



Angiotensin Receptor Blockade Improves Cardiac Surgical Outcomes in Patients With Metabolic Syndrome

Michael W. Manning, MD, PhD, Mary Cooter, MS, Joseph Mathew, MD, MHSc, John Alexander, MD, MPH, Eric Peterson, MD, T. Bruce Ferguson, Jr, MD, Renato Lopes, MD, PhD, and Mihai Podgoreanu, MD

Divisions of Cardiothoracic Anesthesiology and Cardiology, and Duke Clinical Research Institute, Duke University Medical Center, Durham; and Department of Cardiovascular Sciences, East Carolina Heart Institute, East Carolina University, Greenville, North Carolina

Background. Perioperative use of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEis) in patients undergoing cardiac operations remains controversial. The current practice of discontinuing renin-angiotensin-system inhibitors preoperatively may negate their beneficial effects in vulnerable populations, including patients with metabolic syndrome, who exhibit elevated renin-angiotensin system activity. We hypothesized that preoperative ARB use is associated with reduced incidence of postoperative complications, compared with ACEi or no drug, in patients with metabolic syndrome undergoing coronary artery bypass grafting.

Methods. We used propensity matching to derive a cohort of 1,351 patients from 2,998 who underwent coronary artery bypass grafting based on preoperative use of ARBs, ACEis, or no renin-angiotensin-system inhibitors. Our primary end point was a composite of adverse events occurring within 30 days after the operation: new-onset atrial fibrillation/flutter, arrhythmia requiring cardioversion, perioperative myocardial infarction, acute renal

failure, need for dialysis, cerebrovascular accidents, acute respiratory failure, or perioperative death.

Results. At least one adverse event occurred in 524 (38.8%) of matched cohort patients (1,184 [39.6% of all patients]). Adjusting for European System for Cardiac Operative Risk Evaluation and metabolic syndrome in the matched cohort, preoperative use of ARBs was associated with a lower incidence of adverse events in patients with metabolic syndrome compared with preoperative use of no renin-angiotensin-system inhibitors (odds ratio, 0.43; 95% confidence interval, 0.19 to 0.99) or ACEis (odds ratio, 0.38; 95% confidence interval, 0.16 to 0.88).

Conclusions. Preoperative use of ARBs, but not ACEis, confers a benefit within 30 days after cardiac operations in patients with metabolic syndrome, suggesting potential efficacy differences of these drug classes in reducing cardiovascular morbidity and death in ambulatory vs surgical patients.

(Ann Thorac Surg 2017;104:98–106)

© 2017 by The Society of Thoracic Surgeons

Perioperative management of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in cardiac surgical patients remains controversial [1]. ACEi use is associated with an increased incidence of hypotension or vasoplegic syndrome, or both, during general anesthesia, which continues into the postoperative period [2]. ACEis may independently predict death, inotrope use, postoperative renal dysfunction, and new-onset postoperative atrial fibrillation after coronary bypass grafting (CABG) operations [3]. However, more recent meta-analyses concluded that preoperative treatment with renin-angiotensin-system inhibitors (RASis) is associated with a reduced incidence of acute kidney injury [4] and perioperative myocardial injury [5] and may provide perioperative survival benefits in

diabetic patients [6]. Yet, the practice of discontinuing perioperative RASis continues [3, 7].

ARBs and ACEis are often considered interchangeable. However, combining ARBs/ACEis to analyze RASi effects on the incidence of postoperative adverse events after cardiac operations is a critical limitation because these drug classes have different mechanisms of inhibition. ACEis reduce circulating and local levels of angiotensin II (AngII) while increasing bradykinin levels, whereas ARBs can suppress inflammation and interrupt AngII-dependent and -independent receptor activation [8], thereby blocking effects of AngII produced by non-ACE pathways [9] without increasing bradykinin levels. Thus, additional comparative analyses are essential.

Increasing evidence suggests a bidirectional pathogenic relationship between an overactive RAS and metabolic syndrome (MetS). RAS signaling, activated by several factors associated with MetS, contributes to inflammation, reactive oxygen species generation, and impaired insulin signaling [10]. These findings were recently

Accepted for publication Oct 10, 2016.

Address correspondence to Dr Manning, Box 3094, 2301 Erwin Rd, Durham, NC 27710; email: michael.manning@dm.duke.edu.

Abbreviations and Acronyms

ACEi	= angiotensin-converting enzyme inhibitor
AE	= adverse event
AKI	= acute kidney injury
AngII	= angiotensin II
ARB	= angiotensin receptor blocker
AT ₁	= angiotensin receptor type 1
AT ₂	= angiotensin receptor type 2
BMI	= body mass index
CVA	= cerebrovascular accident
CABG	= coronary artery bypass graft
CI	= confidence interval
COPD	= chronic obstructive pulmonary disease
CPB	= cardiopulmonary bypass
EuroSCORE	= European System for Cardiac Operative Risk Evaluation Score
GEE	= generalized estimating equation
HDL	= high-density lipoprotein
LV	= left ventricle
LVEF	= left ventricular ejection fraction
MPAE	= major perioperative adverse events
MetS	= metabolic syndrome
MI	= myocardial infarction
OR	= odds ratio
PCI	= percutaneous coronary intervention
PREVENT IV	= Project of Ex-vivo Vein Graft Engineering via Transfection
POAF	= postoperative atrial fibrillation/flutter
RASi	= renin-angiotensin system inhibitor
SMD	= standardized mean differences
TIA	= transient ischemic attack

verified by a clinical trial showing that RASi reduces cardiovascular events in MetS patients [11]. Therefore, our primary objective was to compare the effect of preoperative use of ARBs vs ACEis on the incidence of adverse postoperative outcomes in the setting of CABG operations, using no RASi therapy as comparator, stratified by the presence of MetS.

Patients and Methods

We retrospectively analyzed patients in the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT-IV) trial (ClinicalTrials.gov: NCT0042081) who underwent primary CABG operations between August 2002 and October 2003 at 107 centers across the United States. The PREVENT-IV protocol was approved by Institutional Review Boards of all participating sites, and all enrolled patients provided written informed consent.

We began with 3,014 PREVENT-IV participants; however, 26 patients who received both ARBs and ACEis preoperatively were excluded to allow for independent assessment of class effects. In the final study population of 2,988 patients, three groups were identified according to their preoperative RASi use: ARBs in 193; ACEis in 1,055, and no RASi therapy in 1,740. Baseline

characteristics of these groups are summarized in [Table 1](#). RASis were started/restarted postoperatively at the discretion of the treating physician. We identified a subpopulation of patients with diagnostic criteria of MetS as set forth by the National Cholesterol Education Program—Adult Treatment Panel III ([Table 2](#)) [12].

Propensity Matching and Modeling Methods

To study treatment effect in this observational data set, we used propensity matching to balance patient factors across the treatment groups. Multinomial logistic regression was used to calculate a propensity for membership in each of the three treatment groups based on the following factors: MetS, age older than 75 years, sex, obesity, diabetes, hypertension, hypercholesterolemia, congestive heart failure, left ventricular (LV) dysfunction, history of atrial fibrillation, recent myocardial infarction (MI), renal failure, and cerebrovascular disease. Using the Pharmacological Toolbox [13] we then matched 3 patients who received no RASi therapy and 3 patients who received ACEi to each ARB patient in three rounds of nearest-neighbor triplet matching with a caliper of 0.25. We compared the covariate balance before and after propensity matching using standardized mean differences and the `tableone` package in R 3.1.1 software (www.r-project.org). Factors with standard mean difference of less than 0.1 after propensity matching were deemed balanced.

Outcome Definition

The primary outcome was a composite of major perioperative adverse events (MPAEs) occurring within 30 days of the index operation ([Table 3](#)). The criteria for all outcomes were in accordance with The Society of Thoracic Surgeons National Adult Cardiac Database, except perioperative MI, which was described as an elevation in the plasma level of creatine kinase-MB of more than 10 times the upper limit of normal within 24 hours after the operation and adjudicated by the PREVENT IV Clinical Events Committee. The secondary end point was incidence of postoperative inotropic requirements.

Statistical Analysis

MODELING METHODS. To account for the data structure in the matched cohort, the univariate association of MPAEs and postoperative inotrope use with the treatment groups was assessed in three generalized estimating equation (GEE) models (comparing ARBs vs no RASis, ARBs vs ACEis, and ACEis vs no RASis, respectively) to account for the data structure in the matched cohort. For the primary MPAEs outcome, we also performed multivariate GEE modeling adjusting the treatment group effect for European System for Cardiac Operative Risk Evaluation (EuroSCORE), MetS, and their interactions. An interaction effect that was nonsignificant was dropped from the final MPAEs outcome model. Modeling was performed in SAS 9.4 software (SAS Institute Inc, Cary, NC), and a *p* value of less than 0.05 was considered statistically significant.

SENSITIVITY ANALYSES. To verify that the association between preoperative ARB use and MPAEs is not

Download English Version:

<https://daneshyari.com/en/article/5596844>

Download Persian Version:

<https://daneshyari.com/article/5596844>

[Daneshyari.com](https://daneshyari.com)