The Growing Burden of Perioperative Heart Failure

W. Scott Beattie, MD, PhD, FRCPC,* and Duminda N. Wijeysundera, MD, PhD, FRCPC*†

Each year, over 2 million patients are admitted to hospitals with some form of congestive heart failure (HF). It is estimated that the current prevalence of HF is over 5.8 million in the United States and over 23 million worldwide.[1] Over half a million new cases are diagnosed every year in the United States, and the chance of developing HF in a lifetime is 1 in 5.[2,3] A diagnosis of HF independently increases the risk of death, and HF is noted on 1 in 8 death certificates. In the Framingham Heart Study, a new diagnosis of HF carried an approximate 30-day mortality of 10%, while the 1-year mortality approaches 30%.[3] HF is predominantly a geriatric disease: 80% of the HF deaths occur in individuals aged ≥65 years.[4,5] HF is known to be a major risk factor in perioperative medicine[6] and is seen in 2.5% to 10% of noncardiac surgical patients.[7–9] Advances in medical care allow people to live longer with more comorbidity, such that patients with HF are often hospitalized for other conditions. The patients with HF listed on the discharge summary are often being treated for other illnesses; chronic obstructive pulmonary disease, chronic renal failure, and cancer are prime examples.[10,11]

HF can be broadly categorized into 2 major subgroups: those with abnormal and those with preserved systolic function. This designation matters little to outcome because cohort studies show the same short- and long-term mortality rates.[12] In HF with preserved left ventricular ejection fraction (LVEF), patients frequently have evidence of diastolic dysfunction, and HF can occur due to impaired ventricular relaxation, requiring elevated filling pressures to obtain normal left ventricular (LV) end-diastolic volumes. Diastolic dysfunction is common in HF patients where over 20% had mild and 7% had moderate while <1% had severe diastolic dysfunction.[13] In comparison, only 6% of HF patients have an ejection fraction of <50%, and <2% have severe systolic dysfunction (LVEF <40%). In the past, we have been critical of the routine preoperative use of screening echocardiograms.[14] Clearly, however, patients with new onset or with worsening symptoms would benefit from a preoperative echocardiogram to obtain high-quality studies of both systolic and diastolic function. By focusing on systolic function alone, we will severely underestimate the risk of adverse outcomes in a majority of our patients.

In this issue of *Anesthesia & Analgesia*, Maile et al.[15] from the University of Michigan address the growing burden of HF and its impact on outcomes after elective noncardiac surgery. Using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database, they investigated the association between worsening HF and morbidity/mortality. In this multicenter cohort study, they found that <1% of elective surgical patients have NSQIP-defined HF. The investigators then used a nonparsimonious propensity score to match patients with HF to those without HF. They found that this definition of HF was associated with a doubled mortality rate compared with a similar cohort but without the NSQIP definition of HF. In addition, this analysis found that renal complications (renal insufficiency and acute renal failure), respiratory complications (need for unplanned intubation, prolonged mechanical ventilation, pneumonia), sepsis, and cardiac arrests were more frequent in patients with HF. Interestingly, this analysis could not find an association between HF and an increased frequency of postoperative myocardial infarction (MI).

Maile et al.[15] have added important information to our existing knowledge base by drawing attention to a very high postoperative complication rate that is, in this instance noncardiac, in excess of 30%. The mortality rate is similarly excessive and approaches 10%. The focus of past HF cohort studies had been on cardiac complications.[16] Indeed, a history of HF has been repeatedly demonstrated to be an important predictor of postoperative cardiac complications.[8,17,18] Now this study draws attention to the as yet unappreciated high incidence of noncardiac complications as well. Increased rates of sepsis and pneumonia are key and novel findings.

As the title suggests, and in contradistinction to the above referenced studies,[8,17,18] the present report was not able to detect a difference in the rates of postoperative MI. Every database has deficiencies. In this respect, NSQIP is not spared, and the evidence would suggest that MI is underreported in this key database. The incidence of MI reported here is 1.3%; however, we would expect, in a cohort of this risk profile, the rate to be 3 to 4 times higher. As an example, the recently completed PeriOperative ISchemic Evaluation (POISE) 2 investigation found an incidence of acute postoperative MI over 6%.[19] The MI rate in POISE 2 occurred in a population with a mortality rate that was less than half of that seen in the present study. The underreporting

From the *Department of Anesthesia and Pain Management, Toronto General Hospital and University of Toronto, Toronto, Ontario, Canada; and †Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada; Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada.

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Address correspondence to W. Scott Beattie, MD, PhD, FRCPC, Toronto General Hospital, Department of Anesthesia, 200 Elizabeth St., EN3-462, Toronto, Ontario M5G2C4, Canada. Address e-mail to scott.beattie@uhn.on.ca.

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phenomena are further demonstrated by the number of cardiac arrests that outnumber the MI by a more than a 2-to-1 ratio, a ratio we consider to be implausible. (The POISE 2 results show an opposite ratio; MIs outnumber arrests in a 30-to-1 ratio.) Many studies now show that postoperative MI is predominantly non–ST segment elevation MI and clinically silent (painless).[20,21] The NSQIP definition for MI is a new Q wave, which as many recent studies now show is a small minority of all perioperative cardiac events. Detection of increased cardiac biomarkers is central to the diagnosis of MI.[22] The clinical silence makes the diagnosis of MI exceedingly difficult, especially if the decision to order a cardiac biomarker is based on clinical signs. This problem would be further compounded in an HF population since postoperative dyspnea will often be attributed to worsening HF leading less aggressive biomarker measurements. Importantly, for this analysis, NSQIP does not mandate the routine measurement of either troponin or creatine kinase. This type of clinically based, and hence sporadic, cardiac biomarker measurement has been shown to underestimate MI by 3-fold.[23] Thus, we are of the opinion that the lack of association between MI and HF in the present study is likely due to both reporting and detection bias.

There are other important aspects of the NSQIP database analysis to be considered. The reported frequency of HF is 0.87%; as stated above, the prevalence of HF in unselected surgical populations ranges from 2.5% to 10%.[7–9] Thus, the NSQIP definition likely fails to capture a large proportion of patients with chronic HF. The definition used by NSQIP is "new or worsening" HF, and the definition itself suggests anything but a stable patient ready for elective surgery and suggests a high degree of unmeasured confounding. Furthermore, unlike MI, perioperative clinicians have no idea of the minimal acceptable recovery period after an episode of decompensated HF before proceeding to "elective" surgery.[24] The process of care involved in the treatment of new or worsening HF is complex and involves the careful titration of several medications[25] (angiotensin-converting enzyme inhibitors, β-blockers, diuretics) with associated continuous follow-up. The fact that surgery was undertaken within a 30-day window would suggest to us that either the patients were not stabilized or the procedures were not elective surgeries. Emergent surgery is in and of itself associated with a 4-fold increase in mortality.[26,27] Ethnicity was not considered, although HF is also more prevalent in African Americans than Caucasians.[28] African Americans have an incidence of early-onset HF that is 20 times that of Caucasian men. Importantly, the development of depressed LVEF occurring 10 to 15 years earlier in African American men was not considered in this analysis.[29]

Anemia is highly prevalent in HF populations (>35%) and is also associated with preexisting renal failure, both of which are well recognized to increase adverse outcomes in HF patients. A meta-analysis found that the presence of anemia in both preserved and decreased LV function HF doubled mortality.[30] It is not clear if either of these confounders was adequately accounted for in the analysis. Thus, we are unsure of the effects that any of these potential confounding factors have on the measured association.

HF is a major, and a potentially lethal, perioperative comorbidity, and as the surgical population ages, the number of patients with HF we encounter will only increase. The report by Maile et al.[15] draws attention to the urgent need for hospitals, and practitioners, to adopt systematic processes of care and conduct research to ameliorate this unacceptably high rate of postoperative complications for patients with HF. We think a first step would be to have a frank discussion of the real risks and potential for complications that includes a mortality rate of 10%, during elective surgery. Only this will constitute informed consent. Perioperative medicine should investigate similar care pathways as outlined by the American Heart Association that insure that medications are titrated to effect and once stabilized should be continued throughout the perioperative period.[24] In response to this postoperative complication rate, we would think that the early postoperative course should be conducted in high-acuity nursing environments, with requisite assessment of cardiac biomarkers (troponin and brain natriuretic peptide). Finally, do not be lulled into a false sense of security by the preoperative demonstration of preserved LV function.

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Worsening Preoperative Heart Failure Is Associated with Mortality and Noncardiac Complications, But Not Myocardial Infarction After Noncardiac Surgery: A Retrospective Cohort Study

Michael D. Maile, MD, MS, Milo C. Engoren, MD, Kevin K. Tremper, MD, PhD, Elizabeth Jewell, MS, and Sachin Kheterpal, MD, MBA

BACKGROUND: Heart failure (HF) is an important risk factor for perioperative morbidity and mortality. While these patients are at high risk for cardiac adverse events, there are few current data describing the types of noncardiac complications that occur in this population.

METHODS: We performed a multicenter cohort study of patients undergoing noncardiac surgery from 2005 to 2010 as part of the American College of Surgeons National Surgical Quality Improvement Program. A HF cohort (HF that is new or worsening within 30 days of surgery) was compared with a control cohort that was matched regarding other surgical risk factors.

RESULTS: Five thousand ninety-four patients with worsening preoperative HF were compared with an otherwise similar cohort of patients without worsening preoperative HF. Worsening preoperative HF was associated with increased risk of 30-day all-cause mortality (relative risk [RR] 2.08; 95% confidence interval [CI], 1.75–2.46; $P < 0.001$) and increased risk of morbidity (any recorded postoperative complication) (RR 1.54; 95% CI, 1.40–1.69; $P < 0.001$). HF patients had increased risk of developing renal failure (RR 1.85; 95% CI, 1.37–2.49; $P < 0.001$), need for mechanical ventilation longer than 48 hours (RR 1.81; 95% CI, 1.52–2.15; $P < 0.001$), pneumonia (RR 1.73; 95% CI, 1.44–2.08; $P < 0.001$), cardiac arrest (RR 1.69; 95% CI, 1.29–2.21; $P < 0.001$), unplanned intubation (RR 1.68; 95% CI, 1.41–1.99; $P < 0.001$), renal insufficiency (RR 1.64; 95% CI, 1.10–2.44; $P = 0.014$), sepsis (RR 1.43, 95% CI, 1.24–1.64; $P < 0.001$), and urinary tract infection (RR 1.29; 95% CI, 1.06–1.58; $P = 0.011$). The incidence of myocardial infarction in the sample was similar between the 2 groups (RR 1.07; 95% CI, 0.75–1.52; $P = 0.719$).

CONCLUSIONS: Worsening preoperative HF is associated with a significant increase in postoperative morbidity and mortality when controlling for other comorbidities. Although these likely have a multifactorial etiology, patients are much more likely to suffer from respiratory, renal, and infectious complications than cardiac complications. (Anesth Analg 2014;119:522–32)

Heart failure (HF) is a prevalent disease that consumes a significant fraction of health care spending. Approximately, 5.7 million people in the United States are affected, with an annual incidence of >500,000 cases.[1] While the incidence rate has remained constant for several decades, patients diagnosed with HF are surviving longer,[2] which will likely result in a 25% increase in HF prevalence by 2030.[1] In addition, as the number of surgeries in elderly patients and patients with comorbidities continues to increase, anesthesiologists may see an increase in the number of patients with HF.[3] Therefore, it is imperative to improve our understanding of the impact of HF on postoperative outcomes.[4] Perioperative management of HF patients is usually focused on preventing cardiac complications through medications such as β-blockers, statins, and aspirin and controlling hemodynamics and fluid balances. While limiting cardiac adverse events, cardioprotective therapies such as β-blockers (commonly carvedilol), angiotensin-converting enzyme inhibitors, and diruetics may contribute to cerebral, pulmonary, renal, or other organ dysfunctions by limiting cardiac output during a time of increased stress or increasing the incidence of perioperative hypotension.[5,6]

Previous studies have focused on the impact of HF on adverse cardiac events or on overall morbidity or mortality;[7–15] however, there are few data on the relationship between HF and specific postoperative noncardiac complications. To better understand the relationship between HF and other organ systems, we performed a multicenter

From the Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan.

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Address correspondence to Michael D. Maile, MD, Department of Anesthesiology, University of Michigan, 4172 Cardiovascular Center, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5861. Address e-mail to mmaile@med.umich.edu.

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retrospective cohort study in a large population of patients for whom the presence or absence of new or worsening preoperative HF was recorded. Our goal was to characterize the types of complications that are experienced by patients with worsening HF. We hypothesized that new or worsening preoperative HF would be associated with an increased risk of 30-day morbidity and mortality compared with subjects with no or stable HF and that this population would be at increased risk of noncardiac complications as well as cardiac complications.

METHODS

Study Population

The IRB of the University of Michigan Medical School (Ann Arbor, Michigan) deemed analysis of these deidentified, publicly available data to be exempt from the need for informed consent. Data were obtained from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) participant use data file. The ACS NSQIP was initially designed as a quality improvement initiative for patients undergoing surgery in the Veterans Health Administration (VA) hospital system.[16] It has since been expanded to non-VA hospitals and is currently used by >200 institutions.[17]

The methods of ACS NSQIP have been described in detail previously.[18–22] Briefly, patients undergoing general, epidural, or spinal anesthesia for a surgical procedure are eligible for inclusion in this program. Patients are recruited at participating institutions over 8-day cycles. Typically, the first 40 general and vascular surgery procedures completed at a participating institution during this cycle are included. The number of high-volume procedures is limited so that they do not comprise most cases in the database. For example, this would prevent the database from containing primarily thyroidectomies at an institution that completes a relatively high volume of this procedure. The sampling methodology excludes trauma, organ donation, transplant surgery, and minor cases. Minor cases are those that do not use general, spinal, or epidural anesthesia, with the exception of carotid endarterectomy, inguinal herniorrhaphy, parathyroidectomy, thyroidecomty, breast lumpectomy, and endovascualar abdominal aortic aneurysm repair, which are always considered to be major surgeries. Institutions have the option of including subspecialties, such as cardiac, neurosurgery, orthopedics, urology, otolaryngology, plastics, thoracic, and gynecology.

A trained surgical clinical reviewer, typically a registered nurse, is responsible for collecting all information collected for the ACS NSQIP. These reviewers must complete a standardized training program and pass a written test (score ≥90%) before collecting data. Sites are routinely audited to ensure accuracy of data collection. Corrective action is taken if there is >5% disagreement between the site and auditors, and involved data are excluded from the dataset. A 1.56% discordance rate was observed in 2008.[23] The participant use data file includes patients from participating institutions with a 30-day follow-up rate >80% and an interrater reliability disagreement rate <5%. The 2005 to 2010 dataset, which was used for this study, involves 250 U.S. medical centers, 211 of which are non-VA hospitals. To maintain institutional, provider, and patient anonymity, all identifying information is excluded from the user dataset. Information is prospectively collected on preoperative patient risk factors, intraoperative events, and postoperative morbidity and mortality. ACS NSQIP defines HF as "newly diagnosed HF within the previous 30 days or a diagnosis of chronic HF with new signs or symptoms in the 30 days before surgery." Common manifestations are listed: abnormal limitation in exercise tolerance due to dyspnea or fatigue, orthopnea, paroxysmal nocturnal dyspnea, increased jugular venous pressure, pulmonary rales on physical examination, cardiomegaly, and pulmonary vascular engorgement.

The 2005 to 2010 ACS NSQIP participant use data file contains 1,331,619 patients. Patients undergoing emergent surgery were excluded from this analysis since there is less opportunity to modify risk factors for these patients before proceeding with surgery. Patients undergoing cardiac surgery were also excluded from this analysis. Figure 1 provides the exclusion criteria used for this study and demonstrates how the cohorts of HF and control patients were derived. Appendix 1 and 2 provide information regarding the definitions used by ACS NSQIP for preoperative and postoperative factors, respectively. This dataset documents HF only if it is newly diagnosed or if the symptoms of chronic HF worsened in the 30 days before surgery.

Preoperative Patient Characteristics

The ACS NSQIP collects information on multiple preoperative subject characteristics. Data are obtained for aspects of multiple organ systems; neurologic: presence of impaired sensorium before surgery and history of transient ischemic attack or stroke; cardiovascular: preoperative angina, history of cardiac surgery, hypertension, myocardial infarction (MI) within 6 months of surgery, and peripheral vascular disease; pulmonary: chronic obstructive pulmonary disease, current smoker, dyspnea, and pneumonia; gastrointestinal: liver disease; renal: renal failure; hematologic: bleeding disorder and significant preoperative blood transfusion; endocrine: diabetes and current steroid use; and infectious: systemic inflammatory response syndrome/sepsis/septic shock. The definition of each of these variables can be found in Appendix 1.

Outcomes

In addition to 30-day mortality, the incidence of 30-day morbidity related to a variety of organ systems that were recorded by ACS NSQIP was analyzed. These complications were MI, cardiac arrest requiring cardiopulmonary resuscitation, renal insufficiency, acute renal failure, unplanned tracheal intubation, need for prolonged mechanical ventilation, pulmonary embolism (PE), pneumonia, sepsis, urinary tract infection, surgical site infections, wound disruption, graft failure, coma for >24 hours, stroke, peripheral nerve injury, postoperative bleeding requiring transfusion of packed red blood cells or whole blood within 72 hours of surgery, ≥4 units packed red blood cells transfused intraoperatively, and deep venous thrombosis (DVT) (Appendix 2). These complications were analyzed separately so that it would be possible for a subject to have >1 complication. Finally, the composite morbidity, defined as the occurrence of 1 or more adverse outcomes within 30 days of surgery, was also analyzed.

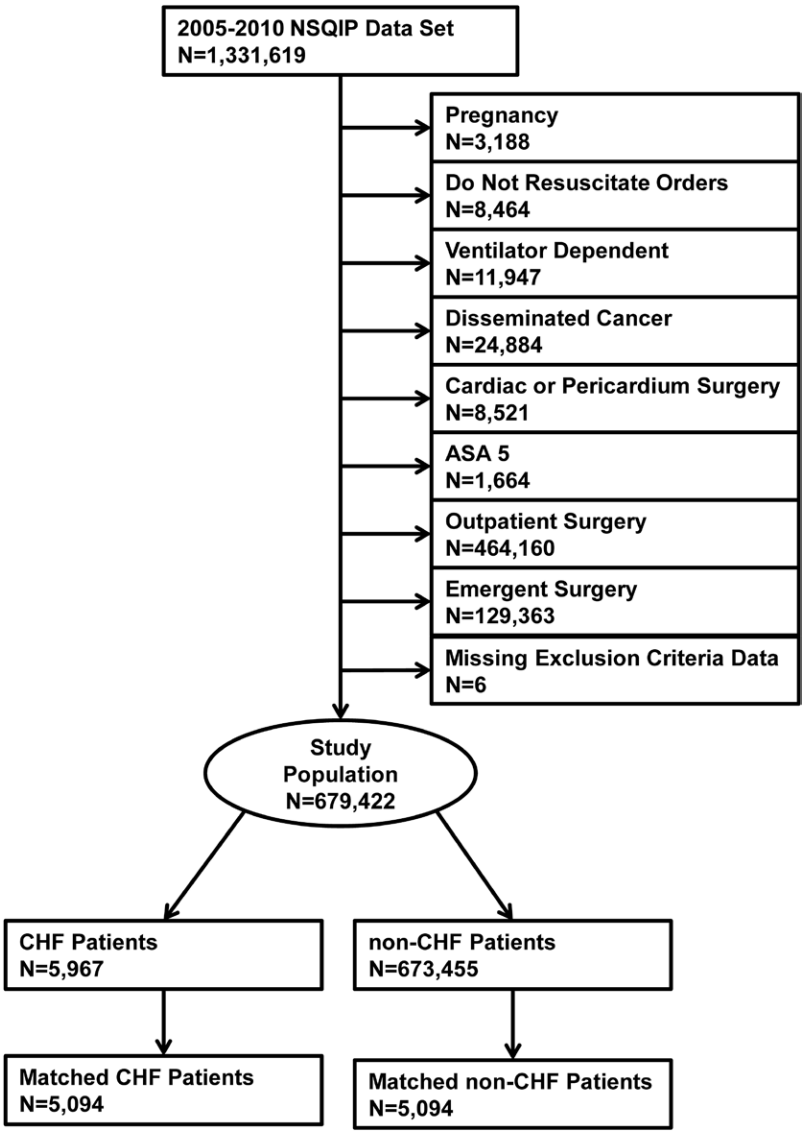

Figure 1. Flow diagram of cohort derivation.

Statistical Analysis

We determined that to have 90% power to detect an increase in the incidence of mortality from 4.5% to 8.8% with a *P*-value of 0.003, to adjust for the 20 outcomes being studied, that we would need to have 1250 subjects in each group. All outcomes were analyzed as dichotomous variables. The overall study population was described by using the median and interquartile range for nonparametric, means and standard deviations (SDs) for parametric continuous variables, and the count and percent for categorical variables. To isolate the independent impact of worsening preoperative HF on perioperative outcomes, patients with HF were matched to patients without HF based on preoperative comorbidities, age, gender, and surgical complexity score. The surgical complexity score was derived from the risk of mortality based on the primary current procedural terminology code similar to the technique described by Raval et al.[24] Given the large number of covariates available for matching, a propensity score for a patient to have HF was derived by using a nonparsimonious logistic regression with all the variables in Table 1 (except for the surgical complexity score) entered and with the presence or absence of worsening HF as the dichotomous outcome. With the use of a greedy matching algorithm, the propensity and surgical complexity scores were then used to match patients with HF to controls. The calipers of the matching algorithm were adjusted to maximize generalizability while still maintaining all standardized differences of the covariates <10% as suggested by Austin.[25] This produced calipers of 0.001 for the propensity score for worsening preoperative HF and 1.0 for the surgical complexity score. To determine the characteristics of the HF subjects who were not matched, standardized differences were calculated comparing the matched HF subjects with the unmatched HF subjects.

Next, in the matched dataset, the incidence of each outcome was compared between patients with and without worsening preoperative HF for nonemergent surgery. Relative risks (RRs) were calculated by comparing the incidence of adverse events between the HF and control groups using Mantel-Haenszel methods. Statistical significance of this difference was assessed using McNemar's test. A *P* value <0.05 denoted statistical significance. The matching

Table 1. Preoperative Demographics and Clinical Characteristics of Matched Heart Failure (HF) and Matched Controls

Variable	Matched HF, (*N* = 5094)		Matched control, (*N* = 5094)		
	Median	IQR[a]	Median	IQR	SD[b]
Age (Ages older than 89 y recorded as 90 y)[a]	71	(61.0 to 80.0)	72	(62.0 to 80.0)	2.85%
Body mass index (kg/m^2)[a]	27.8	(23.9 to 33.7)	27.6	(23.5 to 32.9)	−7.02%
Surgical complexity score[a]	0.3	(−0.2 to 0.8)	0.3	(−0.2 to 0.8)	1.10%
	N	%	*N*	%	SD
Impaired sensorium before surgery	185	(4)	169	(3)	−1.72%
>4 units red blood cells transfused before surgery	105	(2)	103	(2)	−0.28%
Angina within 1 mo of surgery	378	(7)	342	(7)	−2.76%
ASA physical status classification III or IV	4944	(97)	4997	(98)	6.77%
Bleeding disorder	1239	(24)	1332	(26)	4.20%
Chronic obstructive pulmonary disease	1323	(26)	1305	(26)	−0.81%
Current smoker	1104	(22)	1175	(23)	3.35%
Diabetes	2130	(42)	2136	(42)	0.24%
Dyspnea	2614	(51)	2531	(50)	−3.26%
Gender	2747	(54)	2752	(54)	0.20%
Cardiac surgery or percutaneous coronary intervention	2271	(45)	2263	(44)	−0.32%
Transient ischemic attack or stroke	1145	(22)	1213	(24)	3.17%
Hypertension	4372	(86)	4418	(87)	−2.62%
Liver disease	214	(4)	194	(4)	−2.00%
Myocardial infarction within 6 mo of surgery	418	(8)	339	(7)	−5.92%
Peripheral vascular disease	1481	(29)	1621	(32)	5.97%
Pneumonia	201	(4)	153	(3)	−5.15%
Renal failure	829	(16)	878	(17)	2.58%
Sepsis	363	(7)	379	(7)	1.21%
Septic shock	70	(1)	50	(1)	−3.64%
Systemic inflammatory response syndrome	617	(12)	635	(12)	1.08%
Steroid use	405	(8)	392	(8)	−0.95%

SD = standardized difference.
[a]Interquartile range.
[b]Standardized difference.

Table 2. Association of Worsening Preoperative Heart Failure (HF) with Postoperative Outcomes

Outcome	30-d incidence		Mantel-Haenszel relative risk (95% confidence interval)	*P*
	HF *N* (%)	Control *N* (%)		
30-d mortality	445 (8.7)	230 (4.5)	2.08 (1.75–2.46)	<0.001
Composite morbidity	1542 (30.3)	1136 (22.3)	1.54 (1.40–1.69)	<0.001
Acute renal failure	124 (2.4)	68 (1.3)	1.85 (1.37–2.49)	<0.001
Prolonged mechanical ventilation	393 (7.7)	230 (4.5)	1.81 (1.52–2.15)	<0.001
Pneumonia	327 (6.4)	196 (3.8)	1.73 (1.44–2.08)	<0.001
Cardiac arrest	146 (2.9)	88 (1.7)	1.69 (1.29–2.21)	<0.001
Unplanned intubation	379 (7.4)	236 (4.6)	1.68 (1.41–1.99)	<0.001
Renal insufficiency	64 (1.3)	39 (0.8)	1.64 (1.10–2.44)	0.014
Sepsis	532 (10.4)	388 (7.6)	1.43 (1.24–1.64)	<0.001
Pulmonary embolism	37 (0.7)	26 (0.5)	1.42 (0.86–2.35)	0.166
Deep venous thrombosis	107 (2.1)	81 (1.6)	1.33 (0.99–1.78)	0.055
Urinary tract infection	234 (4.6)	183 (3.6)	1.29 (1.06–1.58)	0.011
Peripheral nerve injury	4 (0.1)	5 (0.1)	1.25 (0.34–4.65)	0.739
Postoperative transfusion	58 (1.1)	52 (1.0)	1.18 (0.81–1.73)	0.384
Stroke	41 (0.8)	36 (0.7)	1.14 (0.73–1.80)	0.564
Intraoperative transfusion	94 (1.8)	86 (1.7)	1.10 (0.78–1.56)	0.593
Myocardial infarction	65 (1.3)	61 (1.2)	1.07 (0.75–1.52)	0.719
Surgical site infection	341 (6.7)	323 (6.3)	1.06 (0.90–1.25)	0.464
Wound disruption	77 (1.5)	73 (1.4)	1.06 (0.76–1.46)	0.741
Coma	11 (0.2)	11 (0.2)	1.00 (0.43–2.31)	1.000

and statistical analysis for this study was generated using SAS software, Version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, NC).

RESULTS

Of the 679,422 patients meeting inclusion criteria, 5967 patients (1%) had worsening preoperative HF. Using propensity score and surgical risk score matching, 5094 (85%) of the HF patents were matched to 5094 control patients (Fig. 1). The demographics of the study patient population are summarized in Table 1. The HF and control groups were well balanced for all comorbidities with all standardized differences being <10%. The matched cohorts had a high prevalence of hypertension (86%). About half the subjects had preoperative dyspnea (51%), diabetes (42%), and a history of cardiac surgery or percutaneous coronary intervention.

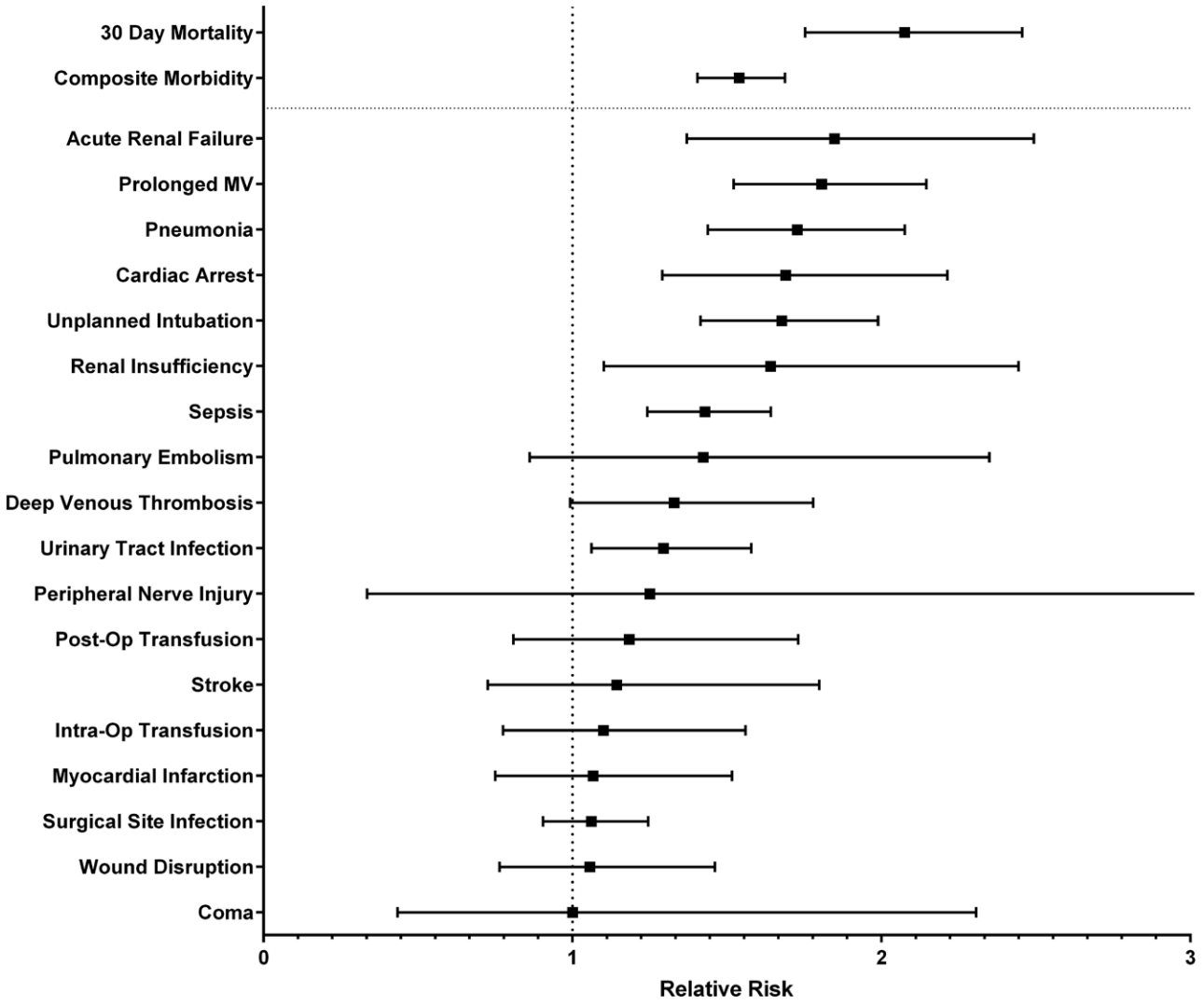

Figure 2. Forest plot of the relative risks for outcomes in patients with worsening preoperative heart failure (HF).

Patients were also well matched for year of surgery (standardized difference of 6.33%).

HF patients in the sample were more likely to die within 30 days of surgery compared with matched control patients (RR 2.08; 95% confidence interval [CI], 1.75–2.46; $P < 0.001$) (Table 2, Fig. 2). This resulted in 4.2 additional deaths for every 100 cases (Fig. 3). The HF group in this sample also had significantly more risk for postoperative complications, notably respiratory (unplanned tracheal intubation, need for prolonged mechanical ventilation, and pneumonia), renal (renal insufficiency and acute renal failure), and infectious (sepsis, urinary tract infection, and pneumonia) complications (Fig. 3). From the sample, for every 100 patients with HF, we calculated 30.3 patients suffered 1 or more complications compared with 22.3 matched patients without worsening HF (RR 1.54; 95% CI, 1.40–1.69; $P < 0.001$). Specifically, approximately 3.2 more patients required prolonged mechanical ventilation (RR 1.81; 95% CI, 1.52–2.15; $P < 0.001$), 2.8 more patients required unplanned intubation (RR 1.68; 95% CI, 1.41–1.99; $P < 0.001$), 2.6 more patients developed pneumonia (RR 1.73, 95% CI, 1.44–2.08; $P < 0.001$), 2.8 more patients had sepsis (RR 1.43; 95% CI, 1.24–1.64; $P < 0.001$), 1 more patient had a urinary tract infection (RR 1.29; 95% CI, 1.06–1.58; $P = 0.011$), and 1.6 more patients had renal insufficiency (RR 1.64; 95% CI, 1.10–2.44; $P = 0.014$) or acute renal failure (RR 1.85; 95% CI, 1.37–2.49; $P < 0.001$). There were also approximately 1.2 more cardiac arrests requiring cardiopulmonary resuscitation per 100 for patients with HF in the sample (RR 1.69; 95% CI, 1.29–2.21; $P < 0.001$). We found that the groups with and without HF in our sample had similar risks of perioperative MI (RR 1.07; 95% CI, 0.75–1.52; $P = .719$), as well as similar risks of DVT, PE, surgical site infections, stoke, transfusion requirements, coma, or peripheral nerve injuries (Table 2, Fig. 2).

To investigate any bias caused by our matching algorithm, matched HF patients were compared with those who were not matched. This demonstrated that HF patients who went unmatched were more likely to be older and have higher preoperative morbidity. Specifically, they were more likely (standardized difference >10%) to have impaired sensorium, angina, bleeding disorders, chronic obstructive pulmonary disease, diabetes, dyspnea, previous cardiac surgery or percutaneous coronary intervention, transient

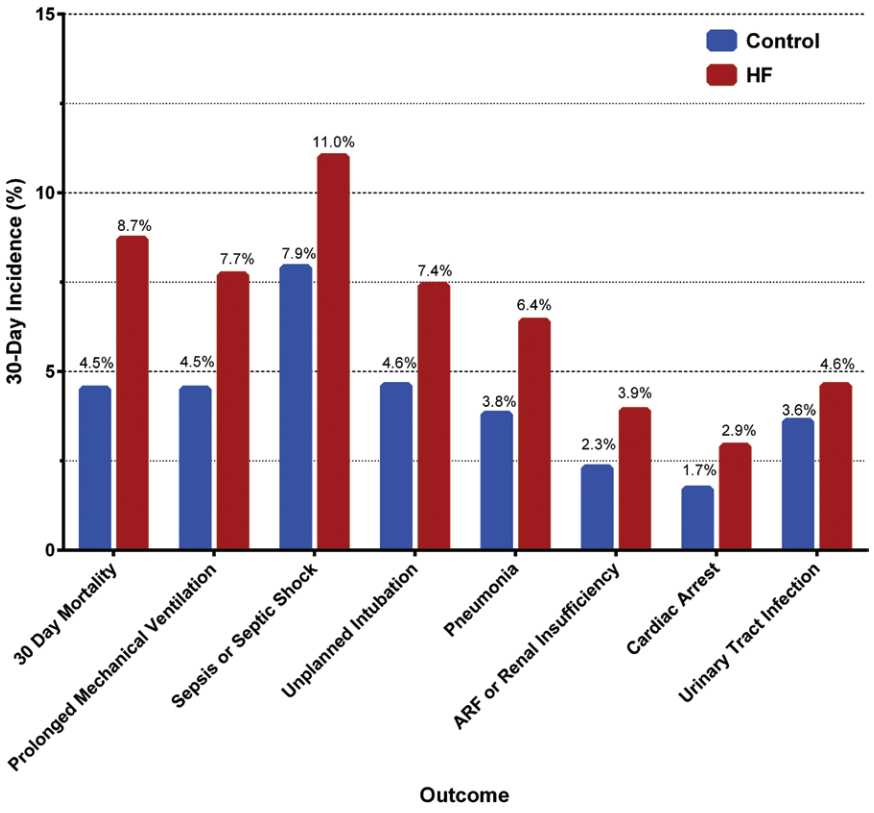

Figure 3. Bar chart demonstrating the proportions of adverse events that are attributable to worsening preoperative heart failure (HF). Outcomes are ordered by the magnitude of the difference between HF and non-HF cohorts (ARF = acute renal failure). All differences are statistically significant ($P < 0.05$).

ischemic attacks or stroke, liver disease, MI, peripheral vascular disease, pneumonia, renal failure, sepsis, septic shock, and systemic inflammatory response syndrome. They also had higher surgical complexity scores.

DISCUSSION

We estimated that patients with worsening preoperative HF were approximately twice (RR 2.08; 95% CI, 1.75–2.46; $P < 0.001$) as likely to die (4.2 more deaths per 100 HF patients) and were 40% to 69% more likely to experience a morbidity (RR 1.54; 95% CI, 1.40–1.69; $P < 0.001$). While patients with HF are frequently thought to be at increased risk for postoperative adverse cardiac events, we demonstrated that most increased morbidity is due to respiratory, infectious, and renal complications. Patients with and without HF had similar estimated risks of postoperative MI (RR 1.07; 95% CI, 0.75–1.52; $P = 0.719$), and the 30-day incidence of cardiac arrest was only slightly higher in the HF group (1.5% vs 0.8%, $P < 0.001$). The American College of Cardiology/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery[26] recommend that patients with decompensated HF should be treated before proceeding to the operating room. The HF cohort in this study contained subjects who proceeded with surgery despite their new or worsening HF within 30 days of surgery. Either these participants were treated before surgery or it was decided that the urgency of the procedure (e.g., surgery for cancer) outweighed the benefit of delaying surgery to treat their HF. Given that the purpose of these guidelines is to reduce the cardiac risk of noncardiac surgery, it is interesting that this cohort was much more likely to suffer from noncardiac morbidity. While it is impossible to isolate organ systems from each other, these results suggest that care of these patients may be overly focused on cardiac events. For example, use of β-blockers may result in a low cardiac outputs state relative to the increased demands of the perioperative period, leading to decreased systemic perfusion and increased likelihood of end-organ injury.[27]

Subjects with worsening HF in this sample had an increased risk of suffering at least 1 morbid event (RR 1.54; 95% CI, 1.40–1.69; $P < 0.001$). The most common group of complications was respiratory (Fig. 3). This high rate (approximately 8 additional patients with complications per 100 HF patients undergoing surgery) has several possible explanations. For example, clinicians may maintain mechanical ventilation longer in patients with HF compared with those without HF due to its potential beneficial effects on cardiac loading conditions. Furthermore, mechanical ventilation may be maintained longer in patients with HF with the goal of decreasing oxygen consumption. However, this course of action may result in an increased incidence of ventilator-associated pneumonia along with subsequent need for reintubation of the trachea and the need for further mechanical ventilation.

Furthermore, we found a frequent incidence of renal complications (renal insufficiency or acute renal failure). Whether this was related to low cardiac output or overly restrictive fluid administration or diuresis in trying to prevent or treat the cardiac complications was not clear. We also found an association between HF and infectious complications that have not been described (Fig. 3). We speculate that perhaps prolonged intubation due to concerns for possible postoperative pulmonary edema or urinary catheter use to accurately monitor diuresis may contribute to the increased infectious complications in patients with HF. Alternatively,

infections may be the result of the interaction of the immune system and failing myocardium (systolic dysfunction, diastolic dysfunction, or both).[28] HF leads to an increase in cytokines and other inflammatory mediators,[29] and it is possible that this immune dysregulation leads to the increased incidence of postoperative infections seen in this study.

In this study, the HF group had no statistically significant estimated increased risk of postoperative MI (RR 1.07; 95% CI, 0.75–1.52; $P = 0.719$), which differs with several previous studies that found an association between HF and postoperative MI.[7–9] There are several possible explanations for this difference. First, studies demonstrating an association between HF and postoperative MI are >20 years old[7–9]; the care of these patients may have subsequently improved. Patients with HF may be more aggressively screened for correctable coronary artery disease, or they may receive medical management associated with reduced mortality such as aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors decreasing the postoperative MI risk.[26,30] Second, perioperative management may be focused on preventing myocardial ischemia at the expense of other organ systems, leading to the higher risk of noncardiac complications observed in our HF population. Also, since subjects participating in ACS NSQIP are not screened for MI with routine checking of serum biomarkers, some cases of silent myocardial ischemia may have gone undiagnosed.

Our finding that HF patients had a statistically insignificant increase in DVT, or PE is not consistent with other studies that have found the incidence of thrombotic complications to be increased in this patient population. However, the wide range of the CI for our estimate of increased risk of thrombotic complications is increased secondary to the lower incidence of this complication in this study. In fact, when we combined PE and DVT into a single outcome in our sample, we calculated that HF patients had an increased risk of a thrombotic complication within 30-days of surgery (RR 1.41; 95% CI, 1.08–1.83; $P = 0.010$). This highlights that complications that are not different between the 2 cohorts may be secondary to a low incidence rather than a lack of association with HF.

This analysis has several limitations that should be considered when interpreting the results. First, this was a retrospective study. Therefore, we were unable to assess why patients with new or worsening HF underwent nonemergent surgery, and data were not available to compare treatment differences between the study cohorts. However, because ACS NSQIP data are collected prospectively by specially trained nurses, bias secondary to misclassification of preoperative comorbidities and postoperative complications is likely minimal.[23] Second, our study design accounted for differences in baseline patient characteristics by creating 2 groups with similar prevalence of comorbid conditions. Thus, we compared patients of comparable age, similar comorbidities, and surgical complexity to identify the added risk of HF on adverse events. This resulted in 15% of the HF patients being excluded from the analysis. Since the unmatched HF patients had significantly more comorbidities, our results may underestimate surgical risk for the entire HF population. Third, similar to regression techniques, propensity score analysis is unable to adjust for unmeasured confounders. Therefore, our findings may have been due to factors such as hospital size that are not recorded in this dataset. Finally, because ACS NSQIP categorized patients as having HF only if their symptoms were worsening within 30 days before surgery, our findings may not be generalizable to patients with stable HF.

There are also multiple strengths to this analysis. First, we used a multicenter database that samples patients throughout the United States. Selection bias is minimized due to the large number of hospitals that participate in this program and results are applicable to both public and private hospitals. The prospective nature of data collection reduces the potential for measurement bias skewing the results. The large number of patients in the database allowed us to create a control group with similar preoperative risk factors compared with the patients with HF. This strategy of using propensity scores allowed us to create balanced cohorts for comparison and allowed us to report risks instead of odds for complications. This provides insight into the amount of morbidity and mortality that can be directly associated with HF. Also, our calculation of an approximately 8.7% risk of 30-day mortality for HF patients and approximately 4.5% for the matched cohort is similar to previously published

Appendix 1. NSQIP Definitions of Preoperative Patient Characteristic Variables (Adapted from Participant Use Data File)

Variable	Definitions
Impaired sensorium before surgery	Patient is acutely confused and/or delirious and responds to verbal and/or mild tactile stimulation. Patient is noted to have developed an impaired sensorium if they have mental status changes, and/or delirium in the context of the current illness. Patients with chronic or long-standing mental status changes secondary to chronic mental illness (e.g., schizophrenia) or chronic dementing illnesses (e.g., multiinfarct dementia, senile dementia of the Alzheimer's type) are not included. This assessment of the patient's mental status is within 48 h before the surgical procedure.
>4 units PRBCs transfused before surgery	Preoperative loss of blood necessitating a minimum of 5 units whole blood/packed red cells transfused during the 72 h before surgery including any blood transfused in the emergency room.
Angina within 1 mo of surgery	Patient reports pain or discomfort between the diaphragm and the mandible, resulting from myocardial ischemia. Typically angina is a dull, diffuse (fist-sized or larger) substernal chest discomfort precipitated by exertion or emotion and relieved by rest or nitroglycerine. Radiation to the arms and shoulders often occurs, and occasionally to the neck, jaw (mandible, not maxilla), or interscapular region. For patients on antianginal medications, the patient has had angina at any time within 1 mo before surgery.
Bleeding disorder	Any condition that places the patient at risk for excessive bleeding requiring hospitalization due to a deficiency of blood clotting elements (e.g., vitamin K deficiency, hemophilias, thrombocytopenia, chronic anticoagulation therapy that has not been discontinued before surgery). Patients who are on chronic aspirin therapy not included. Patients are included if there is no documentation of discontinuation of medication.

(Continued)

Appendix 1. (Continued)

COPD	Chronic obstructive pulmonary disease (such as emphysema and/or chronic bronchitis) resulting in any one or more of the following: • Functional disability from COPD (e.g., dyspnea, inability to perform activities of daily living [ADLs]). Hospitalization in the past for treatment of COPD -Requires chronic bronchodilator therapy with oral or inhaled agents. • An Forced Expiratory Volume in 1 second (FEV1) of <75% of predicted on pulmonary function testing. • Patients are not included whose only pulmonary disease is asthma, an acute and chronic inflammatory disease of the airways resulting in bronchospasm. Patients are not included with diffuse interstitial fibrosis or sarcoidosis.
Current smoker	The patient has smoked cigarettes in the year before admission for surgery. Patients who smoke cigars or pipes or use chewing tobacco are not included.
Diabetes	The individual requires daily dosages of exogenous parenteral insulin or an oral hypoglycemic agent to prevent a hyperglycemia/metabolic acidosis. A patient is not included if diabetes is controlled by diet alone.
Dyspnea	The patient described difficult, painful, or labored breathing. Dyspnea may be symptomatic of numerous disorders that interfere with adequate ventilation or perfusion of the blood with oxygen. The dyspneic patient is subjectively aware of difficulty with breathing. The time frame is at the time the patient is being considered as a candidate for surgery (that is no longer than 30 d before surgery).
Cardiac surgery	If the patient has had any major cardiac surgical procedures or for patient who have undergone percutaneous coronary intervention (PCI) at any time (including any attempted PCI). This includes coronary artery bypass graft surgery, valve replacement or repair, repair of atrial or ventricular septal defects, great thoracic vessel repair, cardiac transplant, left ventricular aneurysmectomy, insertion of left ventricular assist devices (LVAD), balloon dilatation, or stent placement, etc. Not include are pacemaker insertions, automatic implantable cardioverter defibrillator (AICD) insertions, or valvuloplasty.
TIA or stroke	The patient has transient ischemic attacks (TIAs) or a history of a cerebrovascular accident (embolic, thrombotic, or hemorrhagic) with persistent residual motor, sensory, or cognitive dysfunction. (e.g., hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory). TIAs are focal neurologic deficits (e.g., numbness of an arm or amaurosis fugax) of sudden onset and brief duration (usually <30 min) that usually reflects dysfunction in a cerebral vascular distribution.
Hypertension	Patients with a persistent elevation of systolic blood pressure >140 mm·Hg or a diastolic blood pressure >90 mm·Hg or requires an antihypertensive treatment (e.g., diuretics, β-blockers, ACE inhibitors, calcium channel blockers) at the time the patient is being considered as a candidate for surgery (that should be no longer than 30 d before surgery).
Liver disease	Patients with either the presence of fluid accumulation in the peritoneal cavity noted on physical examination, abdominal ultrasound, or abdominal CT/MRI within 30 d before the operation or esophageal varices present preoperatively and documented on an esophagogastroduodenoscopy (EGD) or CT scan performed within 6 mo before the surgical procedure.
MI within 6 mo of surgery	Patients with a history of a non-Q wave or a Q wave infarct in the 6 mo before surgery as diagnosed in the patient's medical record.
Peripheral vascular disease	Patient with any type of angioplasty (including stent placement) or revascularization procedure for atherosclerotic peripheral vascular disease (PVD) (e.g., aorta-femoral, femoral-femoral, femoral-popliteal) or a patient who has had any type of amputation procedure for PVD (e.g., toe amputations, transmetatarsal amputations, below the knee or above the knee amputations). Patients who have had amputation for trauma or a resection of abdominal aortic aneurysms should not be included. Patients with a patient with rest pain or gangrene. Rest pain is a more severe form of ischemic pain due to occlusive disease, which occurs at rest and is manifested as a severe, unrelenting pain aggravated by elevation and often preventing sleep.
Pneumonia	Patients who have evidence of pneumonia at the time the patient is brought to the OR. Patients with pneumonia must meet ONE of the following 2 criteria: criterion 1. Rales or dullness to percussion on physical examination of chest AND any of the following: (a), New onset of purulent sputum or change in character of sputum. (b), Organism isolated from blood culture. (c), Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy OR criterion 2. Chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following: (a), New onset of purulent sputum or change in character of sputum. (b), Organism isolated from blood culture. (c), Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy. (d), Isolation of virus or detection of viral antigen in respiratory secretions. (e), Diagnostic single antibody titer (IgM) or 4-fold increase in paired serum samples (IgG) for pathogen. (f), Histopathologic evidence of pneumonia.
Renal failure	The patient has either acute or chronic renal failure requiring treatment with peritoneal dialysis, hemodialysis, hemofiltration, hemodiafiltration, or ultrafiltration within 2 wk before surgery or the patient has the clinical condition associated with rapid, steadily increasing azotemia (increase in blood urea nitrogen [BUN]), and a rising creatinine of above 3 mg/dL. Acute renal failure should be noted within 24 h before surgery.
Sepsis Septic shock SIRS	SIRS is a widespread inflammatory response to a variety of severe clinical insults. This syndrome is clinically recognized by 2 or more of the following within the same time frame: • Temp >38°C (100.4°F) or <36°C (96.8°F) • HR >90 bpm • RR >20 breaths/min or PaCO2 <32 mmHg (<4.3 kPa) • WBC >12,000 cell/mm^3, <4000 cells/mm^3, or >10% immature (band) forms • Anion gap acidosis Sepsis: Sepsis is the systemic response to infection. This variable reported if the patient has clinical signs and symptoms of SIRS listed above and one of the following: positive blood culture. Clinical documentation of purulence or positive culture from any site thought to be causative. Severe Sepsis/Septic Shock: Sepsis is considered severe when it is associated with organ and/or circulatory dysfunction. This variable reported if the patient has the clinical signs and symptoms of SIRS or sepsis AND documented organ and/or circulatory dysfunction. Examples of organ dysfunction include oliguria, acute alteration in mental status, and acute respiratory distress. Examples of circulatory dysfunction include hypotension, requirement of inotropic or vasopressor agents.
Steroid use	Patient who required regular administration of oral or parenteral corticosteroid medications (e.g., Prednisone, Decadron) in the 30 d before surgery for a chronic medical condition (e.g., COPD, asthma, rheumatologic disease, rheumatoid arthritis, inflammatory bowel disease). Topical corticosteroids applied to the skin or corticosteroids administered by inhalation or rectally are not included. Patients who only receive short course steroids (duration 10 d or less) in the 30 d before surgery are not included.

Appendix 2. NSQIP Definitions of Postoperative Outcome Variables (Adapted from Participant Use Data File)

Acute renal failure	In a patient who did not require dialysis preoperatively, worsening of renal dysfunction postoperatively requiring hemodialysis, peritoneal dialysis, hemofiltration, hemodiafiltration, or ultrafiltration within 30 d of the operation. Patients coded as having both acute renal failure and renal insufficiency were only counted as having acute renal failure for this study.
Renal insufficiency	The reduced capacity of the kidney to perform its function as evidenced by a rise in creatinine of >2 mg/dL from preoperative value but with no requirement for dialysis within 30 d of the operation.
Prolonged mechanical ventilation (MV)	Total duration of ventilator-assisted respirations during postoperative hospitalization was greater than 48 h. This can occur at any time during the 30-d period postoperatively. This time assessment is cumulative, not necessarily consecutive. Ventilator-assisted respirations can be via endotracheal tube, nasotracheal tube, or tracheostomy tube.
Pneumonia	Inflammation of the lungs caused primarily by bacteria, viruses, and/or chemical irritants, usually manifested by chills, fever, pain in the chest, cough, purulent, bloody sputum within 30 d of the operation. The patient has pneumonia if their symptoms meet the definition of pneumonia below AND pneumonia is not present preoperatively. Pneumonia must meet one of the following 2 criteria: criterion 1: Rales or dullness to percussion on physical examination of chest AND any of the following: (a), New onset of purulent sputum or change in character of sputum. (b), Organism isolated from blood culture. (c), Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy. OR criterion 2: chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following: (a), New onset of purulent sputum or change in character of sputum. (b), Organism isolated from blood culture. (c), Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy. (d), Isolation of virus or detection of viral antigen in respiratory secretions. (e), Diagnostic single antibody titer (IgM) or 4-fold increase in paired serum samples (IgG) for pathogen. (f), Histopathologic evidence of pneumonia.
Cardiac arrest	The absence of cardiac rhythm or presence of chaotic cardiac rhythm that results in loss of consciousness requiring the initiation of any component of basic and/or advanced cardiac life support within 30 days of the operation. Patients with automatic implantable cardioverter defibrillator (AICD) that fire but the patient has no loss of consciousness should be excluded.
Unplanned intubation	Patient required placement of an endotracheal tube and mechanical or assisted ventilation because of the onset of respiratory or cardiac failure manifested by severe respiratory distress, hypoxia, hypercarbia, or respiratory acidosis within 30 days of the operation. In patients who were intubated for their surgery, unplanned intubation occurs after they have been extubated after surgery. In patients who were not intubated during surgery, intubation at any time after their surgery is considered unplanned.
Pulmonary embolism	Lodging of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma. The blood clots usually originate from the deep leg veins or the pelvic venous system within 30 d of the operation. PE documented if the patient has a V-Q scan interpreted as high probability of pulmonary embolism or a positive CT spiral exam, pulmonary arteriogram, or CT angiogram. Treatment usually consists of: • Initiation of anticoagulation therapy. • Placement of mechanical interruption (e.g., Greenfield Filter), for patients whom anticoagulation is contraindicated or already instituted.
Deep venous thrombosis	The identification of a new blood clot or thrombus within the venous system, which may be coupled with inflammation wihtin 30 days of the operation. This diagnosis is confirmed by a duplex, venogram or CT scan. The patient must be treated with anticoagulation therapy and/or placement of a vena cava filter or clipping of the vena cava.
Urinary tract infection	Postoperative symptomatic urinary tract infection must meet one of the following 2 criteria within 30 d of the operation: (1), One of the following: fever (>38°C). urgency. frequency . dysuria . suprapubic tenderness AND a urine culture of >105 colonies/mL urine with no >22 species of organisms OR (2), 2 of the following: fever (>38°C). urgency. frequency . dysuria . suprapubic tenderness AND any of the following: • Dipstick test positive for leukocyte esterase and/or nitrate. • Pyuria (>10 WBCs/mL or >3 WBC/hpf of unspun urine). • Organisms seen on Gram stain of unspun urine -2 urine cultures with repeated isolation of the same uropathogen with >102 colonies/mL urine in nonvoided specimen. • Urine culture with <105 colonies/mL urine of single uropathogen in patient being treated with appropriate antimicrobial therapy. • Physician's diagnosis. • Physician institutes appropriate antimicrobial therapy.
Surgical Site Infection (SSI)	An infection that occurs within 30 d after the operation, and appears to be related to the operation and the infection involves any part of the anatomy which was opened or manipulated during an operation.
Sepsis	Sepsis and/or septic shock within 30 d of the operation. This is reported if the patient has 2 of the following clinical signs or symptoms of SIRS: • Temp >38°C (100.4°F) or < 36°C (96.8°F) • HR >90 bpm • RR >20 breaths/min or PaC02 <32 mmHg (<4.3 kPa) • WBC >12,000 cell/mm^3, <4000 cells/mm^3, or >10% immature (band) forms • Anion gap acidosis AND one of the following: • Positive blood culture • Clinical documentation of purulence or positive culture from any site thought to be causative
Stroke	Patient develops an embolic, thrombotic, or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction (e.g., hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) that persists for 24 or more hours within 30 d of the operation.

(Continued)

Appendix 2. (Continued)

Postoperative transfusion	Any transfusion (including autologous) of packed red blood cells or whole blood given from the time the patient leaves the operating room up to and including 72 h postoperatively. Bleeding Transfusion entered for 5 or more units of packed red blood cell units in the postoperative period including hanging blood from the OR that is finished outside of the OR. If the patient receives shed blood, autologous blood, cell saver blood, or pleurovac postoperatively, this is counted if greater than 4 units. The blood may be given for any reason.
Intraoperative transfusion >4 units	For patients with the number of packed or whole red blood cells given during the operative procedure as it appear on the anesthesia record greater than 4 units. The amount of blood reinfused from the cell saver is also noted. For a cell saver, every 500 mL fluid will equal 1 unit packed cells. If there is <250 mL fluid, cell saver is not included.
Myocardial infarction	A new transmural acute myocardial infarction occurring during surgery or within 30 d as manifested by new Q-waves on electrocardiogram (ECG).
Wound disruption	Separation of the layers of a surgical wound, which may be partial or complete, with disruption of the fascia within 30 days of the operation.
Coma	Patient is unconscious or postures to painful stimuli or is unresponsive to all stimuli (exclude transient disorientation or psychosis) for greater than 24 h. Drug-induced coma (e.g., Propofol drips) is not entered within 30 d of the operation.
Peripheral nerve injury	Peripheral nerve damage may result from damage to the nerve fibers, cell body, or myelin sheath during surgery. Peripheral nerve injuries that result in motor deficits to the cervical plexus, brachial plexus, ulnar plexus, lumbar-sacral plexus (sciatic nerve), peroneal nerve, and/or the femoral nerve should be included.

data[10,24] that strengthens the generalizability of this analysis.[14,31] Unfortunately, these results also highlight that there has been little progress over the past 20 years at reducing the perioperative mortality associated with HF.[31]

In conclusion, we found that HF is associated with a near doubling of postoperative death and increased risks of pulmonary complications, infections, and renal complications but not with MI. Our findings imply that to improve perioperative outcomes for patients with preoperative HF, a focus on other organ protection in addition to the heart is necessary.

DISCLOSURES

Name: Michael D. Maile, MD, MS.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Michael D. Maile has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Milo C. Engoren, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Milo C. Engoren reviewed the analysis of the data and approved the final manuscript.
Name: Kevin K. Tremper, MD, PhD
Contribution: This author helped design the study and write the manuscript.
Attestation: Kevin K. Tremper reviewed the analysis of the data and approved the final manuscript.
Name: Elizabeth Jewell, MS.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Elizabeth Jewell has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Sachin Kheterpal, MD, MBA.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Sachin Kheterpal reviewed the analysis of the data and approved the final manuscript.
This manuscript was handled by: Charles W. Hogue, Jr, MD.

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