 0.95; 95% CI, 0.94-0.97) (**Table 2**) (**Figure 1**). The rate of perioperative mortality per 100 000 surgeries declined by 695 (95% CI, 679-711), from 1978 to 1283 (P for trend <.001; aOR, 0.79; 95% CI 0.77-0.81). The rate of perioperative AMI per 100 000 surgeries decreased by 205 (95% CI, 193-217), from 1004 to 799 (P for trend <.001; aOR, 0.87; 95% CI, 0.84-0.89). Conversely, perioperative ischemic stroke per 100 000 surgeries increased over time by 244 (95% CI, 234-254), from 524 to 768 (P for trend <.001; aOR, 1.79; 95% CI, 1.73-1.86). The odds of MACCE over time, after multivariable adjustment for demographics, clinical covariates, and surgical type are shown in eFigure 3 in the Supplement.

Similar trends in perioperative MACCE, death, AMI, and stroke were observed in a sensitivity analysis of patients who were electively hospitalized for noncardiac surgery, as well as in a sensitivity analysis of patients who underwent the principal noncardiac surgery within the first 72 hours of hospital admission (eFigure 4A and B in the Supplement). After excluding patients who underwent major vascular surgery, similar trends in perioperative MACCE and the individual endpoints were also observed (eFigure 4C in the Supplement).

Surgery-Specific Perioperative Cardiovascular Risks

Patients undergoing vascular surgery (7707 events per 100 000), thoracic surgery (6515 events per 100 000), and transplant surgery (6261 events per 100 000) had the highest rates of perioperative MACCE. The lowest risks were observed in patients undergoing obstetric and gynecologic surgery. The frequency of perioperative MACCE by all surgery types is shown in **Figure 2**. After multivariable adjustment, thoracic surgery (OR, 2.07; 95% CI, 2.03-2.11), vascular surgery (OR, 1.96; 95% CI, 1.94-1.98), and transplant surgery (OR, 1.80; 95% CI, 1.67-1.95) remained associated with the highest risks of perioperative MACCE when compared with general surgery (**Table 3**).

Perioperative Cardiovascular Outcomes by Sex and Race/Ethnicity

Perioperative MACCE was more frequent among men than women (3521 events per 100 000 surgeries [3.5%] vs 2611 events per 100 000 [2.6%]; aOR, 1.17; 95% CI, 1.16-1.18; $P < .001$), with higher in-hospital mortality (1984 events per 100 000 surgeries [2.0%] vs 1439 events per 100 000 [1.4%]; aOR, 1.22; 95% CI, 1.20-1.23; $P < .001$), AMI (1118 events per 100 000 surgeries [1.1%] vs 832 events per 100 000 [0.8%]; aOR, 1.14; 95% CI, 1.13-1.16; $P < .001$) and ischemic strokes (771 events per 100 000 surgeries [0.8%] vs 592 events per 100 000 [0.6%]; aOR, 1.05; 95% CI, 1.04-1.07; $P < .001$). Declines in perioperative MACCE, in-hospital death, and AMI, and increases in perioperative acute ischemic stroke were observed over time in both sexes (eFigure 5 in the Supplement).

Table 1. Baseline Characteristics of Patients Undergoing Major Noncardiac Surgery With and Without Perioperative Major Adverse Cardiovascular and Cerebrovascular Events

Characteristic	No. (%)[a]		
	All Surgeries (n = 10 581 621)	Perioperative MACCE (n = 317 479)	No Perioperative MACCE (n = 10 264 142)
Age, mean (SD), y	65.74 (12.32)	72.39 (12.19)	65.53 (12.26)
Female	5 975 798 (56.6)	156 038 (49.2)	5 819 760 (56.8)
Race/Ethnicity			
White non-Hispanic	6 879 066 (65.0)	198 924 (62.7)	6 680 142 (65.1)
Black non-Hispanic	833 320 (7.9)	31 622 (10)	801 698 (7.8)
Hispanic	598 557 (5.7)	18 480 (5.8)	580 077 (5.7)
Other race	404 288 (3.8)	14 245 (4.5)	390 043 (3.8)
Unknown	1 866 390 (17.6)	54 208 (17.1)	1 812 182 (17.7)
Obesity	1 104 639 (10.4)	20 769 (6.5)	1 083 870 (10.6)
Tobacco use	1 044 847 (9.9)	22 313 (7)	1 022 534 (10)
Hypertension	6 128 472 (57.9)	180 930 (57)	5 947 542 (57.9)
Hyperlipidemia	2 999 059 (28.3)	75 769 (23.9)	2 923 290 (28.5)
Diabetes mellitus	2 569 960 (24.3)	88 415 (27.8)	2 481 545 (24.2)
Chronic kidney disease	800 915 (7.6)	58 487 (18.4)	742 428 (7.2)
End-stage renal disease	256 114 (2.4)	21 059 (6.6)	235 055 (2.3)
Coronary artery disease	1 879 010 (17.8)	95 043 (29.9)	1 783 967 (17.4)
Prior PCI	387 717 (3.7)	13 507 (4.3)	374 210 (3.6)
Prior CABG	495 089 (4.7)	19 123 (6)	475 966 (4.6)
Peripheral arterial disease	740 823 (7)	47 358 (14.9)	693 465 (6.8)
Valvular heart disease	450 704 (4.3)	28 143 (8.9)	422 561 (4.1)
History of heart failure	702 432 (6.6)	82 956 (26.1)	619 476 (6)
History of venous thromboembolism	268 866 (2.5)	5786 (1.8)	263 080 (2.6)
Chronic pulmonary disease	1 778 642 (16.8)	74 654 (23.5)	1 703 988 (16.6)
Alcohol abuse	221 396 (2.1)	11 863 (3.7)	209 533 (2)
Malignancy	580 535 (5.5)	35 297 (11.1)	545 238 (5.3)
Anemia	1 624 601 (15.4)	74 147 (23.4)	1 550 454 (15.1)
Elective surgery	6 391 768 (60.6)	69 196 (21.9)	6 322 572 (61.8)
Surgery type			
General	2 262 175 (21.4)	87 372 (27.5)	2 174 803 (21.2)
Breast	108 677 (1)	381 (0.1)	108 296 (1.1)
Endocrine	122 814 (1.2)	1173 (0.4)	121 641 (1.2)
Genitourinary	790 769 (7.5)	12 629 (4)	778 140 (7.6)
Gynecologic	619 975 (5.9)	1927 (0.6)	618 048 (6)
Skin/burn	356 917 (3.4)	13 651 (4.3)	343 266 (3.3)
Neurosurgery	602 129 (5.7)	27 855 (8.8)	574 274 (5.6)
Obstetric	8570 (0.1)	11 (0)	8559 (0.1)
Orthopedic	4 253 221 (40.2)	67 831 (21.4)	4 185 390 (40.8)
Otolaryngology	78 327 (0.7)	1394 (0.4)	76 933 (0.7)
Thoracic	232 928 (2.2)	15 175 (4.8)	217 753 (2.1)
Transplant	11 691 (0.1)	732 (0.2)	10 959 (0.1)
Vascular	1 133 428 (10.7)	87 348 (27.5)	1 046 080 (10.2)

Abbreviations: CABG, coronary artery bypass surgery; MACCE, major adverse cardiovascular and cerebrovascular events; PCI, percutaneous coronary intervention.

[a] All comparisons of patients with and without perioperative MACCE were significant with a *P* value of <.001.

Rates of perioperative MACCE varied by race and ethnicity. Non-Hispanic black patients experienced significantly more MACCE than non-Hispanic white patients (3795 events per 100 000 surgeries [3.8%] vs 2892 events per 100 000 [2.9%]; aOR, 1.14; 95% CI, 1.13-1.16). Black patients also had higher rates of perioperative death (aOR, 1.24; 95% CI, 1.22-1.26) and stroke (aOR, 1.17; 95% CI, 1.14-1.20) than non-Hispanic white patients, although differences in the rates of adverse events narrowed over time. Trends in MACCE by race and ethnicity are shown in eFigure 6 in the Supplement.

Discussion

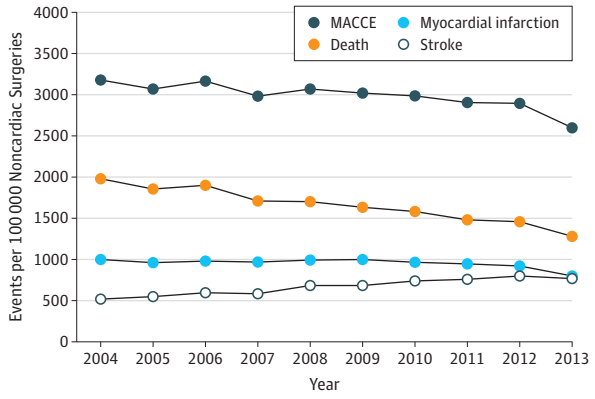
In this analysis of 10.5 million in-hospital major noncardiac surgeries, perioperative MACCE occurred in 3.0% of patients, with

Table 2. Trends in Cardiovascular Outcomes of Major Noncardiac Surgery Over Time

Characteristic	2004-2005 (n = 2 051 557)	2006-2007 (n = 2 117 047)	2008-2009 (n = 2 213 461)	2010-2011 (n = 2 254 360)	2012-2013 (n = 1 945 196)	*P* Value
Age, mean (SD)	65.83 (12.62)	65.79 (12.52)	65.66 (12.38)	65.65 (12.2)	65.75 (11.82)	<.001
Female, sex	1 183 616 (57.9)	1 205 328 (57.1)	1 248 041 (56.5)	1 259 683 (56)	1 079 130 (55.5)	<.001
Surgery type						<.001
General	446 346 (21.8)	447 820 (21.2)	476 111 (21.5)	477 918 (21.2)	413 980 (21.3)	
Breast	29 308 (1.4)	27 417 (1.3)	18 897 (0.9)	17 643 (0.8)	15 412 (0.8)	
Endocrine	25 344 (1.2)	25 621 (1.2)	26 623 (1.2)	27 297 (1.2)	17 929 (0.9)	
Genitourinary	162 811 (7.9)	164 521 (7.8)	168 642 (7.6)	168 173 (7.5)	126 622 (6.5)	
Gynecologic	153 779 (7.5)	146 973 (6.9)	136 614 (6.2)	108 981 (4.8)	73 628 (3.8)	
Skin/Burn	84 416 (4.1)	78 831 (3.7)	71 445 (3.2)	68 569 (3)	53 656 (2.8)	
Neurosurgery	120 867 (5.9)	122 770 (5.8)	120 681 (5.5)	128 126 (5.7)	109 685 (5.6)	
Obstetric	1688 (0.1)	1836 (0.1)	1821 (0.1)	1756 (0.1)	1469 (0.1)	
Orthopedic	738 313 (36)	793 004 (37.5)	882 163 (39.9)	954 739 (42.4)	885 002 (45.5)	
Otolaryngology	16 895 (0.8)	16 027 (0.8)	15 362 (0.7)	15 663 (0.7)	14 380 (0.7)	
Thoracic	42 798 (2.1)	45 258 (2.1)	50 964 (2.3)	51 405 (2.3)	42 503 (2.2)	
Transplant	2106 (0.1)	1623 (0.1)	3065 (0.1)	2617 (0.1)	2280 (0.1)	
Vascular	226 886 (11.1)	245 346 (11.6)	241 073 (10.9)	231 473 (10.3)	188 650 (9.7)	
Major adverse cardiovascular events						
Any MACCE	64 419 (3.1)	65 005 (3.1)	67 858 (3.1)	66 707 (3.0)	53 490 (2.7)	<.001
Death	39 612 (1.9)	38 284 (1.8)	37 302 (1.7)	35 084 (1.6)	26 677 (1.4)	<.001
AMI	20 123 (0.98)	20 496 (0.97)	22 094 (1.0)	21 477 (0.95)	16 763 (0.86)	<.001
Stroke	11 025 (0.54)	12 463 (0.59)	15 188 (0.69)	16 823 (0.75)	15 214 (0.78)	<.001

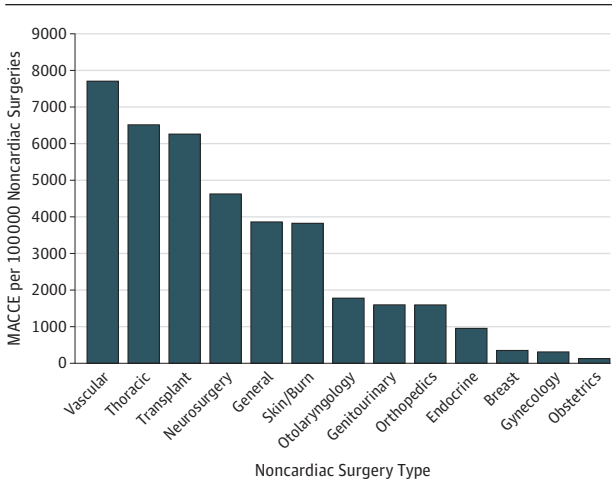
Abbreviations: AMI, acute myocardialinfarction; MACCE, major adverse cardiovascular and cerebrovascular events.

Figure 1. Rates of Perioperative MACCE Over Time



MACCE indicates major adverse cardiovascular and cerebrovascular events.

Figure 2. Frequency of Perioperative MACCE by Type of Noncardiac Surgery



MACCE indicates major adverse cardiovascular and cerebrovascular events.

vascular, thoracic, and noncardiac transplant surgeries conferring the highest risks of cardiovascular morbidity and mortality. The rate of perioperative MACCE declined from 2004 to 2013, due to reductions in perioperative death and AMI. In contrast, rates of perioperative ischemic stroke increased during the study timeframe. Men had higher risk of perioperative MACCE than women in unadjusted and multivariable adjusted models. In analyses of perioperative events by race and ethnicity, non-Hispanic black patients had the highest rates of perioperative death and ischemic stroke in comparison to other racial groups.

Since the publication of the initial Goldman multifactorial index of cardiac risk in 1977,[6] adverse cardiovascular events have been recognized as a major cause of perioperative morbidity and mortality. Nearly 40 years later, efforts to identify patients at the greatest risk for perioperative MACCE and to reduce morbidity and mortality following noncardiac surgery remain ongoing. In this contemporary analysis, perioperative MACCE still occurs in 1 in every 33

Table 3. Adjusted Odds of Perioperative Major Adverse Cardiovascular and Cerebrovascular Events by Type of Noncardiac Surgery

Type of Surgery	Adjusted OR (95% CI)[a] MACCE (Death/MI/Stroke)	*P* Value	Death	*P* Value	Myocardial Infarction	*P* Value	Stroke	*P* Value
Elective surgery	0.27 (0.26-0.27)	<.001	0.22 (0.22-0.23)	<.001	0.42 (0.41-0.42)	<.001	0.23 (0.23-0.24)	<.001
Surgery type								
General	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Breast	0.19 (0.18-0.22)	<.001	0.10 (0.08-0.12)	<.001	0.30 (0.26-0.35)	<.001	0.67 (0.56-0.81)	<.001
Endocrine	0.60 (0.56-0.63)	<.001	0.39 (0.36-0.43)	<.001	0.76 (0.69-0.83)	<.001	1.70 (1.52-1.90)	<.001
Genitourinary	0.52 (0.51-0.53)	<.001	0.34 (0.33-0.35)	<.001	0.81 (0.78-0.83)	<.001	0.99 (0.94-1.04)	.59
Gynecologic	0.25 (0.24-0.26)	<.001	0.17 (0.16-0.19)	<.001	0.39 (0.37-0.42)	<.001	0.41 (0.36-0.45)	<.001
Skin/Burn	0.81 (0.80-0.83)	<.001	0.69 (0.68-0.71)	<.001	0.82 (0.79-0.85)	<.001	1.56 (1.48-1.64)	<.001
Neurosurgery	1.86 (1.84-1.89)	<.001	1.99 (1.96-2.03)	<.001	0.78 (0.75-0.81)	<.001	4.91 (4.75-5.07)	<.001
Obstetric	0.08 (0.04-0.14)	<.001	0.06 (0.02-0.14)	<.001	0.17 (0.07-0.41)	<.001	NA	NA
Orthopedic	0.47 (0.47-0.48)	<.001	0.32 (0.32-0.33)	<.001	0.71 (0.70-0.72)	<.001	0.97 (0.94-1.00)	.03
Otolaryngology	0.54 (0.51-0.57)	<.001	0.37 (0.34-0.40)	<.001	0.70 (0.64-0.77)	<.001	1.50 (1.34-1.66)	<.001
Thoracic	2.07 (2.03-2.11)	<.001	2.02 (1.98-2.07)	<.001	1.69 (1.63-1.75)	<.001	3.78 (3.61-3.97)	<.001
Transplant	1.80 (1.67-1.95)	<.001	1.70 (1.55-1.86)	<.001	1.74 (1.49-2.04)	<.001	2.10 (1.69-2.61)	<.001
Vascular	1.96 (1.94-1.98)	<.001	0.98 (0.97-0.99)	.006	1.62 (1.59-1.65)	<.001	11.97 (11.67-12.28)	<.001

Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; NA, not applicable; OR, odds ratio.

[a] Multivariable models include age, sex, race/ethnicity, obesity, tobacco use, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, end-stage renal disease, coronary artery disease, prior revascularization with either percutaneous coronary intervention or coronary artery bypass surgery, peripheral arterial disease, valvular heart disease, congestive heart failure, prior venous thromboembolism, chronic lung disease, alcohol abuse, malignancy, anemia, and year of hospitalization as covariates.

hospitalizations for noncardiac surgery, corresponding to approximately 150 000 perioperative events each year in the United States. To our knowledge, this is the first study to report national data on the cardiovascular outcomes of in-hospital major noncardiac surgery in the modern era, with multivariable adjusted predictors of perioperative death, ischemic stroke, AMI, and the composite of MACCE. Furthermore, this is the largest analysis of time trends in perioperative cardiovascular outcomes in the United States.

The observed reductions in overall perioperative MACCE are encouraging. These may be due to improved surgical case selection, advances in the management of cardiovascular risk factors and disease, improved surgical techniques, including increased use of minimally invasive surgical interventions, improved anesthetic techniques, enhanced intraoperative monitoring, and advanced postoperative critical care. Reductions in myocardial infarction during the study are surprising, given the increase in the sensitivity of modern cardiac biomarkers necessary for the diagnosis of myocardial infarction during the study timeframe.[16] However, declines in AMI may be attributed to improved pharmacologic and percutaneous strategies in the management of coronary artery disease, and the recognition of thrombotic risks early post-percutaneous coronary intervention.[17-19]

Stroke incidence rates have declined steadily over the past decades in the United States.[20,21] In the context of these national trends, the observed increase in the rate of perioperative ischemic stroke is a concerning finding that warrants additional study. The rising rates of stroke in the perioperative period may be attributable to an increased prevalence of cardiovascular risk factors of surgical patients, carotid stenosis or cerebrovascular disease, atrial arrhythmias, or changes in intraoperative hemodynamic management.[22] Alternatively, increases in perioperative ischemic strokes may be related to increased use of perioperative β blockade.[9] Importantly, in these analyses, we found a strong association between perioperative stroke and patients undergoing vascular surgery. While vascular surgery patients are likely to have the highest atherosclerotic burden and the greatest risk for ischemic complications following surgery, this strong association also raises the possibility that perhaps some patients in this cohort underwent a major vascular procedure or surgery as a consequence of ischemic stroke. After excluding patients who underwent vascular surgery, an increase in the rate of perioperative ischemic stroke over time was still observed. This trend also persisted in sensitivity analyses of patients who were electively hospitalized for surgery, and among patients who underwent the principal noncardiac surgery within the first 72 hours of hospital admission. In these sensitivity analyses, patients were unlikely to have presented with an acute stroke prior to the primary noncardiac surgery.

Limitations

There are some notable limitations of this study. First, analyses are based on administrative coding data, which may be subject to reporting bias or coding errors. Race and ethnicity data was missing for 17% of subjects. Second, the analysis was limited to adults age 45 years or older, the population at risk for cardiovascular complications of noncardiac surgery. Rates of perioperative AMI are lower in this analysis than in some previously published studies, likely due to the inclusion of larger numbers of low-risk patients from the NIS data set.[9] Third, the timing of nonfatal AMI or ischemic stroke after noncardiac surgery cannot be firmly established from this administrative da-

tabase. However, because major noncardiac surgery is contraindicated early after AMI or stroke, patients presenting with these acute cardiovascular conditions were unlikely to undergo major noncardiac surgery during the index hospital admission. Furthermore, trends in perioperative outcomes were similar in sensitivity analyses of patients undergoing surgery during elective hospitalization. Fourth, medical therapy was not available from this administrative data set; consequently, the use of β-blockers, antiplatelet agents, and other cardiovascular therapies in the perioperative period could not be evaluated. Fifth, although a history of heart failure was included in modeling, left ventricular function and other important markers of cardiovascular risk were not available for inclusion in this analysis. Finally, results of perioperative laboratory testing, including cardiac biomarkers, were not available from this administrative data set. Myocardial injury after noncardiac surgery, a well-described independent risk factor for short and long-term mortality, could not be ascertained and was not included in the composite outcome.[4,23,24]

Conclusions

To our knowledge, this is the largest analysis of perioperative MACCE in patients undergoing major noncardiac surgery in the United States. Cardiovascular complications after noncardiac surgery remain a major source of morbidity and mortality. Despite improvements in perioperative outcomes over the past decade, the significant increase in the rate of ischemic stroke in this analysis requires confirmation and further study. Additional efforts are necessary to improve perioperative cardiovascular care of patients undergoing noncardiac surgery.

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