Effect of preoperative angiotensin-converting enzyme inhibitor on the outcome of coronary artery bypass graft surgery

Yiran Zhang and Liang Ma*

Department of Cardiothoracic Surgery, First Affiliated Hospital of Zhejiang University, Hangzhou 310003, China.

* Corresponding author. Department of Cardiothoracic Surgery, First Affiliated Hospital of Zhejiang University, Hangzhou, China. Tel: +86-571-87236841; fax: +86-571-88208323; e-mail: maliang99@yahoo.com. (L. Ma).

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Summary

The safety of the preoperative administration of angiotensin-converting enzyme inhibitors (ACEIs) in patients undergoing coronary artery bypass grafting (CABG) surgery is still uncertain. This systematic review thus evaluated the effect of preoperative ACEIs on the clinical outcomes in patients undergoing CABG surgery. We searched PubMed, the Cochrane Library and the Web of Science for randomized control trials or observational studies that compared the use of ACEIs with that of placebos before isolated CABG. Thirteen studies (3 randomized control trials and 10 observational studies) that included 31,390 patients met the eligibility criteria. Preoperative ACEI treatment increased the risk of hypotension [risk ratio (RR) = 2.36, 95% confidence interval (CI) 1.11–5.02, P = 0.03], postoperative myocardial infarction (RR = 1.14, 95% CI 1.02–1.27, P = 0.02) and postoperative renal dysfunction (RR = 1.26, 95% CI 1.00–1.60, P = 0.05) in patients undergoing on-pump CABG, but had no significant impact on the risk of postoperative atrial fibrillation (RR = 0.79, 95% CI 0.37–1.71, P = 0.56) or postoperative stroke (RR = 1.17, 95% CI 0.74–1.85, P = 0.50), and did not influence the early mortality (RR = 1.21, 95% CI 0.95–1.54, P = 0.12) in patients undergoing on-pump CABG. Preoperative use of ACEIs increased the risk of several postoperative complications in patients undergoing CABG. Further randomized studies are needed to more clearly elucidate the risks and benefits of ACEI therapy before CABG.

Keywords: Angiotensin-converting enzyme inhibitor • Coronary artery bypass grafting • Postoperative complications

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) have various beneficial effects that are independent of their antihypertensive qualities, such as improving endothelial function [1], suppressing inflammatory responses associated with atherosclerosis [2] and limiting hyperplasia in venous grafts [3], and they also play an important role in angiogenesis [4]. Studies have shown that blocking the renin–angiotensin system with ACEIs in patients with myocardial infarction (MI) or congestive heart failure improves ventricular function, prolonged survival and decreased infarct size [5, 6]. Consequently, most patients with coronary artery disease are treated with ACEIs, and patients receiving ACEIs are most likely to undergo more cardiac surgery and anaesthesia [7]. In addition, because of the intense inflammatory response related to the cardiopulmonary bypass (CPB) that involves the activation of platelets, the anti-inflammatory effect of ACEIs may afford protection against the perioperative complications of coronary artery bypass grafting (CABG) surgery such as cerebrovascular [8] and renal [9] adverse events. However, it has also been hypothesized by several authors that the preoperative administration of ACEIs to these patients contributes to the lowering of systemic vascular resistance and vasoplegia in the early postoperative phase [10–13], but the safety of the preoperative administration of ACEIs in patients undergoing CABG surgery is still uncertain [14].

A systematic review and meta-analysis was performed to determine the impact of preoperative ACEIs on the clinical outcomes in patients undergoing CABG surgery.

MATERIALS AND METHODS

Eligibility criteria

The inclusion criteria of this meta-analysis were (i) randomized control trials or observational studies, (ii) human patients older than 18 years, (iii) isolated CABG, either on- or off-pump, (iv) preoperative treatment with ACEIs and (v) end-points that included mortality, postoperative renal dysfunction or injury, postoperative stroke, postoperative atrial fibrillation, postoperative MI and hypertension. The exclusion criteria were (i) non-English language studies, (ii) review articles and case reports and (iii) studies that involved laboratory evaluation of haemodynamics or renal function without clinical end-points (because the aim of this meta-analysis was to determine the effect of preoperative administration of ACEIs on the clinical outcomes after CABG surgery).

Search strategy

A literature search was conducted using multiple databases including PubMed, the Cochrane Library and the Web of Science to

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find relevant manuscripts published through January 2014. The terms used were ‘angiotensin converting enzyme inhibitor’ and ‘coronary artery bypass graft’. Both authors screened the results of the literature search, and the reference lists of the included articles were also screened for potential studies. Both authors independently applied the inclusion and exclusion criteria, and any disagreement was resolved by consensus.

Data abstraction and quality assessment

Data abstraction and quality assessment were performed as described previously [15]. Briefly, both authors extracted the data and assessed the validity of the studies independently and any disagreement was resolved by consensus. The following information was extracted from each paper: author and year of publication, country, study design, number of patients, baseline characteristics and clinical end-points. Both authors independently assessed the quality of the studies included. The quality of the observational studies was assessed using the Newcastle–Ottawa scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The Newcastle–Ottawa scale assesses the quality of study based on the following aspects: (i) the selection of the study cohort (or cases/controls), (ii) the comparability of the cohorts (or cases/controls) and (iii) the outcome assessment for a cohort study, or the determination of the exposure for a case–control study. The quality of randomized trials was assessed using the Jadad scale [16]. The Jadad scale assesses the quality of randomized studies based on the following aspects: randomization, double blinding, withdrawals and dropouts, and a score ≥3 denotes a high-quality study. The meta-analysis was performed according to the PRISMA guidelines [17].

Statistical analysis

The statistical analysis was conducted as described previously [15]. Briefly, Review Manager 5.2 (RevMan 5.2®, Nordic Cochrane Center and Copenhagen, Denmark) was used to perform the meta-analysis. The I² statistic was used to quantify the statistical heterogeneity of the studies included, and I² values of 25–49, 50–74 and ≥75% indicate low, moderate and high heterogeneity [18], respectively. When the I² value was >50%, indicating the presence of variability among the studies, we chose a random-effects models rather than fixed-effects models to perform the meta-analysis. Risk ratios (RRs) with a 95% confidence interval (CI) were used to report the differences in clinical outcomes between the ACEI and control group. Forest plots were used to present the results of the meta-analysis. A P-value <0.05 was considered to be significant.

RESULTS

Description of the included papers

The literature search identified 223 articles, of which 204 articles were excluded as not being relevant. The remaining 19 studies were assessed for eligibility, and 13 studies (3 randomized control trials and 10 observational studies) that included 31 390 patients met our eligibility criteria and were included in this meta-analysis (Fig. 1). Among the 31 390 patients, 15 004 patients received ACEI treatment preoperatively, and 16 386 patients who did not receive ACEI treatment preoperatively served as controls. The characteristics of the studies included are shown in Tables 1–3.

Intra-/postoperative hypotension

Four studies evaluated the intraoperative and postoperative incidence rate of hypotension [24, 26, 28, 29]. Hypotension was defined by haemodynamic changes [26, 29] or postoperative inotropic drug use [24, 26] (details shown in Supplementary Table 1). Preoperative ACEI treatment increased the risk of hypotension (RR = 2.36, 95% CI 1.11–5.02, P = 0.03; Fig. 2). Among the four studies, one study was a randomized control trial [29], in which the rate of hypotension in the ACEI group was higher than that in the control group (RR = 4.14, 95% CI 1.46–11.71, P = 0.007). Three studies were observational studies [24, 26, 28]; in this subgroup, the risk of hypotension in the ACEI group was also higher than that in the control group (RR = 1.25, 95% CI 1.06–1.48, P = 0.01).

Postoperative myocardial infarction

Data on postoperative MI were available from seven studies that included 28 814 patients [19, 20, 23–25, 28, 31]. MI was diagnosed by electrocardiogram changes in six studies [19, 20, 23, 24, 28, 31], and the diagnostic criteria were not described in one study [25] (details shown in Supplementary Table 1). A trend towards a higher risk of postoperative MI was observed in patients treated with ACEI preoperatively (RR = 1.14, 95% CI 1.02–1.27, P = 0.02; Fig. 3). No significant heterogeneity was observed in the pooled group of studies (I² = 10%, χ² = 6.65, P = 0.35; Fig. 3). Among the seven studies, one study was a randomized control trial [31], in which the risk of postoperative MI in the ACEI group was higher than that in the control group (RR = 1.79, 95% CI 1.00–3.22, P = 0.05). Six studies were observational studies [19, 20, 23–25, 28], in which the risk of postoperative MI in the ACEI group was also higher than that in the control group (RR = 1.12, 95% CI 1.01–1.24, P = 0.04). We then performed a subgroup analysis to determine whether a history of MI would influence the results. Among the seven studies, the rate of previous MI in the ACEI and control groups was similar (P > 0.05) at the baseline level in two studies [20, 24]; in this subgroup, the risk of postoperative MI in the ACEI group was similar to that in the control group (RR = 0.88, 95% CI 0.38–2.03, P = 0.76; Fig. 3). The rate of previous MI in the ACEI group was higher (P < 0.05) than in the control group at baseline in four studies [19, 23, 25, 28], and the rate of previous MI was not described in one study [31]; in this subgroup, the risk of postoperative MI was higher in the ACEI group than in the control group (RR = 1.14, 95% CI 1.02–1.27, P = 0.02; Fig. 3).

Postoperative atrial fibrillation

Seven studies evaluated the incidence of postoperative atrial fibrillation [19, 22, 24, 27, 29–31]. Atrial fibrillation was detected by electrocardiogram in these studies (details shown in Supplementary Table 1). Preoperative ACEI treatment increased the risk of postoperative atrial fibrillation (RR = 1.14, 95% CI 1.0–1.29, P = 0.04; Fig. 4). However, after the removal of one study on off-pump CABG [22], the difference was no longer significant (RR = 1.12, 95% CI 0.98–1.29, P = 0.10). Among the seven studies, three studies were randomized control trials [29–31]; in this subgroup, the risk of
postoperative atrial fibrillation in the ACEI group was similar to that in the control group (RR = 0.79, 95% CI 0.37–1.71, P = 0.56; Fig. 4). Four studies were observational studies [19, 22, 24, 27]; in this subgroup, the risk of postoperative atrial fibrillation in the ACEI group was higher than that in the control group (RR = 1.17, 95% CI 1.09–1.26, P < 0.00001; Fig. 4). We then performed a subgroup analysis to determine whether a history of atrial fibrillation would influence the results. Among the seven studies, the rate of previous atrial fibrillation in the ACEI and control groups was similar (P > 0.05) at the baseline level in two studies [19, 24]; in this subgroup, the risk of postoperative atrial fibrillation in the ACEI group was higher than that in the control group (RR = 1.18, 95% CI 1.06–1.31, P = 0.002). The rate of previous atrial fibrillation was not described in five studies [22, 27, 29–31]; in this subgroup, the risk of postoperative atrial fibrillation was similar in the ACEI and control groups (RR = 0.99, 95% CI 0.70–1.40, P = 0.94).

Postoperative renal outcome

Six observational studies evaluated the incidence of postoperative renal outcome [19, 21, 23–25, 28]. Among these studies, five studies [19, 23–25, 28] evaluated the incidence of postoperative renal dysfunction, which was defined as a >50% increase in serum creatinine levels (details shown in Supplementary Table 1). A pooled analysis of these five studies showed that preoperative ACEI treatment increased the risk of postoperative renal dysfunction (RR = 1.26, 95% CI 1.00–1.60, P = 0.05; Fig. 5A). One study [21] evaluated the incidence of postoperative renal injury, which was defined as renal failure requiring dialysis or a >50% decline in the glomerular filtration rate (details shown in Supplementary Table 1), and it showed that preoperative ACEI treatment reduced the risk of postoperative renal injury (RR = 0.53, 95% CI 0.30–0.92, P = 0.02).

Postoperative stroke

Four studies evaluated the incidence of postoperative stroke [19, 23–25], and they were all observational studies. Stroke was defined by computed tomography (CT) or magnetic resonance imagery (MRI) (details shown in Supplementary Table 1). No significant difference in the risk of postoperative stroke was found between the ACEI and control groups (RR = 1.17, 95% CI 0.74–1.85, P = 0.50; Fig. 5B).

30-Day/in-hospital mortality

Early mortality was defined as death during hospitalization or within 30 days postoperatively. Seven studies reported in-hospital mortality or 30-day mortality among the ACEI and control groups [19, 20, 23–25, 28, 31] (details shown in Supplementary Table 1). There was no difference in early mortality between the ACEI group and control group (RR = 1.21, 95% CI 0.95–1.54, P = 0.12; Fig. 5C). Among the seven studies, one study was a randomized control trial [31]; in that study, there was no difference in early mortality between the ACEI group and the control group (RR = 1.26, 95% CI 0.13–12.46, P = 0.84). Six studies were observational studies [19, 20, 23–25, 28]; in this subgroup, there was also no difference in early mortality between the ACEI group and the control group (RR = 1.21, 95% CI 0.94–1.56, P = 0.13).

DISCUSSION

In this systematic review and meta-analysis, we found that preoperative administration of ACEIs increased the risk of intra-/postoperative hypotension, postoperative MI and postoperative renal dysfunction, but had no significant impact on the risk of postoperative atrial fibrillation or postoperative stroke and did not influence the early mortality in patients undergoing on-pump CABG.

Several mechanisms could explain the induction of hypotension by ACEIs during CABG. ACEIs can reduce the plasma level of angiotensin II, which is an important factor in facilitating the release of catecholamines from the adrenal medulla [32] and the inhibition of norepinephrine re-uptake [33], and long-term ACEI treatment also attenuates the vasoconstrictive effects of exogenous norepinephrine during CPB [34]. In addition, ACEIs can interact with adrenergic regulation and lead to the down-regulation of the baroreceptor-mediated reflex [35], and decrease the response to α-adrenergic agents [36].

The results of our meta-analysis showed that the preoperative administration of ACEIs was associated with a higher risk of
Table 1: Outlines of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Country</th>
<th>No-ACEI</th>
<th>ACEI</th>
<th>No-ACEI</th>
<th>ACEI</th>
<th>No-ACEI</th>
<th>ACEI</th>
<th>No-ACEI</th>
<th>ACEI</th>
<th>No-ACEI</th>
<th>ACEI</th>
<th>No-ACEI</th>
<th>ACEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benedetto, 2008 [20]</td>
<td>retrospective observational study</td>
<td>Italy</td>
<td>434</td>
<td>634</td>
<td>250</td>
<td>245</td>
<td>239</td>
<td>245</td>
<td>643</td>
<td>434</td>
<td>251</td>
<td>391</td>
<td>243</td>
<td>339</td>
</tr>
<tr>
<td>Chin, 2012 [22]</td>
<td>retrospective observational study</td>
<td>South Korea</td>
<td>183</td>
<td>183</td>
<td>281</td>
<td>281</td>
<td>236</td>
<td>236</td>
<td>281</td>
<td>281</td>
<td>236</td>
<td>236</td>
<td>281</td>
<td>281</td>
</tr>
<tr>
<td>Drenger, 2012 [23]</td>
<td>retrospective observational study</td>
<td>International</td>
<td>845</td>
<td>845</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
</tr>
<tr>
<td>Miceli, 2009 [24]</td>
<td>retrospective observational study</td>
<td>UK</td>
<td>845</td>
<td>845</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
<td>70.6</td>
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<td>70.6</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitors; ROS: retrospective observational study; POS: prospective observational study; NA: not available.

* p < 0.05: ACEI group versus no-ACEI group.

postoperative MI. Jain et al. [37] reported that a systolic blood pressure of 90 mmHg following CABG was an independent predictor of perioperative MI, which suggested that the hypotension induced by ACEIs during CABG may explain the increased risk of postoperative MI in patients receiving preoperative ACEI therapy. It should be noted that, because the majority of the studies were observational studies, the previous MI rate was higher than that of the control group at baseline in some studies, and our subgroup analysis results suggested that there was a possibility of false positive due to the unbalanced baseline characteristics. More randomized control trials are needed to confirm the impact of preoperative ACEI therapy on postoperative MI in patients undergoing CABG.

Previous studies have reached conflicting conclusions regarding the impact of preoperative ACEI therapy on postoperative atrial fibrillation. Some suggested that preoperative ACEI therapy increased the risk of hypotension in the early postoperative phase, requiring the administration of more fluids and/ or vasoconstrictor drugs [10–12]. Hypotension and volume overload are risk factors for the new onset of postoperative atrial fibrillation [38], and the perioperative use of inotropics and/or vasoconstrictor drugs may also increase the risk of atrial fibrillation [39, 40]. However, our meta-analysis showed that preoperative ACEI therapy did not increase the risk of postoperative atrial fibrillation in patients undergoing on-pump CABG.

Two opposite viewpoints have been expressed regarding the effect of preoperative ACEI therapy on postoperative renal outcome. Some have suggested that ACEI increases the risk of perioperative hypotension, generating a reduction in renal perfusion pressure, which is a risk factor for renal dysfunction [28]. Others have suggested that there was an increased renin–angiotensin system activity during CPB, which has a prominent role in hypoperfusion-related renal injury; thus, ACEIs could improve renal perfusion by blocking the renin–angiotensin system activity [21]. In this meta-analysis, we found that, in studies evaluating the incidence of postoperative renal dysfunction (defined as a >50% increase in the serum creatinine level), preoperative ACEI treatment increased the risk of postoperative renal dysfunction. However, there was only one study evaluating the incidence of postoperative renal injury (defined as renal failure requiring dialysis or a >50% decline in the glomerular filtration rate), and it showed that preoperative ACEI treatment reduced the risk of postoperative renal injury. According to the RIFLE criteria, the definition of a >50% increase of serum creatinine level covers all extents of renal injury, while the definition of a >50% decline in the glomerular filtration rate does not cover the stage of ‘risk of renal dysfunction’ in the RIFLE criteria. Besides, only one observational study [21] used the definition of a >50% decline in the glomerular filtration rate, which is insufficient to justify the conclusion that preoperative ACEIs reduce the risk of postoperative renal injury. Thus, we consider that the definition of a >50% increase of serum creatinine level is more representative for the renal outcome.

Although it has been hypothesized that hypotension could also increase the risk of stroke by affecting the autoregulation in cerebral circulations [26], our meta-analysis study found no significant impact of preoperative ACEIs on the incidence of postoperative stroke. Moreover, we also found no significant impact of preoperative ACEIs on early mortality.

Among the 13 included studies, one study [22] was performed in off-pump CABG patients, and was pooled in the analysis of postoperative atrial fibrillation. After removal of the data from this study, the difference in the risk of postoperative atrial fibrillation...
Table 2: Outline of studies included in the meta-analysis

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-ACEI</td>
<td>ACEI</td>
<td>No-ACEI</td>
<td>ACEI</td>
<td>No-ACEI</td>
</tr>
<tr>
<td>Age</td>
<td>65.0 ± 10.4</td>
<td>65.2 ± 10.4</td>
<td>57.1 ± 6.9</td>
<td>58.1 ± 6.9</td>
<td>NA</td>
</tr>
<tr>
<td>Male</td>
<td>75.60%</td>
<td>76.80%</td>
<td>69.40%</td>
<td>61.80%</td>
<td>NA</td>
</tr>
<tr>
<td>Smoking</td>
<td>NA</td>
<td>NA</td>
<td>34.30%</td>
<td>29.70%</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31.60%</td>
<td>43.40%*</td>
<td>29.60%</td>
<td>25.50%</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63.60%</td>
<td>72.50%*</td>
<td>29.60%</td>
<td>35.90%</td>
<td>NA</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>16.20%</td>
<td>20.40%*</td>
<td>46.30%</td>
<td>35.90%</td>
<td>NA</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous vascular disease</td>
<td>15.80%</td>
<td>19.10%*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>12.40%</td>
<td>16.00%*</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>5.70%</td>
<td>4.10%*</td>
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<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitors; ROS: retrospective observational study; POS: prospective observational study; NA: not available.

*P < 0.05: ACEI group versus no-ACEI group.

Table 3: Outline of studies included in the meta-analysis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No-ACEI</td>
<td>ACEI</td>
<td>No-ACEI</td>
<td>ACEI</td>
</tr>
<tr>
<td>Age</td>
<td>63 ± 9</td>
<td>61 ± 9</td>
<td>60 ± 7</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>Male</td>
<td>84%</td>
<td>85%</td>
<td>70%</td>
<td>57.10%</td>
</tr>
<tr>
<td>Smoking</td>
<td>83%</td>
<td>82%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3%</td>
<td>9%</td>
<td>36.70%</td>
<td>34.70%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16%</td>
<td>23%</td>
<td>40%</td>
<td>44.90%</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>37%</td>
<td>47%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous vascular disease</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>53%</td>
<td>49%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitors; RCT: randomized control trial; NA: not available.

Figure 2: Forest plot presenting intra-/postoperative hypotension from the studies included. ACEI: angiotensin-converting enzyme inhibitors; 95% CI: 95% confidence interval.
between the ACEI and control groups was no longer significant. This result suggested that the effect of preoperative ACEIs on off- and on-pump CABG patients could differ. Further studies are needed to clarify the effect of ACEIs on outcomes in off-pump CABG patients.

The magnitude of the RRs for postoperative MI, postoperative atrial fibrillation and postoperative renal dysfunction was small, which suggested that although the preoperative administration of ACEIs could have a negative effect on these outcomes, the degree of its effect was mild. Owing to the limited number of randomized control trials (3 RCTs among 13 studies included), we pooled observational studies and RCTs together to perform the meta-analysis. Although we had included observational studies in our analysis, the quality of these studies was high, as assessed by the Newcastle–Ottawa scale. Moreover, we performed subgroup analysis to determine the effect of study design on the results, which showed that the results of RCTs and observational studies were similar regarding the postoperative risk of hypotension, MI and mortality. However, the results of RCTs and observational studies were discordance regarding the postoperative risk of atrial fibrillation from the studies included. ACEI: angiotensin-converting enzyme inhibitors; 95% CI: 95% confidence interval. Balanced previous myocardial infarction rate: the rate of previous myocardial infarction in the ACEI and control groups was similar at baseline (P > 0.05); unbalanced previous myocardial infarction rate: the rate of previous myocardial infarction in the ACEI and control groups was different at baseline (P < 0.05) or not described. ACEI: angiotensin-converting enzyme inhibitors.

Figure 3: Forest plot presenting postoperative myocardial infarction from the studies included. ACEI: angiotensin-converting enzyme inhibitors; 95% CI: 95% confidence interval.

Figure 4: Forest plot presenting postoperative atrial fibrillation from the studies included. ACEI: angiotensin-converting enzyme inhibitors; 95% CI: 95% confidence interval.
fibrillation. Because the results of RCTs are more reliable than those of observational studies, we chose the result of RCTs to draw the conclusion on the postoperative risk of atrial fibrillation. Nevertheless, the observational design is a source of potential bias, which might be the reason for the high $I^2$ value in most of the analysis. Thus we chose a random-effects models for the meta-analysis because their assumptions account for the presence of variability among studies.

In conclusion, the present systematic review supports the hypothesis that preoperative administration of ACEIs to patients undergoing on-pump CABG increases the risk of hypotension in the early postoperative phase, which further slightly increases the risk of postoperative complications such as MI and renal dysfunction. Further randomized studies are needed to more clearly elucidate the risks and benefits of ACEI therapy before on- or off-pump CABG.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available at EJCTS online.

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**Conflict of interest:** none declared.
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