The Value of Clopidogrel Administered Postoperatively Following a Non-ST-Segment Elevation Acute Coronary Syndrome

To the Editor:

In their recent article in CHEST (September 2004) on antithrombotic therapy, Stein et al recommended that clopidogrel be added to aspirin for 9 to 12 months in patients undergoing coronary artery bypass grafting (CABG) following a non-ST-segment elevation acute coronary syndrome (NSTE-ACS). The authors assigned this recommendation a grade of 1A, suggesting that the benefits derived from this strategy are clear and are supported by randomized clinical trial data without important limitations. The authors based this recommendation on data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.3

Because no prospective, randomized clinical trials have specifically examined the role of clopidogrel in patients following CABG, the authors are correct in basing their recommendations on data abstracted from the CURE trial. Nevertheless, it is our opinion that currently available trial data do not support a grade 1A recommendation. In fact, recent data have suggested that postoperative treatment with clopidogrel provides no substantial clinical benefit and, if anything, increases the risk of serious bleeding. Because of this, it is our opinion that clopidogrel should not be routinely used after CABG following an NSTE-ACS.

In the CURE trial,3 12,562 patients with NSTE-ACS were randomized to treatment with clopidogrel (300 mg initially followed by 75 mg daily) plus aspirin (75 to 325 mg daily) vs aspirin alone (75 to 325 mg daily). The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or stroke. Patients randomized to receive dual antiplatelet therapy (clopidogrel and aspirin) had a 20% relative risk reduction (RRR) in the primary end point at a mean of 9 months (9.3% vs 11.4%, respectively; p < 0.001), with greater benefit (44% RRR) noted in those patients undergoing revascularization (ie, CABG or percutaneous coronary revascularization). Despite this, the CURE trial investigators cautioned against the interpretation of these latter results, “given the large numbers of subgroup analyses that were performed.”

Although the CURE trial did not initially report the results of the primary end point for those who underwent CABG subsequent to study enrollment, these results were recently published by Fox et al.4 In this post hoc analysis, the addition of clopidogrel to aspirin led to an insignificant 11% RRR in the primary outcome among those undergoing CABG a median of 25.5 days after randomization (14.5% vs 16.2%, respectively; 95% confidence interval [CI], 0.71 to 1.11). This sharply contrasts with the 28% RRR in the primary outcome noted in those receiving clopidogrel in association with percutaneous revascularization (95% CI, 0.57 to 0.90). Further analysis was able to demonstrate a strong trend toward benefit among those receiving clopidogrel in association with CABG during the initial hospitalization (RRR, 19%; 95% CI, 0.59 to 1.12); however, this effect was driven entirely by a reduction in the number of events prior to surgery (18% RRR in the primary outcome; 95% CI, 0.58 to 1.16), with no benefit noted in those receiving clopidogrel postoperatively (3% RRR; 95% CI, 0.74 to 1.26). Patients receiving postoperative clopidogrel also experienced a strong trend toward an excess of life-threatening bleeds (30% increased risk; 95% CI, 0.90 to 1.83).

Based on these findings, clopidogrel should not be routinely used in the postoperative management of patients undergoing CABG for treatment of NSTE-ACS. In fact, available data suggest that treatment with clopidogrel should probably be limited in the postoperative period to those who are intolerant of aspirin therapy. While speculative, it is possible that short-term cessation of clopidogrel treatment after surgery (median duration, 10 days) may have contributed to the failure of study investigators to demonstrate a benefit from postoperative clopidogrel. To further explore this, though, “a dedicated randomized clinical trial of clopidogrel plus aspirin vs aspirin alone after CABG” is warranted.

Ty J. Gluckman, MD
Jeffrey J. Rade, MD
Steven P. Schulman, MD
The Johns Hopkins Hospital
Baltimore, MD

REFERENCES

Risk vs Benefits for Thromboembolic Disease After Total Joint Surgery

To the Editor:

Surgeons and internists frequently weigh their risks and benefits on different scales. I believe this is the case with the guidelines for prophylaxis against thromboembolic disease that were recently published in CHEST (September 2004).1 The risks of bleeding weigh heavily in the surgeons’ decision making, whereas the internists see the pulmonary problems. Therefore, true evidence-based medicine must be applied carefully to derive a set of guidelines that is universally accepted by both groups.

First, recognizing that all of the recommendations in CHEST are based on the presence or absence of deep vein thrombosis (DVT), we must ask whether DVT is an accurate surrogate marker for patients who are at risk for a pulmonary embolism (PE) after undergoing total joint surgery. If they are, we should see a proportional reduction of PE with a reduction in DVT. In fact, we do not. It is well known that after total knee surgery the incidence of DVT is two to three times that of total hip surgery, but there is an equal or reduced number of PEs after total knee surgery, not a twofold to threefold increase.

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Correspondence to: Ty J. Gluckman, MD, The Johns Hopkins Hospital, Division of Cardiology, 600 N Wolfe St, Carnegie 568, Baltimore, MD 21287; e-mail: tgluckma1@jhmi.edu
While it has been well documented that DVT is an accurate marker of risk for medical and thrombophilic patients, the same risks may not apply to those undergoing total joint surgery. In those postoperative patients, up to 60% have experienced a DVT, while the incidence of fatal PE is 0.1 to 0.2%. Postoperative clots may have been formed by local mechanical injury to the venous system at the time of surgery and may not convey the same ominous prognosis.

Second, it is unclear whether we can generalize the safety data on postoperative chemoprophylactic agents, as reported in the literature, to all of our patients. The well-controlled, prospective, randomized drug studies in the literature exclude, by protocol, patients with prior DVT or GI bleeds, and the investigators choose not to enroll elderly, frail, and noncompliant patients. Therefore, the enrollees are a selected, healthier population and may not accurately represent the true bleeding risks.

Third, we must examine carefully the postsurgical morbidity of patients who experience significant bleeding events. The more effective a chemoprophylactic agent is in reducing the incidence of DVT, it may also effectively increase the risk from bleeding. Significant bleeding events occur in 1.8 to 5.1% of patients in the healthiest selected populations, creating significant morbidity for the patient and the surgeon.

Therefore, using evidence-based medicine, we must question the data that show that DVT is an accurate marker for the patient who has undergone total joint surgery and is at risk for PE. Without this evidence, the recommendations, as published in CHEST for the orthopedic medicine community, may be exposing our patients to expensive, risky, and perhaps minimally effective regimens.

Paul A. Lotke, MD
Hospital of the University of Pennsylvania
Philadelphia, PA

FDA Evaluation of Antimicrobials

Subgroup Analysis

To the Editor:

In response to Wunderink and colleagues, we would like to clarify some apparent misunderstandings of how the US Food and Drug Administration (FDA) utilizes data from subgroup analyses in evaluating the safety and efficacy of antimicrobials. In their article on the treatment of nosocomial pneumonia (NP) comparing linezolid and vancomycin, Wunderink et al use a subgroup analysis to make a fundamentally different conclusion than shown in the trial as a whole. That is, they use a subgroup of patients with NP who are infected with one pathogen to claim superior efficacy in trials that overall show noninferiority of linezolid to vancomycin. In contrast, the FDA uses subgroup analyses to investigate the robustness and confirm the overall conclusions of a trial. The FDA also uses subgroup analyses in a risk-benefit assessment of which populations may be most likely to benefit from a drug. This is not the same as drawing different conclusions about the study drug relative to the control drug. For instance, when the overall results of a trial show superiority of the study drug to the control drug, it may be appropriate to look at subgroups of patients treated with the study drug to determine whether there is a consistently favorable risk/benefit across subgroups. This is the case in the example the authors cite with drotrecogin alfa. In this situation, the study drug was overall superior in efficacy to placebo in treating sepsis, but the safety risk of intracranial hemorrhage justified its approval in a subgroup of more severely ill patients where the benefit justified the risk. This did not change the fundamental scientific conclusion that drotrecogin alfa was superior in efficacy to placebo in the trial. However, it did affect the public health conclusion as to the patient population for which the drug could be approved based on safety concerns.

It is fundamentally more difficult to draw a conclusion of superiority in a subgroup of patients when the trial as a whole demonstrates noninferiority or inferiority of the study drug to the control, for the reasons enumerated in our previous correspondence. The results of the trials in NP showed linezolid was noninferior to vancomycin, yet Wunderink and colleagues claim that a subgroup shows superiority for the subset of patients infected with methicillin-resistant Staphylococcus aureus (MRSA). This is a very different way of using subgroup analyses than done by the FDA.

The FDA uses an evaluation of microbiologically evaluable (ME) and clinically evaluable (CE) subgroups of patients as one of the analyses in an overall assessment of drug efficacy in a trial. The authors are incorrect in suggesting that these analyses are “favored” by the FDA, and the previous guidance on design and analysis of clinical trials for NP is currently under revision based on discussions held at a public workshop in November 2002. While drug sponsors may specify the ME and CE subgroups as the “primary” analyses and present this as such in publications, the FDA also evaluates outcomes in a modified intention-to-treat (mITT) population of all randomized patients with the disease under study who receive at least one dose of study medication. The conclusions in the ME and CE subgroups should support the conclusions in the mITT population, and vice versa. The FDA does not analyze the results in either the mITT population or the subgroups in isolation. In noninferiority trials, neither the mITT nor the evaluable populations are optimal; therefore, one should consider the results in both the mITT population and the evaluable subgroups. An analysis of the mITT population, while conservative in a superiority trial, may make the efficacy of drugs appear more similar in the setting of a noninferiority trial. This