

Multivariable Prediction of Renal Insufficiency Developing After Cardiac Surgery

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Background—Renal insufficiency after coronary artery bypass graft (CABG) surgery is associated with increased short-term and long-term mortality. We hypothesized that preoperative patient characteristics could be used to predict the patient-specific risk of developing postoperative renal insufficiency.

Methods and Results—Data were prospectively collected on 11 301 patients in northern New England who underwent isolated CABG surgery between 2001 and 2005. Based on National Kidney Foundation definitions, moderate renal insufficiency was defined as a GFR <60 mL/min/1.73m² and severe renal insufficiency as a GFR <30 . Patients with at least moderate renal insufficiency at baseline were eliminated from the analysis, leaving 8363 patients who became our study cohort. A prediction model was developed to identify variables that best predicted the risk of developing severe renal insufficiency using multiple logistic regression, and the predictive ability of the model quantified using a bootstrap validated C-Index (Area Under ROC) and Hosmer-Lemeshow statistic. Three percent of the patients with normal renal function before CABG surgery developed severe renal insufficiency (229/8363). In a multivariable model the preoperative patient characteristics most strongly associated with postoperative severe renal insufficiency included: age, gender, white blood cell count >12 000, prior CABG, congestive heart failure, peripheral vascular disease, diabetes, hypertension, and preoperative intraaortic balloon pump. The predictive model was significant with χ^2 150.8, probability value <0.0001 . The model discriminated well, ROC 0.72 (95%CI: 0.68 to 0.75). The model was well calibrated according to the Hosmer-Lemeshow test.

Conclusions—We developed a robust prediction rule to assist clinicians in identifying patients with normal, or near normal, preoperative renal function who are at high risk of developing severe renal insufficiency. Physicians may be able to take steps to limit this adverse outcome and its associated increase in morbidity and mortality. (*Circulation*. 2007; 116[suppl I]:I-139–I-143.)

Key Words: surgery ■ risk factors ■ kidney ■ prediction ■ renal insufficiency

Severe renal insufficiency secondary to coronary artery bypass graft (CABG) has morbid and mortal consequences. Severe renal insufficiency is defined as an estimated glomerular filtration rate (eGFR) <30 (mL/min/1.73 m²). Patients developing this renal impairment after surgery have an increased risk of short- and long-term mortality.¹ Each 10 (mL/min) drop in eGFR has been associated with a 14% increased risk of mortality.² Others have shown severe renal insufficiency to be associated with a 4-fold increased risk of mortality over patients with normal or near-normal renal function.³

Because of the dramatic morbidity and mortality resulting from renal impairment (such as developing dialysis dependent renal failure), some authors have developed algorithms to predict the occurrence of renal failure requiring dialysis. The algorithm produced by Chertow et al, using data from 43 medical centers in the Department of Veterans Affairs, were able to identify preoperative risk factors predictive of dialysis dependent renal failure.⁴ The same algorithm was reproduced and validated shortly thereafter.^{5,6} Thakar et al developed a similar model capable of predicting dialysis dependent renal failure using a single-center approach with the same results.⁷

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Mehta et al recently published a similar algorithm predictive of dialysis-dependent renal failure from the Society for Thoracic Surgeons National Database.⁸ However, none of these algorithms focus on the risk of patients with normal or near-normal renal function developing severe renal insufficiency after their procedure. All previous prediction models have focused on predicting dialysis-dependent renal failure after cardiac surgery and have not addressed renal insufficiency without dialysis-dependent renal failure, which is also associated with a high risk of mortality.⁹

In this study, we sought to identify preoperative patient and disease characteristics predictive of severe renal insufficiency (<30 eGFR) among patients with normal or near-normal renal function (>60 eGFR) before CABG surgery. We hypothesized that preoperative patient characteristics could be used to predict the patient-specific risk of developing postoperative severe renal insufficiency.

Methods

The Northern New England Cardiovascular Disease Study Group (NNECDSG) was founded in 1987 as a regional voluntary consortium capturing all of the coronary revascularizations or valve procedures in northern New England at 8 medical centers in Vermont, New Hampshire, and Maine. The group consists of clinicians, hospital administrators, and health care research personnel who seek to improve continually the quality, safety, effectiveness, and cost of medical interventions in cardiovascular disease. The NNECDSG has Institutional Review Board approval for data collection and analysis from all participating centers.

Patient and disease characteristic data were prospectively collected on 11 301 patients in Northern New England who underwent isolated CABG surgery between 2001 and 2005. Based on National Kidney Foundation definitions,^{10,11} moderate renal insufficiency was defined as a GFR <60 and severe renal insufficiency as an eGFR <30 (mL/min/1.73m²). Patients with moderate and severe renal insufficiency (2938) at baseline were eliminated from the analysis, leaving 8363 patients in our study cohort.

Data Collection

The following data were recorded prospectively for all patients. Preoperative characteristics: age, sex, ejection fraction <40%, number of diseased vessels, left main disease, white blood cell count >12 000, previous myocardial infarction within 7 days, emergent and urgent priority, prior percutaneous coronary intervention (PCI) during the same admission, prior CABG surgery, prior valve surgery, congestive heart failure (CHF), atrial fibrillation, peripheral vascular disease (PVD), diabetes, unstable angina, creatinine, chronic obstructive pulmonary disease, body surface area <1.7 (m²), red blood cell transfusion, hypertension, preoperative use of an intraaortic balloon pump (IABP), smoking, ACE-inhibitor use, β -blocker use, calcium channel blockers, 2B3A inhibitors, and preoperative renal failure requiring dialysis (hemodialysis, peritoneal dialysis). Last preoperative serum creatinine (mg/dL) and highest postoperative creatinine (highest for postoperative index-admission) were documented. Methods for data collection and definitions for these variables have been described previously.^{9,12}

Preoperative and postoperative renal insufficiency was calculated using the Modification of Diet in Renal Disease (MDRD) equation (mL/min/1.73 m²): $186 \times (\text{serum creatinine mg/dL})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women})$.¹³ Preoperative eGFR was calculated using the last preoperative serum creatinine, whereas postoperative eGFR was calculated using the highest postoperative serum creatinine. Patients were stratified into preoperative categories of eGFR: ≥ 90 , 60 to 89, 30 to 59, <30 (mL/min/1.73 m²). The outcome of interest in this analysis was severe renal insufficiency, defined as <30 eGFR after CABG surgery.

Statistical Analysis

Patients with missing values for risk factors were considered to not have the risk factor and were therefore set to the null. Univariate analyses were conducted on all potential preoperative risk factors using 2×2 tables, χ^2 tests, and univariate logistic regression, including preoperative characteristics included in Table 1.

All significant univariate risk factors were included in the multivariable logistic model. We conducted a backward stepwise approach to restrict the model to the most predictive risk factors. Risk factors were tested for retention at each step using Likelihood ratio χ^2 tests. Nonsignificant risk factors were removed if they did not significantly add to the model. The predictive ability of the final model was quantified using the C-Index (area under the receiver operating characteristic curve, ROC) and Hosmer-Lemeshow statistic for goodness of fit. A confidence interval for the C-index (ROC) was obtained by bootstrapping 200 times using 100% random sampling by replacement.

The model χ^2 was recorded to develop a χ -pie chart. To determine the contributing χ^2 value of each risk factor, the predictive model was calculated eliminating one risk factor. The reduced model χ^2 was record for each factor. Each factor's χ^2 was subtracted from the full

TABLE 1. Univariate Associations Between Risk Factors and Severe Renal Insufficiency

Variables	Patients (%)	Severe Renal Insufficiency (SRI)			
		SRI (%)	OR	95% CI	P Value
Patients, n	8363	229 (2.7)			
Age, y					
<60	37.0	1.8	1.0		
60–69	31.7	2.5	1.4	(1.0–2.0)	0.075
70–74	15.1	3.6	2.0	(1.4–3.0)	<0.001
75–79	10.7	4.3	2.5	(1.6–3.7)	<0.001
≥ 80	5.5	5.7	3.3	(2.1–5.4)	<0.001
Female	20.3	4.4	1.9	(1.4–2.5)	<0.001
BSA <1.70, m ²	8.1	5.0	2.0	(1.4–2.9)	<0.001
Diabetes	31.1	3.5	1.5	(1.1–2.0)	0.003
PVD	18.5	4.1	1.7	(1.3–2.3)	<0.001
CHF	9.0	7.9	3.7	(2.8–5.1)	<0.001
COPD	9.5	3.8	1.5	(1.0–2.2)	0.058
Hypertension	68.4	3.1	1.5	(1.1–2.1)	0.006
Prior MI within 7 days	17.5	3.8	1.5	(1.1–2.1)	0.009
Prior CABG surgery	4.0	5.4	2.1	(1.3–3.4)	0.003
Prior PCI (same admission)	3.9	2.7	1.0	(0.5–2.0)	0.998
Ejection Fraction <40%	13.3	5.1	2.2	(1.6–3.0)	<0.001
Left Main disease					
50%–89%	25.7	2.8	1.1	(0.8–1.5)	0.513
$\geq 90\%$	5.6	4.3	1.7	(1.0–2.7)	0.030
Urgent	65.4	2.7	1.4	(1.0–1.9)	0.065
Emergent	7.4	5.4	2.8	(1.7–4.3)	<0.001
Preoperative IABP	9.3	6.9	3.2	(2.3–4.3)	<0.001
WBC count >12 000	6.6	4.7	1.9	(1.2–2.8)	0.004

SRI indicates severe renal insufficiency; OR, odds ratio from univariate logistic model; 95% CI, 95 percent confidence intervals; BSA, body surface area; PVD, peripheral vascular disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; IABP, intraaortic balloon pump; WBC, white blood cell.

model's χ^2 to determine its percent contribution. A pie chart was plotted to denote the relative contribution of each factor for prediction severe renal insufficiency.

A clinical risk score card was created to assist clinicians in identifying patients before surgery at risk of developing severe renal insufficiency. Odds ratios from the multivariable model were rounded to the nearest 0.5. This value represented the score for that risk factor. Each patient in the registry was assigned a preoperative score. Patients were stratified by score and the rate was calculated using the observed (severe renal insufficiency) for each score. This event rate was then plotted and a fitted trend line was estimated across the categories.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Three percent, or 229, of the patients with normal or near normal renal function before CABG surgery developed severe renal insufficiency. Patients developing severe renal insufficiency had an increased risk of in-hospital mortality compared with patients without severe renal insufficiency (26.2% versus 0.7% dead at discharge). New onset of dialysis dependent renal failure resulted in 31 (0.37%) patients.

Significant univariate predictors of severe renal insufficiency after CABG were age ≥ 70 (years), female, BSA < 1.70 (m^2), diabetes, PVD, CHF, hypertension, prior MI within 7 days, prior CABG, ejection fraction $< 40\%$, left main disease $\geq 90\%$, emergent priority, preoperative IABP use, white blood cell count $> 12\,000$ (Table 1). All significant univariate risk factors were tested in a multivariable model. Risk factors not significant in the multivariable model were dropped. The final multivariable model is shown in Table 2. The final model incorporated 11 preoperative risk factors for developing severe renal insufficiency, including: age 70 to 74, 75 to 79, ≥ 80 years, female, diabetes, CHF, PVD, hypertension, prior CABG, preoperative IABP use, and white blood cell count $> 12\,000$. The coefficients (Table 2) can be used before CABG surgery to predict the risk of developing

TABLE 2. Multivariate Prediction of the Risk of Severe Renal Insufficiency

Variables (1=yes; 0=no)	Adj OR	Coefficients	95% CI	P Value
Age, y				
70–74	1.5	0.4298	(1.1–2.2)	0.018
75–79	1.9	0.6222	(1.3–2.7)	0.001
≥ 80	2.4	0.8684	(1.5–3.7)	< 0.001
Female	1.7	0.5043	(1.2–2.2)	0.001
Diabetes	1.4	0.3113	(1.0–1.8)	0.029
PVD	1.4	0.3130	(1.0–1.9)	0.044
CHF	2.7	0.9777	(1.9–3.7)	< 0.001
Hypertension	1.4	0.3192	(1.0–1.9)	0.049
Prior CABG surgery	2.1	0.7459	(1.3–3.5)	0.004
Preoperative IABP	2.7	1.0111	(2.0–3.8)	< 0.001
White blood cell count $> 12\,000$	1.5	0.3825	(0.9–2.3)	0.090
Constant		-4.7227		< 0.001

Adj OR indicates adjusted odds ratio; 95% CI, 95 percent confidence intervals; PVD, peripheral vascular disease; CHF, congestive heart failure; CABG, coronary artery bypass graft surgery; IABP, intraaortic balloon pump.

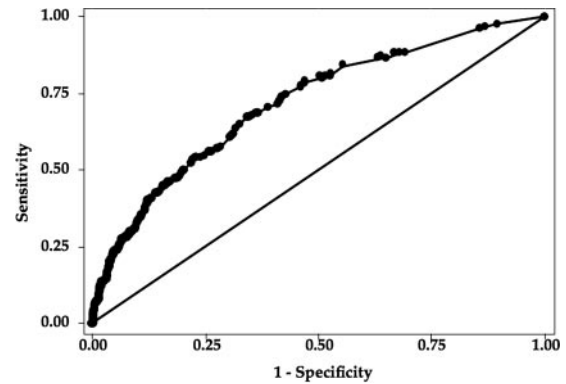


Figure 1. Discrimination: Area under ROC curve. The receiver operating characteristic curve (ROC) for severe renal insufficiency demonstrated good ability to discriminate between those patients who developed severe renal insufficiency (eGFR < 30 mL/min/1.73 m^2) and those who did not.

severe renal insufficiency (eGFR < 30 mL/min/1.73 m^2) for a patient with normal or near-normal renal function (eGFR > 60 mL/min/1.73 m^2).

The multivariable model significantly predicted the occurrence of severe renal insufficiency (model $\chi^2 = 150.78$, probability value < 0.001). The model discriminated well between patients who did and did not develop severe renal insufficiency after CABG surgery (ROC: 0.72; 95%CI: 0.68 to 0.75, Figure 1). The model was well calibrated among deciles of observed and expected risk (Hosmer-Lemeshow $\chi^2 = 8.68$, probability value 0.28). Observed and expected deciles of risk were highly correlated ($R = 0.97$, probability value < 0.001 , Figure 2).

We calculated the relative contribution of each risk factor's predictive ability in the multivariable model (Figure 3): CHF (27%), preoperative use of IABP (26%), age ≥ 70 (18%), female gender (10%), prior CABG (6%), diabetes (4%), PVD (3%), hypertension (4%), and white blood cell count $> 12\,000$ (2%).

We created a score card by rounding off the odds ratios in the multivariable model to the nearest 0.5 value. Patient-specific risk scores can be calculated by summarizing the

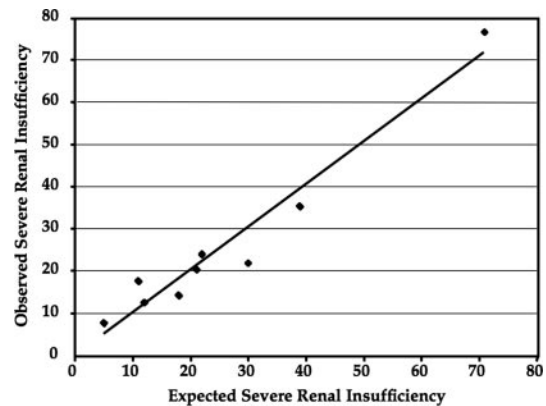


Figure 2. Calibration: Hosmer-Lemeshow χ^2 . We tested the model calibration between observed and expected severe renal insufficiency among increasing deciles of risk. The correlation between observed vs expected severe renal insufficiency was 0.97. The Hosmer-Lemeshow goodness of fit statistic was $\chi^2 = 8.68$, $P = 0.28$.

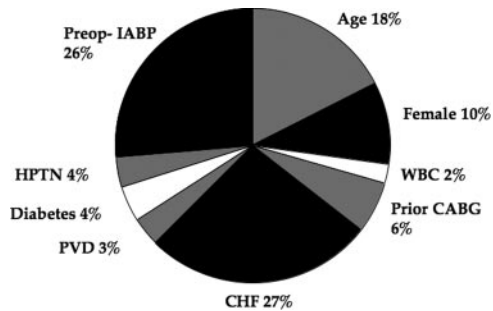


Figure 3. Relative contribution of predictors for severe renal insufficiency. The relative contributions of predictors for severe renal insufficiency are plotted. The size represents the percent of contribution to the prediction model. HPTN indicates hypertension; PVD, peripheral vascular disease; CHF, congestive heart failure; CABG, coronary artery bypass graft surgery; WBC, white blood cell count >12 000; IABP, Intra-aortic balloon pump.

individual risk scores and looking up the patient-specific risk on the graph (Figure 4).

Discussion

Patient-specific risk for severe renal insufficiency can be predicted before undergoing CABG surgery for patients with normal or near-normal renal function. We identified preoperative patient and disease characteristics most predictive of a patient with normal renal function before CABG surgery at risk of developing severe renal insufficiency after the procedure. We have shown severe renal insufficiency is an infrequent but lethal outcome for patients entering surgery with normal or near-normal renal function. Patients developing severe renal insufficiency were at a 50-fold increased risk of index-admission mortality. Severe renal insufficiency is a serious consequence to CABG surgery, even among patients with normal preoperative renal function. A prediction card (Figure 4) was developed and can be used to risk stratify patients for developing severe renal insufficiency. Once identified, clinicians can implement preventative measures for high-risk patients.

We restricted our analysis to patients with near or near-normal renal function calculated by the established MDRD equation ($eGFR \geq 60$). We defined severe renal insufficiency as postoperative $eGFR < 30$ and required patients with normal or near-normal renal function to develop a marked decrease in renal function defined as a drop of more than 30 ($mL/min/1.73m^2$); that is at least a drop from ≥ 60 to < 30 ($mL/min/1.73m^2$). Severe renal insufficiency has been previously defined as < 30 ($mL/min/1.73m^2$) by the National Kidney Foundation.^{10,11} Others have shown each 10- $(mL/min/1.73m^2)$ drop in $eGFR$ to be associated with a 14% increased risk of mortality²; in our analysis this would be a minimum of a 42% increase risk of mortality. A drop in renal function of this magnitude is clinically important. Because of the severity of severe renal insufficiency and its strong association with mortality, it is common to see similar patient and disease characteristics also be preoperative risk factors for mortality, low-output failure, and stroke.

Previously we demonstrated that a 50% change in creatinine was associated with a 7- to 22-fold increased risk of

90-mortality.⁹ We proposed hypotension, inflammation, and nephrotoxins may be responsible for causing nephrotoxicity during or after CABG surgery, showing an association between low output failure and infection with changes in creatinine.⁹ Our previous finding supports the identification of preoperative hypertension, IABP use (markers of low output), and white blood cell count >12 000 (markers of inflammation) as strong predictors of severe renal insufficiency before CABG surgery. Low output and inflammation are likely clinical cascades that progress to renal insufficiency supported both in our previous findings and as preoperative predictors before CABG surgery in these findings.

Furthermore, we speculated nephrotoxins such as contrast dose could be placing patients at increased risk for renal insufficiency after CABG surgery. In this study we tested the predictive ability of patients undergoing a percutaneous coronary intervention before CABG surgery during the same admission, believing this would be an indicator of nephrotoxic agent use. However, we were unable to show a significant increased risk for this nephrotoxic marker. This can be explained by the fact that patients were allowed to recover from the nephrotoxic effects of contrast before undergoing CABG surgery, or contrast was used sparingly, or patients were adequately hydrated to prevent nephrotoxicity. There are several explanations for this finding. The influence or effect of contrast-induced nephropathy among patients with a PCI may have been masked by the all patients undergoing angiography before CABG surgery whereby subjecting all patients to a contrast-induced nephropathy not limited to those patients undergoing PCI before CABG. Another explanation could be the elimination of patients with contrast-induced nephropathy in this analysis as we withdrew patients with at least moderate renal insufficiency before CABG (< 60 $eGFR$). We would speculate all patients with compromised renal function would have been withdrawn by this definition.

Our study is in agreement with previous models using preoperative patient and disease characteristics to predict renal outcomes. Chertow et al (Fortescue and Eriksen validation of Chertow's prediction rule) demonstrated preoperative patient characteristics predicted dialysis dependent renal failure.⁴⁻⁶ Bahar et al used both pre- and intraoperative risk

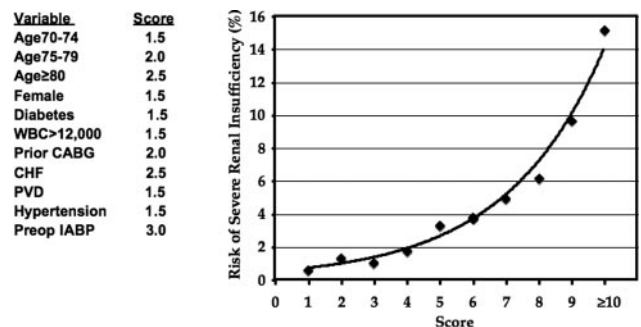


Figure 4. Calculation of predicted risk. Risk prediction for severe renal insufficiency (SRI). For example, the predicted probability of severe renal insufficiency for a 78-year-old woman with normal renal function, diabetes, peripheral vascular disease, hypertension would be $(2.0+1.5+1.5+1.5+0.5) = 8.0$. Risk of severe renal insufficiency = 6.1%.

factors to predict dialysis dependent renal failure.¹⁴ Thakar et al also predicted dialysis dependent renal failure using preoperative risk factors for patients undergoing CABG, CABG/valve, or valve only procedures.⁷ Mehta et al were also successful in predicting dialysis-dependent renal failure in the national STS database among patients undergoing CABG, CABG/valve, or valve only procedures.⁸ Risk factors in common with Chertow's model and our analysis included PVD, preoperative IABP use, and prior heart surgery.⁴ Similar risk factors in Bahar's model and ours included advanced age, diabetes, and hypertension.¹⁴ Risk factors in common with Thakar's model included female gender, CHF, preoperative IABP use, diabetes, and prior CABG surgery.⁷ Mehta's model also identified similar risk factors in our model, including age, diabetes, lung disease, and prior cardiac surgery.⁸ Our analysis extends these findings by identifying preoperative risk factors predictive of severe renal insufficiency defined as an eGFR <30 (as opposed to dialysis-dependent renal failure) among patients with normal to near-normal renal function before CABG surgery. We also developed a simple score card for quick assessment of renal insufficiency risk before CABG surgery.

Janssen et al used a combined outcome for predicting renal dysfunction after CABG surgery.¹⁵ Nephrological morbidity was defined as dialysis or creatinine ≥ 150 ($\mu\text{mol/L}$). They identified similar preoperative risk factors to our model: age ≥ 75 , diabetes, and hypertension. Our model extends this analysis by developing a more robust outcome using estimated GFR and restricted the outcome to at least a 30 ($\text{ml/min}/1.73\text{m}^2$) drop in eGFR from baseline among patients with normal to near-normal renal function.

There is one limitation with this analysis. The model was generated using prospective registry data in the NNECDSG. Other models generated by the NNECDSG have been found to be generalizable in other geographic areas and validated across other institutions.¹⁶ However, this model should be validated by another national or regional registry to confirm these preoperative risk factors among patients with normal or near-normal renal function are predictive of developing severe renal insufficiency after CABG surgery.

Renal insufficiency after CABG surgery in patients who have normal renal function preoperatively occurs as a consequence of factors leading to patients' death, such as hypotension and cytotoxicity. Future studies are required to identify subsets of patients who develop renal failure and link these characteristics to preventative measures. Nally and colleagues have identified several prevention strategies to help reduce the occurrence of renal insufficiency after CABG surgery.¹⁷ Nally suggests to rapidly correct hypotension and prevent its occurrence, avoid nephrotoxic drugs, preoperative hydration to assure adequate volume, use nonionic contrast sparingly for angiography or PCI before CABG, treat infection and oliguria quickly, and assess preoperative renal function (preferably using MDRD equation for eGFR).¹⁷ Quality improvement strategies should be incorporated at institutions to identify and track quality indicators relevant to the prevention of renal insufficiency during the index admission for CABG surgery.

In summary, we developed a prediction rule to assist clinicians in identifying patients with normal or near normal

preoperative renal function who are at high risk of developing severe renal insufficiency. Physicians may be able to take steps to limit the occurrence of renal insufficiency before surgery and its associated increase in morbidity and mortality.

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Disclosures

None.

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