LITERATURE REVIEW

C. David Collard, MD
Section Editor
M. Boris Zuchner, MD, PhD
Guest Reviewer

INTERNAL MEDICINE

Grines CL, Bonow RO, Casey DE, et al: Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. Circulation 115:813-818, 2007

This clinical advisory was commissioned by the American Heart Association and was prepared by a committee consisting of representatives from the American Heart Association, the American College of Surgeons, the American Dental Association, the Society of Cardiovascular Angiography, and the American College of Physicians. It was endorsed in December 2006 by all associations except the American College of Physicians.

A large number of patients receive treatment for coronary artery disease with coronary artery stents, most commonly drug-eluting stents (DESs). These patients, as well those with non–ST-segment elevation coronary syndromes, then receive a combination of aspirin (acetylsalicylic acid) and a thienopyridine (clopidogrel or ticlopidine) to reduce the incidence of major adverse cardiac events, including stent thrombosis, which is associated with high morbidity and mortality. Multiple studies are listed that provide the rationale for current guidelines that mandate preventative treatment with dual antiplatelet agents for at least 1 year after stent placement. Dual antiplatelet therapy is especially important with DESs, in which premature discontinuation of thienopyridines results in a well-documented increase in late stent thrombosis. The advisory panel also emphasizes 2 reports showing increased mortality when thienopyridine is discontinued for noncardiac surgery performed within 3 months of bare metal stent placement.

The recommendations made here are all directed toward the minimization of discontinuation or interruption of combined ASA and thienopyridine therapy. Recommendations include careful patient selection for coronary stenting, increasing patient compliance, improving patient and health care professional education, and delaying surgical procedures that need interruption of thienopyridine therapy because of increased bleeding risk. If a patient requires an invasive procedure with an increased bleeding risk, the recommendations are to restart thienopyridines as soon as possible after the procedure.

Implication: This clinical advisory is useful for questions that commonly arise when treating patients with coronary stents. However, some pressing issues remain. This advisory does not provide recommendations for the management of high-risk patients requiring surgery with recent or off-label use of DES or bare metal stents (ie, the patient in whom most guidance is needed). Of note, the Winter 2006 newsletter published by the Anesthesia Patient Safety Foundation contains a protocol recommending both eptifibatide and heparin as "bridging therapy" (APSF Newsletter 21:81-82, 2006). Although various combinations of eptifibatide and direct thrombin inhibition are safe in percutaneous coronary and vascular procedures, there is insufficient evidence to support the perioperative safety of these agents. Preoperative cardiology clearance of operative patients should include detailed description of the type and location of coronary stents and information about on- or off-label DES use. The absolute duration of dual antiplatelet therapy also remains to be determined in patients with bare metal or DES.

HEART FAILURE

Van Campen CMC, Visser FC, de Cock CC, et al: Comparison of the hemodynamics of different pacing sites in patients undergoing resynchronization treatment: Need for individualization of lead localization. Heart 92:1795-1800, 2006

Patients with New York Heart Association class III/IV heart failure and left ventricular dyssynchrony, often evidenced by a wide QRS complex, have high mortality. In addition to increasing survival, biventricular pacing (BVP) has been proven to improve exercise capacity, systolic and diastolic function, and heart failure symptoms. BVP partially reverses left ventricular adaptation to continued pressure and volume overload.

This investigation was designed to examine whether the pacing site location is a potential cause of the observed 30% to 50% nonresponder rate of resynchronization therapy. Forty-eight consecutive patients with New York Heart Association III or IV heart failure presenting for pacemaker implantation were enrolled. All patients were in sinus rhythm with either a right or left bundle-branch block or diffuse ventricular conduction block. Twelve patients had idiopathic dilated cardiomyopathy, and 36 had ischemic heart failure, mostly with multivessel coronary artery disease. The patients' average ejection fraction was 27% ± 9% (range, 12%-40%), with 1.8 (standard deviation = 0.8) mitral regurgitation.

VDD pacing was performed at 9 sites: 4 single sites (right ventricular [RV] apex, right ventricular outflow tract [RVOT], coronary sinus anterolateral [CS-AL], coronary sinus posterolateral [CS-PL], 5 multisites [bifocal right: RV apex and RVOT, RV apex and CS-PL, RVOT and CS-PL, RV apex and CS-AL, and RVOT and CS-AL]). Cardiac indices for each pacing site were calculated for 3 consecutive beats from the time-velocity integral of the aortic valve corrected for the aortic valve area. Intraobserver variation in the cardiac index (CI) calculation was 1.6%.

Compared with a baseline CI of 1.75 L/min/m^2, the sites with the highest mean increase were the CS-PL + RV apex (1.99 ± 0.42 L/min/m^2, 11.1%) and the CS-PL + RVOT locations (1.99 ± 0.44 L/min/m^2, 10.8%, $p < 0.001$). For the site with the highest increase in CI, there was a 14.8% increase to 2.0 L/min/m^2 ± 0.43. A subgroup of patients was tested 8 weeks after identification of their maximal hemodynamic response pacing site, and a BVP was then implanted using that lead combination. The baseline and newly obtained data correlated closely ($p < 0.001$).

Implication: BVP in the setting of cardiac surgery represents a largely unstudied but potentially beneficial treatment option for patients with heart failure. Many patients with ischemic or other cardiomyopathy who present for coronary revascularization and/or mitral valve surgery have easily accessible pacing sites. The use of tissue Doppler imaging and 3-dimensional echocardiography to identify fa-

vorable responses to BVP may provide exciting new challenges and opportunities for the cardiac anesthesiologist.

CARDIAC SURGERY

Magne J, Pibarot P, Dagenais F, et al: Preoperative posterior mitral valve leaflet angle accurately predicts outcome after restrictive mitral valve annuloplasty for ischemic mitral regurgitation. Circulation 115:782-791, 2007

Ischemic mitral regurgitation (MR) often persists after restrictive mitral valve (MV) surgery and is associated with worsened clinical outcomes. This study investigated whether MR persistence after restrictive MV annuloplasty could be predicted from the preoperative echo and whether these echo data could be used to predict postoperative outcome. Fifty-one consecutive patients in this single-center study were evaluated between January 2002 and December 2005. Cardiac ultrasound was performed approximately 1 week before and after surgery.

A complete MV ring was implanted in 88% of the patients. Mitral ring size was determined by measuring intertrigonal length and downsizing that distance by 2 sizes. If postoperative MR was >1+, either a smaller size mitral ring was implanted or MV replacement performed, and these patients excluded from the study. Revascularization was performed whenever possible. All echocardiographic data were highly reproducible, with measured intra- and interobserver differences of <5%. Another set of 17 patients was examined prospectively after the initial 51 patients were examined retrospectively. MV configuration was assessed in midsystole by using parasternal long-axis and 4-chamber views. Measurements included the anterior leaflet angle and the posterior leaflet (PL) angle between the annular plane and the respective mitral leaflets. Also measured were coaptation distance (defined as the distance between annular plane and tip of the PL), tenting area (defined as the area enclosed between the annular line and MV valve leaflets), and other parameters of the left ventricle and left atrium.

Postoperatively, 40 patients with no (n = 30) or mild (n = 10) MR and 11 patients with moderate-to-severe MR were identified. Mild MR was defined as vena contracta <3 mm. In receiver-operating curve analysis, persistent MR was most accurately predicted by PL angle, coaptation distance, and tenting area (area under the curve = 0.98, 0.87, and 0.90, respectively). A preoperative PL angle ≥45° had 100% sensitivity, 95% specificity, and 85% positive and 100% negative predictive value for persistent MR. Tenting area ≥2.5 cm^2 and coaptation distance ≥1 cm both had high specificity (≥90%) but only a 64% sensitivity for persistent MR. Of the 8 patients with all of the previously mentioned 3 findings, 7 had persistent MR on leaving the hospital. No patient with a PL angle <45°, tenting area of <2.5 cm^2, and a coaptation distance of <1 cm had persistent MR. After 3 years, patients with persistent MR had a lower event-free survival compared with those with nonpersistent MR (26% ± 20% versus 75% ± 12%, $p = 0.01$). A PL angle ≥45° significantly increased the risk of an adverse cardiac event (hazard ratio = 2.5; 95% confidence interval, 1.4-4.9; $p = 0.002$).

Seventeen patients were enrolled into the prospective arm of this study. Fourteen were determined to have a PL angle of ≤45°, underwent coronary artery bypass graft surgery and MV repair, and had no persistent MR after the operation. Three patients had a ≥45° angle. One underwent MV repair, and residual moderate MR was detected immediately after surgery. Although the remaining 2 were scheduled to receive a restrictive MV annuloplasty, they received an MV replacement instead.

Implication: Persistence of MR and 3-year event-free survival after MV annuloplasty can be predicted by preoperative analysis of MV configuration. Specifically, patients with a PL angle ≥45° scheduled to undergo restrictive annuloplasty for ischemic MR may be poor candidates for this procedure. Although the results of this study require further validation, practitioners can add PL angle, coaptation distance, and tenting area to their perioperative echo evaluation of ischemic MR.

Gandhi GY, Nuttall GA, Abel MD, et al: Intensive insulin therapy versus conventional glucose management during cardiac surgery. Ann Intern Med 146: 233-243, 2007

Since van den Berghe et al reported in 2001 that postoperative blood glucose (BG) control reduces surgical morbidity and mortality, tight glycemic control has become standard treatment. However, no consensus of ideal intraoperative glucose control is available, mainly because of the lack of prospective, randomized trials. This single-center study enrolled adults undergoing cardiac surgery with cardiopulmonary bypass (CPB). Subjects (n = 400) were randomized to either receive an intraoperative continuous infusion of insulin once BG levels exceeded 100 mg/dL or to a conventional group in which insulin by bolus was given only if BG levels exceeded 200 mg/dL. In the conventional group, if BG levels exceeded 250 mg/dL, patients received insulin by infusion. A target BG level of 80 to 100 mg/dL was used in both groups upon arrival in the intensive care unit (ICU). Primary outcomes were defined as death, infection, prolonged ventilation, cardiac arrhythmia, stroke, and renal failure within 30 days of surgery. Secondary outcomes were length of ICU and hospital stay.

Mean post-CPB glucose levels were 123 mg/dL and 148mg mg/dL in the treatment and conventional arm, respectively. Similar mean BG levels were reached 4 hours after ICU admission. Mean ICU glucose levels in the first 24 hours were 103 and 104 mg/dL in the intensive and conventional groups. The most common adverse events were atrial fibrillation and prolonged intubation. The treatment groups did not differ significantly in any of the primary outcome measures; 82 of 185 (44%) patients analyzed in the treatment group and 86 of 186 (46%) in the conventional group had an adverse event (risk ratio = 1.0; 95% CI, 0.8-1.2). Similar results were obtained after multiple logistic regression analyses adjusting for age, sex, diabetes mellitus, type of surgery, body mass index, and smoking status. Increased incidences of death (2.1% versus 0%, $p = 0.06$) and strokes (4.3% versus 0.5%, $p = 0.02$) were detected in the intensive protocol versus the conventional group.

Implication: Compared with a conventional protocol, intensive insulin therapy during cardiac surgery does not reduce postoperative morbidity and mortality. Indeed, postoperative morbidity was increased in patients receiving intraoperative intensive insulin therapy despite the fact that 24-hour BG levels in the ICU did not significantly differ between groups. More study is thus necessary to determine the risks and benefits of targeting normoglycemia in the cardiac operating room. Until then, avoiding possible intraoperative hypoglycemia by choosing a moderate BG target appears to be a safe strategy.

Ingels C, Debaveye Y, Milants I, et al: Strict blood glucose control with insulin during intensive care after cardiac surgery: Impact on 4-year survival, dependency on medical care, and quality of life. Eur Heart J 27:2716-2724, 2006

In a previously published randomized controlled trial of 1,548 surgical patients, application of an intensive glucose control protocol in the intervention group resulted in a total reduction of mortality in the cardiac surgical subgroup (n = 970) from 7.5% to 3.4%. The present study is a follow-up study of the cardiac subgroup of patients from that same trial exploring the impact of strict blood glucose control on 4-year survival, the incidence of hospital readmission, and quality of life.

Of 941 analyzed cardiac surgical patients, 477 were in the conventional and 464 in the intensive treatment group. Although both ICU (5.1% *v* 2.1%, $p = 0.01$) and in-hospital (7.5% *v* 3.4%, $p = 0.005$) mortality were significantly reduced in the intensive treatment group, the greatest benefit occurred in patients whose ICU stays exceeded 3 days. In particular, in-hospital mortality of those ICU patients was reduced from 22.1% to 7.9% ($p = 0.002$). Similarly, long-term mortality at 2 years and 3 years after admission was reduced from 29.2% to 10.2% ($p = 0.0003$) and 30.8% to 14.8% ($p = 0.004$), respectively. Benefits of intensive insulin therapy compared to conventional treatment included a shorter number of days on the ventilator (5 versus 4 days, $p = 0.004$ for patients >3 days in the ICU), a lower incidence of dialysis or continuous venovenous hemofiltration (all patients, n = 28 *v* n = 10, $p = 0.004$; patients >3 days in the ICU, n = 27 *v* n = 9, $p = 0.007$) and electromyographic evidence of critical-illness polyneuropathy (all patients, n = 34 *v* n = 9, $p = 0.0002$; patients >3 days in the ICU, n = 34 *v* n = 9, $p = 0.0004$). The cumulative hazard plots for intervention and conventional treatment subgroups of the 199 patients who stayed longer than 3 days in the ICU and in whom long-term follow up data were available showed a cumulative hazard that differed significantly by log-rank Mantel-Cox test ($p = 0.006$). The Karnofsky Performance Scale in patients staying at least 3 days in the ICU was also significantly higher (median 70% *v* 60%, $p = 0.04$).

Implication: Intensive glucose control in the ICU resulted in sustained survival benefits. These data thus suggest that BG should be tightly controlled in the cardiac surgical ICU and possibly until discharge. It should be noted, however, that all but 10 of the 765 intensive treatment group patients (cardiac and other surgical procedures) received insulin compared with only 39.2% of the conventional patients. Additionally, all patients received glucose infusions on admission followed by enteral or parenteral nutrition. Thus, the long-term benefit seen in the intensive treatment group might be an effect of a combination of early feeding and insulin administration.

Koster A, Dyke CM, Aldea G, et al: Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: Results of the CHOOSE-ON Trial. Ann Thorac Surg 83:572-577, 2007

Heparin-induced thrombocytopenia (HIT) is an acquired prothrombotic disorder that is caused by the administration of heparin and is most prevalent in surgical patients. The clinical syndrome may include deep vein thrombosis, myocardial infarction, pulmonary embolism, and limb ischemia. HIT with thrombosis has a high mortality. Coronary artery bypass graft (CABG) surgery with heparin-induced thrombocytopenia thrombosis syndrome (CHOOSE-ON) trial was designed to assess the use of bivalirudin for anticoagulation during cardiopulmonary bypass (CPB). Forty-nine patients undergoing CABG or CABG/valve surgery with suspected (n = 6) or confirmed (n = 43) HIT were enrolled at 18 centers. The study did not include a control arm or provide a historical comparison group at each respective institution. Patients with creatinine clearance <30 mL/min, on hemodialysis, or with ejection fraction <0.3, or undergoing multiple valve operations were excluded from the study. The primary study endpoint was acute procedural success, determined by the absence of death, Q-wave myocardial infarction, repeat operation for coronary revascularization, and stroke at postoperative day 7 or at discharge, whichever occurred first. The secondary study endpoints were the absence of the same factors at 30 days and 12 weeks postoperatively. The protocol for CPB management was specifically designed to accommodate the unique properties of bivalirudin. This was accomplished by using closed systems, by the avoidance or minimization of stasis in the circuit, storing excess blood in citrated bags, eliminating hemofiltration during CPB, and using a cell saver blood-collecting system.

Procedural success was achieved in 46 (94%) patients, at 30 days in 42 patients (86%), and after 12 weeks in 40 (82%) patients. Four deaths occurred. One death in the first week was caused by a torn right atrium; the remaining deaths were related to ventricular arrhythmia on postoperative day 11, respiratory failure on postoperative day 27, and sepsis on postoperative day 54. Other adverse events during the first postoperative week included stroke (2%, n = 1) and the need for repeat revascularization (2%, n = 1). Adverse events at 12 weeks postoperatively included the need for repeat revascularization (2%, n = 1), stroke (2%, n = 1), and need for mediastinal re-exploration (4%, n = 2). The average 24-hour blood loss was 998 ± 595 mL (mean ± standard deviation). Forty-one of 49 patients (83.7%) received 5.6 ± 3.8 units of red packed blood cells, 8.6 ± 7.2 units of platelets, and 6.0 ± 4.7 units of fresh frozen plasma within the first week of surgery. A subgroup of patients with creatinine clearance in the 30 to 60 mL/min range (n = 10) received approximately the same number of transfusions.

Implication: This prospective study adds to the growing body of evidence that bivalirudin may be safely used for anticoagulation during CPB in patients with HIT. Unlike the elimination of other direct thrombin inhibitors that are dependent on renal (argatroban) or hepatic function (recombinant hirudin and lepirudin), the termination of bivalirudin action is independent of renal or hepatic function. The advantages of bivalirudin also overcome some of the problems associated with other heparin alternatives such as the monitoring of lepirudin activity or allergic reactions. Because there was no control group or specific transfusion triggers used in this study, it is difficult to evaluate bivalirudin-associated blood product use. This will be important in future studies of bivalirudin.

ACKNOWLEDGMENT

Articles reviewed in this issue were selected from those published in the following journals: *Annals of Internal Medicine*, *Annals of Thoracic Surgery*, *Circulation*, *European Heart Journal*, and *Heart*.

doi:10.1053/j.jvca.2007.05.008