



Impact of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Mortality of Coronary Artery Bypass Grafting

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Abstract

Background: There is controversy over the potential benefits/harms of the usage of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as regards the postoperative mortality of coronary artery bypass grafting (CABG). This study investigates the correlation between the in-hospital mortality of CABG and the preoperative administration of ACEI/ARB.

Methods: Out of 10055 consecutive patients with isolated CABG from 2006 to 2009, 4664 (46.38%) patients received preoperative ACEI/ARB. Data were gathered from the Cardiac Surgery Registry of Tehran Heart Center. In-hospital mortality was defined as death within the same admission for surgery. Adjusted for confounders, multivariable logistic regression models were used to evaluate the impact of preoperative ACEI/ARB therapy on in-hospital death.

Results: The mean age of the patients was 60.04 ± 9.51 years and 7364 (73.23%) were male. Eighty-seven (0.86%) patients expired within 30 days. Multivariate analysis revealed that the administration of ACEI/ARB significantly protected against in-hospital deaths inasmuch as there were 33 (0.70%) vs. 54 (1.0%) deaths in the ACEI/ARB positive and negative groups, respectively (OR: 0.628; p value = 0.09). Patients without ACEI/ARB were more likely to have a higher global ejection fraction.

Conclusion: Preoperative ACEI usage in patients undergoing CABG can be associated with decreased in-hospital mortality. Large-scale randomized clinical trials are suggested.

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Introduction

Although angiotensin-converting enzyme inhibitors (ACEIs) have been proven to reduce the cardiovascular complications and mortality in patients with coronary artery disease,¹⁻⁴ particularly in post-myocardial infarction patients,^{5, 6} the consumption of ACEIs prior to coronary artery bypass grafting (CABG) has remained controversial.⁷⁻⁹

Some authors have hypothesized that preoperative consumption of ACEIs contributes to early post-CABG morbidity and mortality (through hypotension and renal dysfunction secondary to decreased systemic vascular resistance and vasoplegia).¹⁰⁻¹² Others, however, have proposed that ACEIs can be used safely in patients undergoing CABG.¹³⁻¹⁵ While the majority of cardiac surgeons in the United Kingdom believe that the preoperative administration of ACEIs would increase the need for fluids, inotropes, and vasoconstrictors, a national survey revealed that only 39% discontinued ACEIs before the procedure.¹⁶ A combination of a lack of data and controversial achievements prompted us to perform further investigation.

The aim of this study was to compare the in-hospital mortality of CABG between patients receiving ACEIs or angiotensin receptor blockers (ARBs) and patients not receiving ACEIs or ARBs before CABG.

Methods

Retrospectively, 10081 consecutive patients who underwent isolated CABG between 2006 and 2009 at Tehran Heart Center (Tehran University of Medical Sciences, Tehran, Iran) and were registered in the Cardiac Surgery Registry were recruited in this cohort study. Taking the very similar effects of ACEIs and ARBs into account, we considered all patients as ACEI users. Twenty-six patients were excluded because of unknown ACEI or ARB usage before CABG, preoperative cardiogenic shock, and loss to follow-up. Out of a total of 10055 patients, 4664 (46.38%) received preoperative ACEIs or ARBs (ACEI group), while the remaining patients were placed in the control group. Anesthetic and surgical techniques and postoperative management were based on standardized routine procedures.^{17, 18} The Ethics Committee of the hospital approved the study and waived the need for a signed informed consent because all the patients had signed a general informed consent form authorizing the treating team to use the data for research on condition of anonymity.

In-hospital mortality was defined as all deaths occurring within the same admission for surgery.⁷

ACEI/ARB administration was defined as the administration of ACEI/ARB within 24 hours before CABG.

Priority of procedure was defined as elective (patients readmitted for surgery after a preceding discharge), urgent (patients' clinical status does not allow hospital discharge,

waiting for the operation), and emergent (the operation needs to be performed within hours given the risk of morbidity or mortality). The decision for performing off-pump surgery was left to the discretion of the individual surgeon.

The quantitative results are presented as mean \pm standard deviation (SD), while the categorical variables are shown by raw numbers (%). The continuous variables were compared using the Student t-test or the nonparametric Mann-Whitney U test when the presumption of normality was not met, while the categorical variables were compared using the chi-squared or Fisher exact test, as appropriate.

Multivariable logistic regression models were applied to assess the impact of preoperative ACEI/ARB therapy on in-hospital death. For this purpose, adjustment was made for the confounding effects of age, smoking, hypertension, diabetes mellitus, ejection fraction, left main coronary disease, beta-blocker usage, statin usage, and New York Heart Association functional class III-IV (CCSIII-IV). The association between in-hospital morbidity and ACEI/ARB usage was expressed as odds ratio (OR) with 95% confidence interval (CI).

All the statistical calculations were done with SPSS (version 13.0) and the statistical package SAS (version 9.1) for Windows (SAS Institute Inc., Cary, NC, USA). All the p values were 2-tailed, with statistical significance defined as a p value \leq 0.05.

Results

The baseline characteristics of the study participants are summarized in Table 1. The frequency of smoking, hypertension, and diabetes mellitus as well as the incidence of off-pump CABG was greater in the ACEI/ARB users. The patients not taking ACEI/ARB were more likely to have a history of atrial fibrillation and higher global ejection fraction.

In-hospital mortality occurred in 87 (0.86%) patients. The findings of unadjusted univariate analysis showed an OR of 0.704 and a p value of 0.112. Multivariate analysis demonstrated that the administration of ACEI/ARB tended to have a protective effect against in-hospital death. Multivariate analysis also implied that preoperative ACEI/ARB therapy was statistically associated with a lower risk of in-hospital death insofar as there were 33(0.7%) versus 54(1.0%) deaths in the ACEI/ARB positive and negative groups, respectively (OR: 0.628, 95% CI:0.367-1.076; p value = 0.09). The relevant data are shown in Table 1.

Discussion

The results from the present study suggest that the preoperative administration of ACEI/ARB in the patients undergoing isolated CABG was correlated with a tendency to decrease perioperative mortality.



Table 1. Frequency of the characteristics of the patients candidated for CABG stratified by ACEI administration*

Characteristics	Total (n=10,055)	ACEI(+)(n=4664)	ACEI(-) (n=5391)	P value
Age (y)	60.04±9.51	60.14±9.45	59.95±9.55	0.327
Gender				
Male	7364 (73.23)	3441 (73.77)	3923 (72.76)	0.255
Female	2691 (26.76)	1223 (26.22)	1468 (27.23)	
Smoking	2759 (27.43)	1358 (29.11)	1401 (25.98)	< 0.001
Hypertension	4053 (40.30)	2048 (43.91)	2005 (37.19)	< 0.001
Diabetes mellitus	2797 (27.81)	1347 (28.88)	1450 (26.89)	0.027
Hyperlipidemia	4917 (48.90)	2258 (48.41)	2659 (49.32)	0.363
Family history	3546 (35.26)	1612 (34.56)	1934 (35.87)	0.170
CCS III-IV	2737/8670 (31.56)	1323/4021 (32.90)	1414/4649 (30.41)	0.013
NYHA III-IV	2418/9154 (26.41)	1134/4239 (26.75)	1284/4915 (26.12)	0.497
History of MI	3763 (37.42)	2061 (44.18)	1702 (31.57)	< 0.001
History of CABG	15 (0.15)	5 (0.11)	10 (0.19)	0.310
Global EF (%)	48.74±9.25	47.78±9.34	49.61±9.08	< 0.001
Left main disease	631/9972 (6.32)	288/4626 (6.22)	343/5346 (6.41)	0.697
3VD	6721/9107 (73.80)	3106/4157 (74.71)	3615/4950 (73.03)	0.068
Number of grafts	3.50±0.90	3.53±0.88	3.46±0.91	< 0.001
Priority				
Urgent	1113/10008 (11.12)	685/4643 (14.75)	428/5365 (7.97)	< 0.001
Emergent	17/10008 (0.16)	3/4643 (0.06)	14/5365 (0.26)	
Off-pump CABG	209 (2.08)	75 (1.60)	134 (2.49)	0.002
Beta blocker usage	8215/10028 (81.92)	3941/4651 (84.73)	4274/5377 (79.49)	< 0.001
Statins usage	2721/10028 (27.13)	1309/4651 (28.14)	1412/5377 (26.26)	0.034

*Data are presented as mean±SD or n (%)

CABG, Coronary artery bypass grafting; ACEI, Angiotensin-converting enzyme inhibitor; CCS, Canadian cardiovascular society; NYHA, New York Heart Association; MI, Myocardial infarction; EF, Ejection fraction; 3VD, Three-vessel disease

Besides anti-inflammatory, anti-atherosclerotic, and anti-thrombotic effects,¹⁹⁻²¹ ACEIs affect left ventricular remodeling and afterload, diminish ventricular mass, and recuperate cardiac hemodynamic via reducing angiotensin II and increasing bradykinin.^{19, 21-23} Studies have proposed that ACEIs can reduce the rate of mortality and morbidity in patients with coronary artery disease.^{4, 7, 24} This role is even more prominent in patients with recent acute myocardial infarction.^{5, 6, 25}

Miceli et al.⁷ compared 3052 patients receiving preoperative ACEIs with a matched control group. They suggested that the use of preoperative ACEIs is an independent risk factor for early clinical outcomes in patients undergoing isolated CABG and showed that the administration of ACEIs is associated with a doubled risk of death (1.3% vs. 0.75). The other complications associated with or aggravated by ACEIs in their study were a rise in postoperative renal dysfunction, use of inotropic drugs, and risk of new-onset postoperative atrial fibrillation. The study in question suffers from a lack of distinction between ACEI and ARB usage and also a lack of data about the duration of ACEI/ARB usage; these are limitations that we had in our study as well.

The story in other studies, however, is not exactly the

same. A prospective study on 9129 patients over 21 years of age undergoing CABG and/or valve surgery concluded that preoperative medical therapy with ACEIs, beta blockers, and Aspirin decreased 30-day mortality after cardiac surgery, while the use of diuretics was independently associated with increased risk of mortality in these patients (Barodka V, Hogue CW, Nyhan D, Shah A, Pustavoitau A. The Role of Preoperative Medications on Mortality after Cardiac Surgery. <http://www.asaabstracts.com/strands/asaabstracts/abstract.htm?jsessionid=5FEB04799C475A5570A65C066AFEE5E1?year=2009&index=4&absnum=1370>). The Barodka study is a prospective work and is, thus, preferable to our retrospective study. Furthermore, it allocated patients to two groups based on their survival status: alive and expired. This approach limits the benefits of a large group of matched control patients (an advantage from which our study benefited) because the number of expired patients is disproportionately smaller than that of the surviving ones. Furthermore, the patients' characteristics were different between these two studies. For instance, the frequency of diabetes mellitus and hypertension was significantly different between the study and control patients in our study, whereas Brodka et al. reported a significant difference between the

mean age of the surviving and expired groups instead.

In a more recent cohort study, Kalavrouziotis et al.²⁶ evaluated the effect of ACEIs, beta blockers, and statins on 3718 patients over 65 years old who underwent CABG. The authors found no independent correlation between ACEI administration and post-CABG mortality. The patients, nevertheless, benefited from the other two drugs. This finding chimes in with the results of our study. The similarity in terms of patient characteristics between our study and the Kalavrouziotis et al. study may support this conclusion that the administration of ACEI/ARB in older patients undergoing CABG most likely does not influence post-CABG mortality.

The present study was a retrospective analysis of data in a single referral center. Moreover, data regarding the duration of ACEIs were not available. Since we were unable to distinguish patients on ACEIs from those on ARBs, we used the term "ACEI user" for both ACEI and ARB users. Another drawback of our study is that the data on atrial fibrillation, hypotension, post-CABG renal dysfunction, and cerebrovascular accidents were not recorded in our databank; that is why we were not able to use and present the relevant data in the present study.

Conclusion

Preoperative ACEI/ARB usage in the patients undergoing CABG was nearly associated with protection against in-hospital mortality. Our study showed that ACEI/ARB administration did not increase post-CABG mortality.

Our study may generalize the potential benefits of ACEI usage to ARB usage. Considering that many candidates for CABG receive ACEI and given the fact that the useful effects of the long term use of ACEIs in patients with diabetes mellitus, coronary artery disease, and heart failure have been proven, it seems advisable that the administration of ACEIs be continued in patients undergoing CABG. Appropriate randomized clinical trials will help us to assess how ACEI administration affects peri-CABG mortality.

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