

# Anjiotensin Dönüştürücü Enzim İnhibitörlerinin Koroner Arter Baypas Cerrahisi Yapılan Hastalarda Mortalite ve Morbidite Üzerine Etkisi

## The Effect of Angiotensin Converting Enzyme Inhibitor Therapy on Mortality and Morbidity in Patients Undergoing Coronary Artery Bypass Grafting Surgery

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### ÖZ

**GİRİŞ ve AMAÇ:** Bu çalışmanın amacı, koroner arter baypas greftleme (KABG) operasyonu geçiren hastalarda anjiyotensin dönüştürücü enzim inhibitörü (ADEİ) tedavisinin mortalite ve morbidite üzerindeki etkilerini değerlendirmektir.

**YÖNTEM ve GEREÇLER:** KABG ameliyatı geçiren hastaların hastane kayıtları geriye dönük olarak değerlendirildi. Hastaların demografik özellikleri, komorbiditeleri, fonksiyonel sınıflaması ve postoperatif komplikasyonları kaydedildi.

**BULGULAR:** Çalışmaya 42'si kadın 101'i erkek toplam 143 hasta dahil edildi. ADEİ kullanmayan 65 kişide ortalama yaş  $59.8 \pm 8.86$  yıl, ADEİ kullanan 78 kişide ise  $58.15 \pm 8.59$  yıl idi. Grupların ameliyat öncesi özellikleri değerlendirildiğinde; diabetes mellitus, hiperlipidemi, sigara içme alışkanlıkları, yakın miyokard enfarktüsü, kronik obstrüktif akciğer hastalığı ve New York Heart Association fonksiyonel kapasite sınıflaması açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu ( $p > 0.05$ ). ADEİ grubunda hipertansiyon ve anstabil angina pectoris sıklığı, istatistiksel olarak anlamlı yüksek bulundu ( $p > 0.05$ ). Gruplar arasında postoperatif komplikasyonlar ve mortalite açısından istatistiksel olarak anlamlı bir fark yoktu ( $p > 0.05$ ); zira postoperatif majör olaylar ADEİ kullanan grupta kullanmayanlara göre daha yüksekti ( $p = 0.007$ ). ADEİ kullanan hastaların %50'sinde yoğun bakım ünitesinde kalış süresi uzundu. Gruplar arasında yoğun bakım ünitesinde kalış süresi açısından istatistiksel olarak anlamlı fark vardı ( $p = 0,012$ ).

**TARTIŞMA ve SONUÇ:** ADEİ kullanan ve kullanmayan gruplar arasında istatistiksel olarak anlamlı bir mortalite ve morbidite farkı olmamasına rağmen, preoperatif ADEİ kullanımı, KABG operasyonu yapılan hastalarda yoğun bakım ünitesinde uzun süreli kalışla ilişkilidir.

**Anahtar Kelimeler:** KABG, ADEİ, mortalite, morbidite

### ABSTRACT

**INTRODUCTION:** The aim of this study was to evaluate the effects of angiotensin-converting enzyme inhibitor (ACEI) therapy on mortality and morbidity in patients undergoing coronary artery bypass grafting (CABG) operation.

**METHODS:** Hospital records of patients undergoing CABG surgery were evaluated retrospectively. Demographic characteristics, comorbidities, functional classification and post-operative complications of patients were recorded.

**RESULTS:** 42 women and 101 men, totally 143 patients were included in the study. There were 65 cases, mean aged  $59.8 \pm 8.86$  years in non-user group and 78 cases, mean aged  $58.15 \pm 8.59$  years in ACEI user group. When pre-operative specialties of groups were evaluated; there were no statistically significant difference of diabetes mellitus (DM), hyperlipidemia, smoking habits, pre-operative and recent MI, chronic obstructive pulmonary disease (COPD) and NYHA classification between groups ( $p > 0.05$ ). Hypertension and unstable angina pectoris (USAP) frequency were statistically significantly high in ACEI group ( $p > 0.05$ ). There was no statistically significant difference of post-operative complications and mortality between groups ( $p > 0.05$ ), but post-operative major events were higher in ACEI groups than non-users ( $p = 0.007$ ). Duration of stay in intensive care unit (ICU) was long in 50% of patients in ACEI group. There was a statistically significant difference for duration of ICU among groups ( $p = 0.012$ ).

**DISCUSSION AND CONCLUSION:** Pre-operative therapy with ACEI is associated with a prolonged stay in ICU even though there is no statistically significant difference of mortality and morbidity between ACEI user and non-user groups.

**Keywords:** CABG, ACEI, mortality, morbidity

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## INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEI) has been used frequently in patients with hypertension (HT) and heart failure since first description of captopril as an ACEI drug in 1977 (1). ACEI targets the renin-angiotensin-aldosterone system and it is one of the first-choice antihypertensive drugs (2). In addition to the antihypertensive effect, ACEI have also cardioprotective effects. They reduce the mortality rates in patients with coronary artery disease and prevent the cardiovascular complications (1,3). These effects of ACEI are prevalent especially after myocardial infarction (4).

ACEI provide both primary and secondary protection of cardiovascular diseases including left ventricle failure. Primary protection is an indirect effect with respect to decreases of HT and left ventricle hypertrophy. Antihypertensive effect of ACEI provides vascular protection. Also, they inhibit atherogenesis and thrombosis. They decrease the mortality when they are used in the initial phase of myocardial infarction. The anti-arrhythmic effect plays a role in the prevention of post-infarction sudden death. They are helpful for the post-infarction remodeling by reducing wall stress. ACEI have an important role in a wide range from preventing risk factors to left ventricle failure (5).

Consequently, most patients with coronary artery disease are treated with ACEI. However, the use and safety of the pre-operative administration of ACEI in patients undergoing CABG operation is still controversial. It is suggested that pre-operative use of ACEI do not cause hypotension, so they can be used safely in patients undergoing CABG surgery (6). However, another study reveals that pre-operative use of ACEI causes decreased systemic vascular resistance resulting to hypotension and renal dysfunction and increased need of inotropic agents in early post-operative period (7). The aim of this study was to evaluate the effect of ACEI on mortality and morbidity of the patients undergoing CABG surgery.

## MATERIAL AND METHODS

The hospital records of the 400 patients undergoing CABG surgery were evaluated retrospectively. Age, gender, body mass index

(BMI), smoking history, ejection fraction, and medical histories were recorded. Medical history of the patients was classified as follows;

- Hypertension (HT),
- Diabetes Mellitus (DM); fasting blood glucose  $\geq 126$  or documented diagnosis of DM,
- Hyperlipidemia (HL); Low density lipoprotein (LDL)  $\geq 130$  mg/dl or triglyceride (TG)  $\geq 300$  mg/dl,
- Pre-operative atrial fibrillation (AF),
- Pre-operative myocardial infarction (MI); within 90 days,
- Recent MI; within last 7 days,
- Chronic obstructive pulmonary disease (COPD); post-bronchodilator FEV1/FVC  $\leq 70\%$ , negative result for reversibility),
- Functional classification; New York Health Association grade 3/4,
- Unstable angina pectoris (USAP),
- Intra-operative aortic balloon pump (IABP),
- Post-operative inotropic support,
- Post-operative ventricular tachycardia/fibrillation (VT, VF),
- Post-operative major event; stay in ICU  $\geq 3$  day, need for dialysis, cerebrovascular event and post-operative / PreO exitus.

### Inclusion criteria

Patients who were 18-75 years old and undergone isolated CABG surgery were included in the study. Pre-operative ACEI use was defined as a patient taking ACEI until the day of CABG. Patients on any ACEI (lisinopril, enalapril, ramipril, quinapril, benazepril, or perindopril) irrespective of dose were included in the analyses.

### Exclusion criteria

Patients with;  $>75$  years of age, rheumatic heart disease, heart valve surgery with CABG, pre-operative history of chronic renal failure (serum creatinine  $\geq 1.6$  mg/dL or creatinine clearance  $\leq 50$  (Creatinine clearance was calculated for male and females by Cockcroft-Gault formulation), pre-operative cerebrovascular disease, history of malignancy, peripheral arterial occlusive disease, emergent CABG operation, pre-operative need of

IABP, PreO history of VF/VT or cardio-pulmonary resuscitation (CPR) and pre-operative cardiogenic shock were excluded from the study.

#### Study protocol

The medical records of 400 patients were evaluated. Totally 143 patients were included in the study in accordance to inclusion and exclusion criteria. The primary endpoint of the study was evaluation of mortality. ACEI related mortality was defined as exitus within 30 days after the CABG operation. Secondary endpoints were post-operative AF, post-operative VT/VF, post-operative intraaortic balloon pump, need of inotropic drugs and post-operative major events.

The study was approved by the Kocaeli University Medical Faculty Ethical Committee.

#### Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as mean  $\pm$  standard deviation, median (25th-75th percentiles), and categorical variables were expressed as counts (percentages). Comparisons of normally distributed continuous variables between the materials/groups were performed using the Student's t test, One Way Analysis of Variance and Tukey Post Hoc Test.

Comparisons of nonnormally distributed continuous variables between the groups were performed using the Mann Whitney U Test and Kruskal Wallis One Way Analysis of Variance and Dunn's Post Hoc test.

Comparisons of normally distributed continuous paired variables between the times were performed using the Paired Samples t test and Two way ANOVA and Tukey Post Hoc Test.  $p < 0.05$  was considered significantly significant.

## RESULTS

There were 42 females (29%) and 101 males (71%), totally 143 patients in study population. Patients were divided in two groups according to ACEI use; user or non-user groups. The mean ages of ACEI user (n=78) and non-user groups (n=65) were  $59.8 \pm 8.86$  years and  $58.15 \pm 8.59$  years, respectively. There was no statistically significant

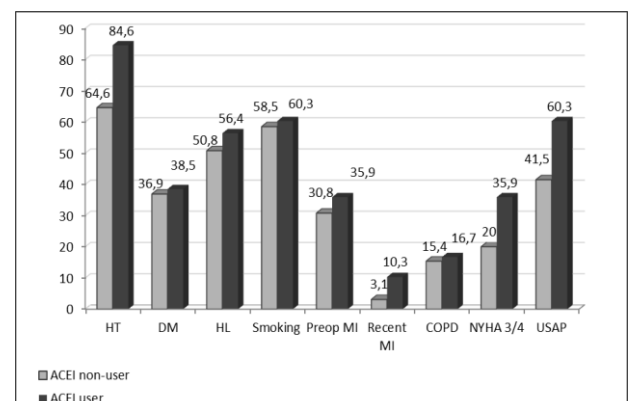
difference of age and BMI between the groups ( $p > 0.05$ ). When evaluating the ejection fraction; it was found that EF was  $> 70\%$  at 21,5% of the non-user group and 20,5% of the ACEI user group. Demographic characteristics of the ACEI user and non-user groups were shown in Table 1.

**Table 1: Demographic characteristics of the groups according to Angiotensin Converting Enzyme Inhibitor (ACEI) use**

	ACEI (-)	ACEI (+)
Female n (%)	19 (29.2%)	23 (29.5%)
Male n (%)	46 (70.8%)	55 (70.5%)
Mean age, years	$59.8 \pm 8.86$ (min:40, max:74)	$58.15 \pm 8.59$ (min:40, max:75)
BMI, mean	$27.1 \pm 3.66$ (min:18.75, max:40.8)	$28.6 \pm 4.42$ (min:18.38, max:41.02)
EF % $\geq 70$	14 (21.5%)	16 (20.5%)
50-69	28 (43.1%)	20 (25.6%)
30-49	20 (30.8%)	37 (47.4%)
$\leq 29$	3 (4.6%)	5 (6.4%)

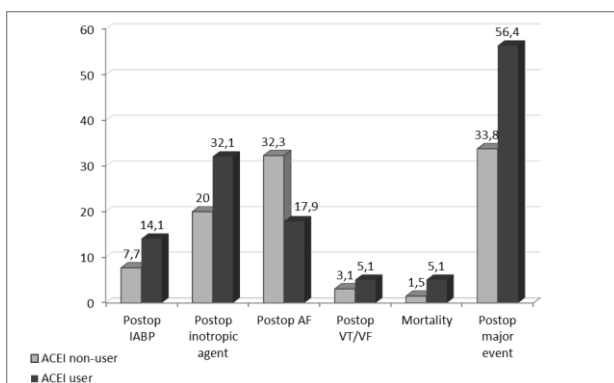
Abbreviations: **BMI**: Body Mass Index; **EF**: Ejection Fraction

The pre-operative operative and post-operative findings of the groups were compared. There was no statistically significant difference of pre-operative specialties such as DM, hyperlipidemia (HL), smoking history, pre-operative /recent MI, COPD and functional class between the user and non-user groups ( $p > 0.05$ ). Forty-two patients (64.6%) in non-user group and 66 patients (84.6%) in user group had diagnosis of hypertension (HT). The diagnosis of HT was higher in ACEI user group than non-users, and the difference was statistically significant ( $p = 0.01$ ). Also, there was a significant difference of USAP between the groups ( $p = 0.039$ ). It was found that 41.5% of non-user group and 60.3% of ACEI user group had USAP (Figure 1).



**Figure 1: Pre-operative medical history of the groups (%)**

Patients with left main coronary artery (LMCA) lesion were higher in ACEI user group than non-users. But the difference was not statistically significant ( $p=0.19$ ). There was no significant difference of average number of bypass among the groups ( $p=0.303$ ). When evaluating the post-operative complications including post-operative mortality, IABP, VT/VF, AF, need of inotropic agent; it was found that there was no significant difference between the groups ( $p>0.05$ ). The distribution and percentages of post-operative complications according to groups were shown in Figure 2.



**Figure 2:** Comparison of postoperative complications (%)

It was found that 22 patients (33.8%) in non-user group and 44 patients (56.4%) in ACEI user group had post-operative major events such as prolonged stay in ICU, need of dialysis, cerebrovascular event and post-operative/per-operative exitus. In both groups there was no case with post-operative cerebrovascular disease. Post-operative major event was higher in ACEI user group than non-user group. And the difference was statistically significant ( $p=0.007$ ). The post-operative major events according to groups were shown in Table 2.

**Table 2: The distribution of post-operative major events according to groups**

	ACEI (-)	ACEI (+)
<b>Hospitalization time in ICU, mean (min, max)</b>	2.57 ± 1.29 (min:1, max:7)	3.22 ± 2.21 (min:1, max:14)
<b>Prolonged stay in ICU ≥3 days</b>	20 (30.8%)	39 (50%)
<b>Post-operative dialysis</b>	1 (1.5%)	1 (1.3%)
<b>Post-operative exitus</b>	1 (1.5%)	3 (3.8%)
<b>Per-operative exitus</b>	0	1 (1.3%)
<b>Cerebrovascular event</b>	0	0

Abbreviations: ICU: Intensive Care Unit

The mean days of stay in ICU was  $2.57 \pm 1.29$  days (min:1, max:7) in non-user group while it was  $3.22 \pm 2.21$  days (min:1, max:14) in ACEI user group. Nearly 50% of the ACEI users had prolonged hospitalization in ICU. The difference was statistically significant ( $p=0.012$ ).

## DISCUSSION

This study demonstrated that there was no significant difference between the groups with respect to post-operative complications including post-operative mortality, IABP, VT/VF, AF and need of inotropic agent. However, PreO use of ACEI was related with post-operative major events, especially prolonged stay in ICU.

ACEI has been used frequently in patients with HT and heart failure. In addition to anti-HT effects, ACEIs have some beneficial effects on endothelial function and inflammatory responses associated with arteriosclerosis. Also, they have an important role in angiogenesis (8). ACEI decrease the mortality rates and prevent the cardiovascular events in patients with coronary artery disease (1,3). This effect is especially prominent after acute MI (4). The blockage of the renin-angiotensin system with ACEI in patients with myocardial infarction (MI) or congestive heart failure improves ventricular function, prolong survival and decrease infarct size (8,9).

Most of the patients with coronary artery disease use ACEI drugs. There are some different opinions about the role of pre-operative administration of ACEI on postoperative hypotension after CABG operation. Arora et al. suggest that pre-operative use of ACEI is related with decreased systemic vascular resistance and it can cause post-operative hypotension and renal dysfunction (6). In contrast, Rady et al. report that pre-operative ACEI do not influence the clinical outcome after cardiac surgery (7). Also, Lazar et al. suggest that all patients with CABG surgery will benefit from ACEI due to their potential vasculo-protective and anti-atherogenic properties (10). In a national survey, it is shown that majority (63%) of the surgeons believe that the use of ACEI leads to vasodilatation resulting in increased usage of inotropic and vasoconstrictor drugs. 39% of them feel that it is beneficial to stop the ACEI prior to surgery whereas 38% of them

think it is harmful to stop it (11). Recently, in a meta-analysis evaluating the effect of pre-operative ACEI on outcomes of CABG in 31390 patients; it is suggested that pre-operative ACEI therapy increases the risk of post-operative hypotension (8).

Fluids, inotropic and vasoconstrictor drugs are used in the treatment of post-operative hypotension. The administration of pre-operative ACEI increases the risk of hypotension in the early post-operative phase, requiring the administration of these agents (12,13). In recent studies, the use of pre-operative ACEIs is described as an independent risk factor of hypotension requiring inotropic support (13-17). In a prospective randomized study, it was demonstrated that more severe hypotensive episodes requiring vasoconstrictor treatment occurred in patients receiving this drug on the morning before operation, in comparison with those in whom ACEI were discontinued on the day before operation. And also, it was recommended that patients should have discontinued these drugs on the day before the surgery (15). It was suggested that pre-operative use of ACEI might have important effects on central venous pressure, positive inotrope and intravenous fluid requirement in operative and early post-operative period (17). The need of inotropic drugs was also higher in ACEI user group than non-users in our study. But the difference was not statistically significant. It was suggested that non-significant difference might be related with limited number of patients in their study population.

Furthermore, peri-operative hypotension is a well-known risk factor of the post-operative renal dysfunction in patients with cardiac surgery. However, the role of pre-operative ACEI administration on post-operative renal dysfunction is not clear (18). There are two opposite views regarding the effect of pre-operative ACEI therapy on post-operative renal outcome. Some authors suggest that ACEI increases the risk of pre-operative hypotension, generating a reduction in renal perfusion pressure, which is a risk factor for renal dysfunction (6,14,19,20). It is also reported that pre-operative use of ACEI is an independent risk factor of post-operative renal dysfunction (14). On the other hand, Rady et al. reports that pre-operative ACEI do not influence the clinical outcome after cardiac surgery (7). Benedetto et al. suggests that

there is an increased renin-angiotensin system activity during CABG, which has a prominent role in hypoperfusion-related renal injury; thus, ACE can improve renal perfusion by blocking the renin-angiotensin system activity (21). In a recent meta-analysis evaluating the role of pre-operative ACEI on incidence of post-operative renal dysfunction, it was found that pre-operative ACEI treatment increased the risk of post-operative renal dysfunction (8). There was only one patient who had post-operative dialysis in both ACEI user and non-user groups in our study. So, there was no significant difference between the groups with respect to need of post-operative dialysis. While we defined renal dysfunction as need of dialysis, some authors classified renal dysfunction according to creatinine clearance. So, it was thought that different methodologies and definitions of renal dysfunction might explain these different results.

Although there is a hypothesis that hypotension can also increase the risk of stroke by affecting the auto regulation in cerebral circulations (22), it is demonstrated that pre-operative ACEI have no impact on the incidence of post-operative stroke in a meta-analysis (8). As similar to literature, there was no significant difference of post-operative stroke since both ACEI user and non-user groups had no cases of stroke after surgery in our study.

It is known that hypotension and volume overloads are risk factors of new onset post-operative AF after cardiac surgery (23). Also, the use of inotropic and/or vasoconstrictor drugs after cardiac surgery may also increase the risk of arrhythmias (24,25). However, the impact of pre-operative ACEI on development of post-operative AF is controversial. Some authors suggest that pre-operative ACEI therapy increases the risk of post-operative AF (14,20). However, in a study evaluating the risk factors of post-operative AF, there is no significant difference of ACEI use between the patients with or without post-operative AF (26). Recent meta-analysis also demonstrates that pre-operative ACEI therapy does not increase the risk of post-operative AF in patients undergoing CABG (8). On the other hand, analyses of randomized trials suggest that ACEI may reduce the new onset AF since the renin-angiotensin-aldosterone system (RAAS) has emerged as an

important hormonal system in the initiation and pathogenesis of AF. It is suggested that ACEIs may decrease the left atrial enlargement and prevent post-operative AF secondary to decreases in atrial remodeling and afterload (27,28). It is also reported that there is a non-significant decrease of post-operative AF development in patients who use PreO ACEI (29). The incidence of post-operative AF was lower in ACEI user group than non-users in our study. But the difference was not statistically significant. It was thought that non-significant difference might be explained by the characteristics of study population since it was relatively small and included only isolated CABG patients.

Furthermore, the role of pre-operative administration of ACEIs on mortality is not clear. It is suggested that administration of these drugs in pre-operative period is an independent predictor of mortality after cardiac surgery (14). In contrast, in a study evaluating short- and long-term outcomes of pre-operative use of ACEI, there is no causal relationship between ACEI and mortality (30). In a study with isolated CABG patients, it is shown that there is no relation between pre-operative use of ACEI and adverse outcomes including mortality, stroke and post-operative MI. However, it is suggested that pre-operative administration of ACEI is an independent predictor of post-operative major events including mortality, post-operative renal dysfunction, MI, stroke and AF (20). As similar to literature, our study group included only isolating CABG surgery patients and there was no relation between the mortality and pre-operative ACEI treatment in our study. The mortality was higher in ACEI user group than non-users, but the difference was not statistically significant. However, post-operative major events were found to be higher in pre-operative ACEI user group than non-users and the difference was statistically significant. The definition of post-operative major event was different from Bandealli et al.'s study since ours included prolonged stay in ICU, need of dialysis, cerebrovascular event, post-operative/ pre-operative exitus. Fifty percent of the ACEI users had history of prolonged stay in ICU more than 3 days. In subgroup analysis of post-operative major events, it was found that the significant difference was related to the prolonged stay in ICU. In contrast, it was reported

that pre-operative ACEI was not related with durations of mechanical ventilation and prolonged stay in ICU in other studies (7,30). This different result about the length of stay in hospital might be related with characteristics of our study population which had a relatively small size and included only isolated CABG patients. It is suggested that more randomized trials are needed to evaluate the effect of pre-operative ACEI therapy on post-operative mortality and adverse outcomes in patients undergoing CABG surgery.

There are several limitations of this study that should be considered. First, it is a retrospective investigation, and data collection is based on medical records. Second, study population may not reflect the general population because of its relatively small size. Third, different classifications and definitions of post-operative complications such as renal dysfunction in both our study and the literature may be related to different results. It is suggested that further prospective, multicenter and randomized studies with standardized definitions of outcomes are needed to confirm these results.

## CONCLUSIONS

The use of ACEI drugs before CABG surgery are not related with the mortality and morbidities such as post-operative AF, VT/VF, need of inotropic agents and dialysis. However, it is related with post-operative major events, especially prolonged stay in ICU. It is suggested that long term prospective, randomized studies are needed to evaluate the role of the using of pre-operative ACEI on post-operative mortality and morbidities.

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