

**CME CREDIT** **EDUCATIONAL OBJECTIVE:** Readers will consider the findings of recent studies when caring for cardiac patients undergoing noncardiac surgery

**STEVEN L. COHN, MD, MS, FACP, SFHM**

Medical Director, UHealth Preoperative Assessment Center; Director, Medical Consultation Services, University of Miami Hospital/Jackson Memorial Hospital; Professor of Clinical Medicine, University of Miami Miller School of Medicine, Miami, FL

**PAUL J. GRANT, MD, SFHM, FACP**

Assistant Professor of Medicine and Director, Perioperative and Consultative Medicine, Division of General Medicine, University of Michigan Health System, Ann Arbor, MI

**SUPARNA DUTTA, MD, MPH**

Assistant Professor, Rush University Medical Center, Chicago, IL; Associate Division Chief, Division of Hospital Medicine, and Medical Director, Attending Directed Service, Rush University Medical College, Chicago, IL

**GERALD W. SMETANA, MD, FACP**

Professor of Medicine, Harvard Medical School; Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Boston, MA

**BARBARA A. SLAWSKI, MD, MS, FACP, SFHM**

Professor of Medicine and Orthopedic Surgery; Chief, Section of Perioperative and Consultative Medicine; Medical College of Wisconsin, Milwaukee

# Update in perioperative cardiac medicine

## ABSTRACT

Recent studies have shed light on preoperative risk assessment, medical therapy to reduce postoperative cardiac complications (beta-blockers, statins, and angiotensin II receptor blockers [ARBs]), perioperative management of patients with coronary stents on antiplatelet therapy, and perioperative bridging anticoagulation.

## KEY POINTS

Outcomes are worse in patients with poor functional capacity or stable angina, and these factors should be considered in preoperative risk assessment.

Perioperative use of beta-blockers may benefit only patients at highest risk and may harm other patients.

Statins seem to provide perioperative protection.

If an ARB is withheld for surgery, it should be restarted soon after.

For patients with a coronary stent, the type of stent and duration of dual antiplatelet therapy need to be considered before noncardiac surgery.

Bridging anticoagulant therapy should not be used in patients at intermediate or low risk of thromboembolism.

**P**ERIOPERATIVE MEDICINE is an evolving field with a rapidly growing body of literature. Because physicians and patients are often concerned about cardiac risk, we focus this review on perioperative cardiology.

The information we present here is derived from presentations at the Perioperative Medicine Summit and the annual meetings of the Society of Hospital Medicine and Society of General Internal Medicine in 2016. We surveyed perioperative literature from January 2015 through March 2016 and chose the final articles by consensus, based on relevance to clinicians who provide preoperative evaluations and postoperative care to surgical patients.

We have divided this review into four sections:

- Preoperative cardiac risk assessment
- Medical therapy to reduce postoperative cardiac complications (beta-blockers, statins, and angiotensin II receptor blockers [ARBs])
- Perioperative management of patients with a coronary stent on antiplatelet therapy
- Perioperative bridging anticoagulation.

## ■ PREOPERATIVE ASSESSMENT OF CARDIAC RISK

### Functionally independent patients do better

Visnjevac O, Davari-Farid S, Lee J, et al. The effect of adding functional classification to ASA status for predicting 30-day mortality. *Anesth Analg* 2015; 121:110–116.

Functional capacity is an independent predictor of perioperative death and is included in the algorithm of the current joint American College of Cardiology/American Heart Association (ACC/AHA) guidelines,<sup>1</sup> but it is not in the Revised Cardiac Risk Index<sup>2</sup> or

the American Society of Anesthesiologists (ASA) classification.<sup>3</sup>

**The study.** Visnjevac et al<sup>4</sup> performed a retrospective, observational cohort study of 12,324 patients who underwent noncardiac surgery, stratifying rates of all-cause mortality and 30-day postoperative complications based on ASA class and functional capacity.

The ASA physical status classification is defined as:

- 1—Normal healthy patient
- 2—Patient with mild systemic disease
- 3—Patient with severe systemic disease
- 4—Patient with severe systemic disease that is a constant threat to life
- 5—Moribund patient not expected to survive without surgery.

Functional capacity was defined as the ability to perform all activities of daily living. It was prospectively assessed during the patient interview by pre-anesthesia personnel and entered into the database of the Veterans Affairs Surgical Quality Improvement Program.

**Results.** Within each ASA class, the mortality rate was significantly lower for functionally independent patients than for partially or fully dependent patients:

- In class 2—odds ratio (OR) 0.14 for functionally independent patients
- In class 3—OR 0.29 for functionally independent patients
- In class 4—OR 0.5 for functionally independent patients.

The mortality rate was higher for dependent patients than for independent patients who were one ASA class higher, despite the higher class having greater rates of comorbidity.

Adding functional capacity to the ASA classification improved the area under the receiver operating curve from 0.811 to 0.848 (a perfect test would have a value of 1.0), suggesting that physicians should incorporate functional capacity into their preoperative evaluation, perhaps by increasing a patient's ASA class to the next higher class if he or she is functionally dependent.

**Angina portends poor outcomes**

**Pandey A, Sood A, Sammon JD, et al.** Effect of preoperative angina pectoris on cardiac outcomes in patients with previous myocardial infarction undergoing major noncardiac surgery (data from ACS-NSQIP). *Am J Cardiol* 2015; 115:1080–1084.

Coronary artery disease is a risk factor for adverse perioperative outcomes, but the risk varies depending on whether the patient has had a myocardial infarction (and how long ago) and whether he or she has anginal symptoms (and how severe they are).

**The study.** Pandey et al<sup>5</sup> used data from the American College of Surgeons National Surgical Quality Improvement Program to evaluate the impact of stable angina in 1,568 patients who underwent noncardiac surgery after a myocardial infarction.

**Results.** Postoperative myocardial infarction or cardiac arrest occurred in 5.5% of patients. The incidence was significantly greater in those who had anginal symptoms before surgery than in those without symptoms (8.4% vs 5%,  $P = .035$ ); reintervention rates and length of stay were also higher in this group. In multivariate analysis, preoperative angina remained a significant predictor of postoperative myocardial infarction (OR 2.49, 95% confidence interval [CI] 1.20–5.81) and reintervention (OR 2.4, 95% CI 1.44–3.82).

The authors cautioned against relying on predictive tools such as the Revised Cardiac Risk Index that do not consider stable angina and previous myocardial infarction as separate independent risk factors.

**Implications for clinical practice.** While functional capacity is an integral part of the ACC/AHA guideline algorithm,<sup>1</sup> the findings of these two studies suggest that other current tools to calculate perioperative risk (ASA class and Revised Cardiac Risk Index) could be improved by including functional capacity and stable angina.

**■ PERIOPERATIVE MEDICAL THERAPY**

**Beta-blockers help only those at high risk and may harm others**

**Friedell ML, Van Way CW 3rd, Freyberg RW, Almenoff PL.**  $\beta$ -blockade and operative mortality in noncardiac surgery: harmful or helpful? *JAMA Surg* 2015; 150:658–663.

Beta-blockers have been used perioperatively for nearly 2 decades to try to reduce rates of postoperative major adverse cardiovascular events. However, in view of recent trials, fewer patients are likely to benefit from this intervention than has been thought.

**Consider increasing a patient's ASA class if he or she is functionally dependent**

**The study.** Friedell et al<sup>6</sup> retrospectively analyzed data from 343,645 patients in Veterans Affairs hospitals to determine the effect of beta-blockers on major adverse cardiac event rates after major noncardiac surgery. Beta-blockers were considered to have been used perioperatively if given any time between 8 hours before and 24 hours after surgery. The outcome studied was the mortality rate at 30 days.

The authors derived a novel risk score and used multivariate analysis to attempt to adjust for confounding factors. The risk score was based on four risk factors identified a priori:

- Serum creatinine level > 2.0 mg/dL
- Coronary artery disease
- Diabetes
- Surgery in a major body cavity (abdomen or chest).

**Results.** In this cohort, 43.2% of patients had received a beta-blocker. The unadjusted mortality rates by risk category for patients receiving or not receiving a beta-blocker were:

- No risk factors: 1.0% with a beta-blocker vs 0.6% without
- One or two risk factors: 1.7% vs 1.5%
- Three or four risk factors: 2.3% vs 4.5%.

After adjustment for confounding factors, the 30-day mortality rate was higher in low-risk patients and lower in high-risk patients who received beta-blockers. Odds ratios for death in beta-blocker users (entire cohort) by risk category were:

- No risk factors: 1.19
- One or two risk factors 0.97
- Three or four risk factors 0.76.

In the 3.8% of the total cohort who underwent cardiac surgery, beta-blockers had no significant effect—beneficial or harmful—in any risk group.

**Jørgensen ME, Hlatky MA, Køber L, et al.**  $\beta$ -blocker-associated risks in patients with uncomplicated hypertension undergoing noncardiac surgery. *JAMA Intern Med* 2015; 175:1923–1931.

**The study.** Jørgensen et al<sup>7</sup> investigated the association between chronic beta-blocker use for the treatment of hypertension and 30-day rates of mortality and major adverse cardiac events. Eligible patients (N = 55,320) were at least 20 years old and were undergoing any type of noncardiac surgery. The authors established that hypertension was present through use of an algorithm based on the International

Classification of Diseases (10th edition). Patients with existing cardiovascular disease and renal disease were excluded. The authors used multivariate analysis to adjust for confounding factors.

**Results.** Twenty-six percent of the patients were on chronic beta-blocker therapy for hypertension. The mortality rate at 30 days was 1.93% in patients treated with a beta-blocker alone or in combination with other antihypertensive drugs; the rate was 1.32% for patients receiving any combination of renin-angiotensin system inhibitor, calcium antagonist, or thiazide, but no beta-blocker. Similarly, the 30-day major adverse cardiac event rates were 1.32% with beta-blockers and 0.84% without beta-blockers.

In subgroup analysis, each medication combination that included a beta-blocker was associated with higher rates of death and major adverse cardiac events than the same combination without a beta-blocker. Odds ratios for major adverse cardiac events with beta-blocker combinations ranged from 1.22 to 2.16 compared with regimens with no beta-blocker.

**Implications for clinical practice.** These two studies added to a growing chorus of concerns about the value and safety of beta-blockers in surgical patients. Friedell et al<sup>6</sup> made an observation that was remarkably similar to one reported by Lindenauer et al<sup>8</sup> in 2005: when patients were stratified by baseline risk of death, only those with the highest baseline risk benefited from beta-blocker therapy. Those in the lowest risk group actually were harmed by beta-blocker use, ie, the mortality rate was higher.

More interesting is the novel observation by Jørgensen et al<sup>7</sup> that even in patients with no known cardiovascular disease who are on chronic beta-blocker therapy—presumably on stable doses and not solely for perioperative risk reduction—rates of mortality and major adverse cardiac events were higher than for patients not on chronic beta-blocker therapy.

The current studies support a cautious, selective approach to the perioperative use of beta-blockers—they should be used only in high-risk patients undergoing high-risk surgery, as has been proposed by the ACC/AHA.<sup>1</sup>

**Use beta-blockers only in high-risk patients undergoing high-risk surgery**

**Statins protect**

Antoniou GA, Hajibandeh S, Hajibandeh S, Vallabhaneni SR, Brennan JA, Torella F. Meta-analysis of the effects of statins on perioperative outcomes in vascular and endovascular surgery. *J Vasc Surg* 2015; 61:519–532.

The study<sup>9</sup> was a comprehensive meta-analysis of randomized controlled trials and observational studies of the effects of HMG-CoA reductase inhibitors (statins) on perioperative outcomes in patients undergoing vascular surgery (but not for intracranial or coronary artery disease). Twenty-four studies were included, 4 randomized controlled trials and 20 observational studies (including 16 cohort and 4 case-controlled studies), with a total of 22,536 patients, 8,052 receiving statins and 15,484 not receiving statins.

**Results.** Although there was no significant difference in cardiovascular mortality rates, patients receiving statins had significantly lower rates of all-cause mortality, myocardial infarction, stroke, and a composite of myocardial infarction, stroke, and death at 30 days postoperatively than patients not receiving statins. Additionally, there was no difference in the incidence of kidney injury between groups. The possibility of publication bias was thought to be low for all of these outcomes.

Berwanger O, Le Manach Y, Suzumura EA, et al.

Association between pre-operative statin use and major cardiovascular complications among patients undergoing non-cardiac surgery: the VISION study. *Eur Heart J* 2016; 37:177–185.

**The study.** The Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) study<sup>10,11</sup> was an international prospective cohort study of more than 40,000 patients age 45 and older undergoing major noncardiac surgery with either general or regional anesthesia. Postoperative troponin measurements were obtained in all patients 6 to 12 hours after surgery and for the first 3 postoperative days. The authors evaluated the effect of preoperative statin use on cardiovascular outcomes at 30 days after surgery using a multivariate logistic model and propensity score analysis to correct for confounding factors. Statin use was defined as exposure within 7 days before surgery or 3 days after.

**Results.** In the 15,478 patients included in the analysis, statin use conferred a significant reduction in the primary outcome (composite of all-cause mortality, myocardial injury after noncardiac surgery, or stroke); the absolute

risk reduction was 2.0%. Statin users also had a significantly lower risk of all-cause mortality, cardiovascular mortality, and myocardial injury after noncardiac surgery, but not of postoperative myocardial infarction or stroke. This analysis did not address the type of statin, dosing, or safety markers such as liver and muscle function.

**Implications for clinical practice.** With largely observational data and a few small randomized trials, these meta-analyses provide important information with respect to perioperative cardiovascular protection by statins. Starting a statin before surgery and continuing it perioperatively seems appropriate in patients at high risk (as recommended by the ACC/AHA guidelines<sup>1</sup>). Based on other data, the benefit may be evident in as little as 5 days, as this is when statins appear to reach their plateau with regard to their vascular pleiotropic effects.<sup>12</sup> The incidence of adverse effects of statins, including muscle and liver injury, appears to be low in the perioperative setting.<sup>13</sup>

Given the inconsistent data regarding perioperative beta-blocker therapy, statins may very well be the most important perioperative medication with respect to cardiovascular risk reduction. However, a large randomized trial would help to confirm this belief.

**Restart angiotensin II receptor blockers soon after surgery**

Lee SM, Takemoto S, Wallace AW. Association between withholding angiotensin receptor blockers in the early postoperative period and 30-day mortality: a cohort study of the Veterans Affairs Healthcare System. *Anesthesiology* 2015; 123:288–306.

A concern about perioperative use of ARBs is that they impair the renin-angiotensin-aldosterone system, which maintains blood pressure under general anesthesia. ARB-induced intraoperative hypotension is particularly difficult to control, as it is often refractory to treatment with conventional adrenergic vasopressors.

**The study.** Lee et al<sup>14</sup> conducted a retrospective cohort trial to evaluate the effects of continuing to withhold ARBs postoperatively. Of the 30,173 patients admitted for surgery in the Veterans Affairs system from 1999 through 2011 who were taking an ARB before surgery and who met the inclusion criteria, 10,205 (33.8%) were not restarted on their medication by postoperative day 2.

Statins may be the most important perioperative medication for cardiovascular risk reduction



**Results.** The mortality rate at 30 days was higher in those whose ARBs were withheld than in those in whom it was resumed, with a multivariable-adjusted hazard ratio of 1.74 (95% CI 1.47–2.06;  $P < .001$ ). The risk of withholding ARBs was more pronounced in younger patients (hazard ratio 2.52; 95% CI 1.69–3.76 in those under age 60) than in older patients (hazard ratio 1.42, 95% CI 1.09–1.85 in those over age 75).

**Implications for clinical practice.** While not addressing whether to continue or withhold ARBs preoperatively, this retrospective study presented evidence that delay in resuming chronic ARB therapy after surgery was common and appeared to be associated with a higher 30-day mortality rate. The ACC/AHA guidelines<sup>1</sup> state:

- Continuing angiotensin-converting enzyme (ACE) inhibitors or ARBs perioperatively is reasonable (class IIa recommendation, level of evidence B) (Table 1).
- If an ACE inhibitor or ARB is withheld before surgery, it is reasonable to restart it postoperatively as soon as clinically feasible (class IIa recommendation, level of evidence C).

Close attention to medication reconciliation in the postoperative period is necessary to facilitate early resumption of ARBs.

## ■ CORONARY STENTS AND ANTIPLATELET THERAPY IN NONCARDIAC SURGERY PATIENTS

Considerations in the management of noncardiac surgery patients with stents include risks of stent thrombosis, bleeding, and potentially delaying procedures to continue uninterrupted dual antiplatelet therapy. Evidence is evolving regarding the risks of perioperative complications in patients with bare-metal stents and drug-eluting stents, as well as the optimal timing before noncardiac surgery.

### Bare-metal vs drug-eluting stents

Bangalore S, Silbaugh TS, Normand SL, Lovett AF, Welt FG, Resnic FS. Drug-eluting stents versus bare metal stents prior to noncardiac surgery. *Catheter Cardiovasc Interv* 2015; 85:533–541.

**The study.** Bangalore et al<sup>15</sup> compared the safety of drug-eluting vs bare-metal stents in noncardiac surgery patients and investigated adverse events stratified by time since stent

TABLE 1

### American College of Cardiology/American Heart Association classes of recommendations and levels of evidence

#### Class of recommendation

- I = Treatment should be given
- IIa = Treatment is reasonable
- IIb = Treatment may be considered
- III = Treatment is not beneficial or may harm

#### Level of evidence

- A = Multiple populations evaluated
- B = Limited populations evaluated
- C = Very limited populations evaluated

Based on information in reference 1.

placement. This was a retrospective observational study of 8,415 patients in the Massachusetts claims database who underwent noncardiac surgery 1 year or less after percutaneous coronary intervention.

**Results.** There was no significant difference in the incidence of the primary outcome (composite of death, myocardial infarction, and bleeding) between the two groups.

With drug-eluting stents, patients had lower 30-day postoperative mortality rates, and their rate of the primary outcome decreased with time from percutaneous coronary intervention to surgery, being lowest beyond 90 days:

- 8.6% in days 1–30
- 7.5% in days 31–90
- 5.2% in days 91–180
- 5.8% in days 181–365 ( $P = .02$ ).

With bare-metal stents, the event rate remained high over time:

- 8.2% in days 1–30
- 6.6% in days 31–90
- 8.1% in days 91–180
- 8.8% in days 181–365 ( $P = .60$ ).

This study did not report information about perioperative antiplatelet management and was limited to first-generation drug-eluting stents.

**Continuing ACE inhibitors or ARBs perioperatively is reasonable**

Saia F, Belotti LM, Guastaroba P, et al. Risk of adverse cardiac and bleeding events following cardiac and noncardiac surgery in patients with coronary stents: how important is the interplay between stent type and time from stenting to surgery? *Circ Cardiovasc Qual Outcomes* 2015; 9:39–47.

**The study.** Saia et al<sup>16</sup> retrospectively examined predictors of periprocedural ischemic and bleeding events among cardiac and noncardiac surgical patients who had previously undergone percutaneous coronary intervention. They also assessed the risks associated with stent type and time from percutaneous coronary intervention to surgery.

Of 39,362 patients, 13,128 underwent procedures during the 5-year study period. The cumulative incidence of surgery was 3.6% at 30 days, 14% at 1 year, and 40% at 5 years after percutaneous coronary intervention. Almost 30% of the procedures were done urgently.

**Results.** The 30-day rate of postoperative cardiac death was 2.5%, nonfatal myocardial infarction 1.5%, and serious bleeding events 6.5%. Older drug-eluting stents were associated with higher risks of adverse events than newer drug-eluting stents at any time point (odds ratio 2.1 at 0–180 days, 1.9 at 6–12 months, and 1.45 after 12 months). Surgery performed 6 to 12 months after percutaneous coronary intervention had lower rates of adverse outcomes than surgery performed within 6 months. Beyond 6 months from percutaneous coronary intervention, bare-metal stents and newer drug-eluting stents did not have significantly different adverse event rates; however, newer drug-eluting stents appeared safer than bare-metal stents from 0 to 180 days.

Limitations of this study included lack of information regarding periprocedural antiplatelet management and a relatively small subset of newer drug-eluting stent patients.

**Implications for clinical practice.** These studies added to earlier work that demonstrated that the risk of perioperative adverse events differs by both the stent type and the time from percutaneous coronary intervention to noncardiac surgery. In patients with a drug-eluting stent, the risk levels off 90 days after percutaneous coronary intervention, suggesting that the previously recommended 12 months of uninterrupted dual antiplatelet therapy (per the 2014 ACC/AHA guidelines<sup>1</sup>) may not be needed, particularly with newer-generation drug-eluting stents. Based

on new evidence, the ACC/AHA guidelines regarding perioperative management of dual antiplatelet therapy in noncardiac surgery patients were updated,<sup>17</sup> as noted below.

### An update to the ACC/AHA guidelines on dual antiplatelet therapy

Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation* 2016 Mar 29. DOI: 10.1161/CIR.0000000000000404. [Epub ahead of print]

The 2016 update<sup>17</sup> provides the following recommendations for patients with coronary stents who undergo noncardiac surgery:

- Delay elective surgery for 30 days after placement of a bare-metal stent (class I recommendation, level of evidence B).
- It is optimal to delay elective surgery 6 months after drug-eluting stent placement (class I recommendation, level of evidence B).
- If dual antiplatelet therapy must be discontinued, then continue aspirin if possible and restart the P2Y<sub>12</sub> inhibitor as soon as possible postoperatively (class I recommendation, level of evidence C).
- A consensus decision among treating clinicians is useful regarding the risks of surgery and discontinuation or continuation of antiplatelet therapy (class IIa recommendation, level of evidence C).
- If dual antiplatelet therapy must be discontinued, then elective surgery should not be performed less than 30 days after bare-metal stent placement, or less than 3 months after drug-eluting stent placement (class III recommendation, level of evidence B).
- Elective surgery after drug-eluting stent placement when the P2Y<sub>12</sub> inhibitor must be discontinued may be considered 3 months after drug-eluting stent placement if the risk of surgical delay is greater than the risk of stent thrombosis (class IIb recommendation, level of evidence C).

The basic differences are the new recommendations for a minimum of 6 months of dual antiplatelet therapy as opposed to 12 months after drug-eluting stent placement before elective noncardiac surgery, and to allow surgery after 3 months (as opposed to 6 months) if the risk of delaying surgery outweighs the risk of stent thrombosis or myocardial infarction.

Risk differs by stent type and time from percutaneous coronary intervention to noncardiac surgery

## PERIOPERATIVE ANTICOAGULATION

The optimal perioperative management of patients with atrial fibrillation who are on warfarin is uncertain. The American College of Chest Physicians guidelines<sup>18</sup> categorized patients with atrial fibrillation into low, moderate, and high thromboembolic risk. Based primarily on observational data, these guidelines recommended perioperative bridging anticoagulation for those at high risk but not for those at low risk. For intermediate-risk patients, there were insufficient data to make any recommendation.

### Bridging may not benefit those at intermediate risk

Douketis JD, Spyropoulos AC, Kaatz S, et al; BRIDGE Investigators. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2015; 373:823–833.

**The study.** The Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial<sup>19</sup> was the first randomized controlled trial to examine the effects of perioperative bridging anticoagulation in patients with atrial fibrillation without mechanical heart valves.

**Results.** In 1,884 patients undergoing elective surgery, the incidence of arterial

thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group (95% CI –0.6 to 0.8;  $P = .01$  for noninferiority). Major bleeding occurred in 1.3% of patients in the no-bridging group and 3.2% in the bridging group (95% CI 0.20–0.78;  $P = .005$  for superiority).

These results suggest that the risks of bridging therapy are greater than the benefits. Of note, the mean CHADS<sub>2</sub> score (1 point each for congestive heart failure, hypertension, age  $\geq 75$  years, and diabetes mellitus; 2 points for previous stroke or transient ischemic attack; a total score  $> 2$  indicates significant risk of stroke) for patients enrolled in this trial was 2.3, and it may be difficult to extrapolate these results to the limited number of patients at highest risk, ie, who have a CHADS<sub>2</sub> score of 5 or 6. Also, this study did not address patients with arterial or venous thromboembolism.

**Implications for clinical practice.** Despite the limitations noted above, this study does provide guidance for management of the intermediate-risk group with atrial fibrillation as defined by the American College of Chest Physicians: a no-bridging strategy is the best option. ■

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ADDRESS: Steven L. Cohn, MD, University of Miami Miller School of Medicine, 1120 NW 14th St., CRB-1140, Miami, FL 33136; scohn@med.miami.edu



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