Preoperative calcium-channel blockade in cardiac surgery: The good, the bad, the issues

T. Bruce Ferguson, Jr, MD

See related articles on page 625 and 755.

For years, cardiothoracic surgeons have focused on care factors that affect outcomes. These efforts have directly resulted in documented declines in mortality and morbidity from major cardiac surgical interventions with time, despite an increase in severity of the risk profile of patients coming to surgical intervention.¹⁻³

Part of this focus has been to recognize pharmacologic agents that could affect outcomes, mostly in an adverse manner. At one time, preoperative aspirin, β -blocker, and clopidogrel therapies were relative contraindications to surgical intervention. Now most patients undergoing coronary artery bypass grafting (CABG) are on aspirin therapy before the operation, there are compelling data documenting the benefits of preoperative β -blocker therapy⁴ and perioperative aspirin therapy^{5,6} in patients undergoing CABG, and many surgeons administer clopidogrel before off-pump CABG.

This reversal in our thinking about β -blockers⁴ and to some extent aspirin⁶ therapy was inspired by large, multicenter observational studies rather than randomized clinical trials. These observational studies have provided scientific data to reevaluate previous practices in light of newer information. By using sufficiently large patient populations, controlling for such confounding factors as site and provider effects, and using statistical techniques such as propensity score analyses, important information has been obtained that has improved the quality of care. In the case of β -blocker therapy, these findings challenged surgical providers to change not only their own practice but also the practice of their referring cardiologists.⁷

In this issue of the *Journal*, Wijeyesundera and colleagues⁸ have done just such a reevaluation of the role of calcium-channel blockers (CCBs) as preoperative pharmacologic therapy in patients undergoing cardiac surgery. Through the years, CCBs have been investigated in cardiac surgery as cardioplegia additives,^{9,10} as antiarrhythmic agents,¹¹ and as additives to ameliorate vasospasm in radial artery grafts.¹² Wijeyesundera and colleagues⁸ raise the question of whether CCBs might convey a mortality and morbidity benefit in patients undergoing cardiac surgery. The primary pharmacologic effects of CCBs addressed here are the antianginal and potentially myoprotective effect of CCBs in patients undergoing the stress of surgical intervention.¹³ This important study is of interest because it highlights both the good and the bad related to calcium-channel blockade.

The Good

On the "good" side of the ledger, this is a well-designed observational clinical study that relies on a robust clinical information system to address the question being asked. The scientific analysis uses appropriate techniques in the careful evaluation of these observational data. Wijeyesundera and colleagues⁸ have asked an important clinical question about a class of cardiovascular drugs that most cardiac surgeons have not thought much about during the past 5 years. And finally, the study and its presentation highlight both the importance of these carefully analyzed observational studies and the limitations in their interpretation. Clearly, this study suggests that further investigation of the role of preoperative CCBs is warranted.

This was a single-center study, and therefore, as Wijeyesundera and colleagues⁸ point out, site confounding cannot be ruled out as possibly contributing to the results. For example, the risk-adjusted mortality for the CABG subset was some-

From the Departments of Surgery and Physiology, LSU Health Sciences Center, New Orleans, La.

Received for publication Oct 29, 2003; accepted for publication Nov 3, 2003.

Address for reprints: T. Bruce Ferguson, Jr, MD, LSU Cardiovascular Outcomes Research Group, 3535 Bienville St, Suite E-325, New Orleans, LA 70119 (E-mail: tbruceferg732@pol.net).

J Thorac Cardiovasc Surg 2004;127:622-4
0022-5223/\$30.00

Copyright © 2004 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2003.11.001

what lower than national US data⁴; this could be due to a lower risk study population at this site, differences in the risk models, or other indeterminate factors that are specific to the study institution.

The Bad

On the “bad” side of the ledger related to calcium-channel blockade, it is important to recognize that this study could not differentiate between different classes of CCBs. The adverse cardiovascular effects of short-acting, dihydropyridine calcium antagonists are well-documented.^{14,15} This is a potentially important confounding issue in light of the relatively diverse negative inotropic effects, conduction system effects, and coronary vascular resistance effects of the different subtypes of these drugs.^{11,13}

Table 1 in the article of Wijeysondera and colleagues⁸ shows that the percentage of patients in this study receiving both CCBs and β -blocker therapy was significantly higher than that of those receiving β -blocker therapy but not CCBs. This illustrates an additional difficulty with interpretation of the study, that of separating preoperative β -blocker therapy effects on outcomes from CCB effects on outcomes. This study confirms previous studies^{4,16} documenting the benefit of preoperative β -blocker therapy (Table 3 in the Wijeysondera and colleagues⁸ article). While the Society of Thoracic Surgeons database analysis⁴ did not address CCB use, the study of Weightman and coworkers¹⁶ did not document CCBs to be of benefit, in contrast to the study of Wijeysondera and colleagues.⁸ However, preoperative therapy with CCBs does appear not to lessen a survival benefit in patients receiving both drugs. In addition, CCBs may provide some independent benefit (overall data set *P* value .42, as stated in Table 4 of the Wijeysondera and colleagues⁸ article, and CABG subset *P* value .44, as stated in Table 6 of the Wijeysondera and colleagues⁸ article), although this question can only ultimately be answered by a prospective trial.

Furthermore, although the study indicates that CCBs did not significantly increase morbidity, the odds ratios for major morbidity outcomes were 1.00 or greater for 8 of 10 morbidities assessed. Clearly, these results from this robust analysis should be confirmed.

The Issues

The use of CCBs in ischemic heart disease has become more focused during the past 5 years, in part through the recognition that some CCBs can be harmful in certain subsets of patients.¹³ In addition, the effectiveness of combination therapies for angina control and prevention of myocardial infarction has been shown,¹³ and efforts to improve the use of β -blockers in ischemic heart disease patients have been more successful.^{17,18} There was a substantial decline in patients presenting for surgery receiving CCBs in this study population, presumably reflecting a

decline in the use of these drugs by the referring cardiologists. Unlike the situation with preoperative β -blocker therapy, if the suggested benefit of CCB therapy in surgical patients is confirmed, a reversal of this trend on the part of the cardiology community would be necessary to realize this benefit in the surgical population.

One important finding from the study is the suggestion that CCBs may be of benefit in patients undergoing valve and combined valve and coronary procedures. Because the benefit of preoperative β -blocker therapy has only been demonstrated for patients undergoing CABG, the conclusion that a prospective investigation is warranted is timely and fully supportable.

The current American College of Cardiology and American Heart Association guidelines for management of patients with chronic stable angina recommend that long-acting CCBs be used in combination with β -blocker therapy when initial treatment with β -blockers is not successful or as a substitute for β -blocker therapy when initial treatment leads to unacceptable side effects.¹³ Perhaps these recommendations can provide some structure for identifying patients in whom preoperative CCB therapy would be potentially beneficial in surgical revascularization and possibly other cardiac procedures.

Wijeysondera and colleagues⁸ have readdressed an important issue in cardiac surgery in their article. Without such observational analyses, the ability of the cardiac surgical community to successfully propose randomized trials, particularly pharmacologic trials, has been limited. Studies such as this create the opportunity to partner with the pharmaceutical industry to address the impact of preoperative medications on short-term outcomes. Perhaps more importantly, the cardiac surgical community needs to address the impacts of perioperative and postoperative pharmacologic therapies on long-term surgical outcomes.^{19,20} Through these efforts, cardiac surgeons and their care teams can positively influence both short-term outcomes and the long-term benefits of our surgical interventions. In turn, these efforts will greatly facilitate the placement of these surgical interventions, and their efficacy and appropriateness evaluations, into the larger context of chronic disease processes.

References

1. Loop FD, Lytle BW, Cosgrove DM, Stewart RW, Goormastic M, Williams GW, et al. Influence of the internal mammary artery graft on 10-year survival and other cardiac events. *N Engl J Med*. 1986;314:1-6.
2. Grover FL, Shroyer AL, Hammermeister K, Edwards FH, Ferguson TB, Dziuban SW, et al. A decade's experience with quality improvement in cardiac surgery using the Veterans Affairs and Society of Thoracic Surgeons national databases. *Ann Surg*. 2001;234:464-74.
3. Ferguson TB, Hammill BG, Peterson ED, DeLong ER, Grover FL, STS National Database Committee. A decade of change—risk profiles and outcomes for isolated coronary artery bypass grafting procedures,

- 1990-1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Society of Thoracic Surgeons. *Ann Thorac Surg.* 2002;73:480-90.
4. Ferguson TB, Coombs LP, Peterson ED, Society of Thoracic Surgeons National Adult Cardiac Surgery Database. Preoperative beta-blocker use and mortality and morbidity following CABG surgery in North America. *JAMA.* 2002;287:2221-7.
 5. Chesebro JH, Clements IP, Fuster V, Elveback LR, Smith HC, Bardsley WT, et al. A platelet-inhibitor-drug trial in coronary artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein graft patency. *N Engl J Med.* 1982;307:73-8.
 6. Mangano DT, Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. *N Engl J Med.* 2002;347:1309-17.
 7. Ferguson TB, Peterson ED, Coombs LP, Eiken MC, Carey ML, Grover FL, et al. Use of continuous quality improvement to increase use of process measures in patients undergoing coronary artery bypass graft surgery. A randomized controlled trial. *JAMA.* 2003;290:49-56.
 8. Wijeyundera DN, Beattie WS, Rao V, Ivanov J, Karkouti K. Calcium antagonists are associated with reduced mortality after cardiac surgery: a propensity analysis. *J Thorac Cardiovasc Surg.* 2004;127:755-62.
 9. Clark RE, Ferguson TB, West PN, Shuchleib RC, Henry PD. Pharmacological preservation of the ischemic heart. *Ann Thorac Surg.* 1977;24:307-14.
 10. Ferguson TB, Damiano RJ, Smith PK, Buhrman WC, Cox JL. The electrophysiological effects of calcium channel blockade during standard hyperkalemic, hypothermic cardioplegic arrest. *Ann Thorac Surg.* 1986;42:399-405.
 11. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens.* 1997;15:105-15.
 12. Bond BR, Zellner JL, Dorman HD, Multani MM, Kratz JM, Crumbley AJ, et al. Differential effects of calcium channel antagonists in the amelioration of radial artery vasospasm. *Ann Thorac Surg.* 2000;69:1035-41.
 13. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania PC, Douglas JS, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation.* 2003;107:149-58.
 14. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation.* 1995;92:1326-31.
 15. Opie LH, Messerli FH. Nifedipine and mortality. Grave defects in the dossier. *Circulation.* 1995;92:1068-73.
 16. Weightman WM, Gibbs NM, Sheminant MR, Whitford EG, Mahon BD, Newman MA. Drug therapy before coronary artery surgery: nitrates are independent predictors of mortality and beta-adrenergic blockers predict survival. *Anesth Analg.* 1999;88:296-1.
 17. Marciniak TA, Ellerbeck EF, Radford MJ, Kresowik TF, Gold JA, Krumholz HM, et al. Improving the quality of care for Medicare patients with acute myocardial infarction: results from the Cooperative Cardiovascular Project. *JAMA.* 1998;279:1351-7.
 18. Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. *JAMA.* 1997;277:115-21.
 19. Charlson ME, Isom OW. Care after coronary artery bypass surgery. *N Engl J Med.* 2003;348:1456-63.
 20. Foody JM, Ferdinand FD, Galusha D, Rathore SS, Masoudi FA, Havranek EP, et al. Patterns of secondary prevention in older patients undergoing coronary artery bypass grafting during hospitalization for acute myocardial infarction. *Circulation.* 2003;108(Suppl 1):II24-8.

JTCVS On-Line Manuscript Submission and Review

Please visit <http://www.editorialmanager.com/jtcvs/>

Effective September 15, 2001, authors and reviewers may submit manuscripts and reviews electronically via Editorial Manager, our new Web-based system with full electronic submission, review, and status update capabilities.

As we move from paper to electronic submissions, the Editorial Office will make proxy submissions of all manuscripts accompanied by a diskette containing the electronic files of the text, tables, and figures. Editors, authors, and reviewers will receive automatic e-mails when significant events occur.

We strongly encourage all authors and reviewers to use Editorial Manager. Although we will continue to accommodate the submission of paper manuscripts for some months, our goal is to be completely electronic within 9 to 12 months.

All individuals currently in our database for whom we have e-mail addresses will receive via e-mail a system-assigned username and password that can be used to log in to the system without prior registration. All those not receiving the e-mail must register the first time they use the system.

As with any broad systemic change, the conversion to the new system will take some time to complete. We ask your patience as we replace our in-office database with the new system. We also encourage you to take advantage of the speed and efficiency that the new system will provide for us all: editor, author, reviewer, and publisher.