Angiotensin-Converting Enzyme Inhibitor Therapy at the Time of Coronary Artery Bypass Surgery

When a Friend Turns Mean-Spirited*

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Therapy with an angiotensin-converting enzyme inhibitor (ACEI) reduces cardiovascular mortality and morbidity in patients with stable coronary artery disease (CAD) (1) and in patients with CAD and left ventricular systolic dysfunction (2) or early after acute myocardial infarction (3). For these reasons, ACEI therapy has become as omnipresent among patients with CAD as has therapy with beta-adrenergic antagonists, statins, and aspirin. As testimony to the weight of medical literature supporting their use, no patient is discharged from the inpatient cardiovascular medicine or surgical services of the University of Michigan Medical System (as is surely the case at many other institutions) without documentation of having been prescribed 1 of each of these medications, or a good reason why not. The ubiquity of their use has led some to quip that, for purposes of public health certainly no less critical than fluoride for cavity prevention, these 4 medications should be considered as additives to the public water supply.

By definition, patients who undergo coronary artery bypass graft (CABG) surgery have CAD; many have systemic hypertension and diabetes mellitus, and the sequelae of these diseases including left ventricular systolic dysfunction or chronic renal insufficiency—each an indication for ACEI therapy. Intuition holds that this group of patients should benefit the most from ACEI therapy. Yet, intuition has led us astray before. Who would have predicted that the successful suppression of premature ventricular beats, themselves a marker for adverse outcome after acute myocardial infarction, would result in excess cardiac death (4)? If ACEI therapy is beneficial for the diseases that bring patients to CABG, could it be that it is actually detrimental at the time of surgery?

The present study. In this issue of the Journal, Miceli et al. (5) report a large, retrospective, observational cohort study analyzing prospectively collected data from >10,000 patients undergoing CABG at a single institution in England between 1996 and 2008. Using propensity score matching, a subgroup of 3,052 patients receiving ACEI therapy pre-operatively was compared with a control group. The authors found that pre-operative ACEI therapy within 24 h of CABG was associated with an increased risk of death, post-operative inotropic support, post-operative renal dysfunction, and atrial fibrillation. The authors suggest that suspending ACEI therapy before CABG and restarting it post-operatively might improve early surgical outcomes, while retaining the long-term cardioprotective effects of therapy.

This study comes in the context of several others suggesting similar conclusions, even if the literature is not completely homogeneous. As the authors note in their discussion, the majority of published data support the presence of risk associated with preoperative ACEI therapy among patients undergoing CABG or major vascular surgery. The proposed mechanism is that of perioperative hypotension and resulting inotropic and vasoconstrictor therapy leading to impaired renal perfusion.

Study limitations. The present report, relying on large patient numbers and propensity score matching, makes a powerful statement. The authors are to be congratulated on a carefully performed and important study. However, potential limitations should be recognized.

The population studied comprised patients at the Bristol Heart Institute in the United Kingdom, and might not be representative of patients undergoing CABG in the U.S. Based on available data, patients undergoing CABG in the U.S. likely have more comorbidities than those undergoing CABG in this study (6). But if underlying risk factors predispose patients to adverse outcomes independent of, or synergistically with, the use of ACEI therapy, differences in outcomes might even be amplified in the U.S. However, this study reports perioperative mortality and morbidity rates that appear higher than anticipated for the patients described and, unlike the U.S. population (6), no decrease in operative risk over the 13 years of the study. Taking the case of a 65-year-old man (body surface area 1.95 m²) with hypertension, moderate chronic lung disease, remote myocardial infarction, ejection fraction 54%, and creatinine 1.3 mg/dl (110 μmol/l) undergoing isolated first-time 3-vessel CABG—approximating the average patient in this study—

The Society of Thoracic Surgery risk calculator estimates 0.7% perioperative mortality (7), substantially lower than the 1.0% observed. On the basis of current practice, it could be assumed that most patients undergoing CABG in the
U.S. are treated with an ACEI. If it is true that perioperative mortality in the U.S. is lower despite a sicker population, then it remains unknown whether the risks associated with ACEI therapy apply here, as well.

If the mechanism of death and post-operative renal dysfunction associated with ACEI therapy is mediated by perioperative hypotension and requirement for inotropic support, then 1) why was ACEI therapy barely among the independent predictors of requirement for postoperative inotropic support (ranking 8 of 10 factors); and 2) why is risk related specifically to ACEI therapy and not to treatment with any antihypertensive agent?

The latter question begs at least a comment regarding propensity score matching. As a sophisticated tool to reduce bias caused by observed differences between groups in an observational study (by balancing covariates across groups) (8), the temptation is to treat the subjects as if they had been randomly assigned. However, propensity score matching can only account for factors that were measured, and only as well as they were measured. If antihypertensive therapy in general was not a risk for perioperative inotropic support or other end points, then ACEI therapy must be different. But is ACEI therapy an intrinsic risk factor, or is it a marker for something else—perhaps for more severe hypertension? Or perhaps even for hypertension that was better controlled?

**How dogmatic is dogmatic enough?** For patients with CAD, ACEI therapy is good. Therapy with a beta-blocker is good. Therapy with a statin is good. And we love aspirin, too. But is it necessary, or even advisable, that every medication is used simultaneously and maintained indefinitely for all patients who carry the diagnosis? Are we necessarily helping patients by inducing hypotension and renal insufficiency in the setting of an acute myocardial infarction? Yet, we risk censure if we do not.

To put some data in perspective, the EUROPA (EUropean trial On reduction of cardiac events with perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782–8) study found that 50 patients would need to be treated for 4 years to prevent 1 major cardiac adverse event (1). And the ACE Inhibitor Myocardial Infarction Collaborative Group found that only 5 lives would be saved per 1,000 patients treated with ACEI therapy, and that therapy was associated with a 2-fold incidence of both persistent hypotension and renal dysfunction (3).

It may not be in every patient’s best interest to be treated with every pharmacologic agent that has been shown, on average, to be associated with an improved outcome, because our patients are not averages. While we await prospective randomized data from patients who most resemble those we routinely treat, the study by Miceli et al. (5) should provide pause. Even if there is a net benefit over the long term, there may be short-term risk associated with some pharmacotherapies. Being dogmatic in our use of these agents should be balanced by a modicum of caution and a willingness to keep our eyes open for possible short-term (and avoidable) risks that they may pose.

**Key Words:** coronary artery disease • coronary bypass surgery • risks • angiotensin–converting enzyme inhibitor therapy.

**REFERENCES**