Angiotensin-converting Enzyme Inhibitors Decrease the Risk of Cardiac Rupture after Acute Myocardial Infarction: A Meta-analysis of Randomized Controlled Trials

Siyi Li¹,², Jinan Wang³, Yan Yan¹,², Wei Gong¹,² and Shaoping Nie¹,²

¹Center for Coronary Artery Disease, Division of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China
²Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, China
³Department of Cardiovascular Medicine, Peking University Third Hospital, Beijing, China

Received: 28 November 2022; Revised: 1 April 2023; Accepted: 23 May 2023

Abstract

Background: ACEI therapy decreases mortality in patients with acute MI. However, the effects of ACEIs on CR are unclear.

Methods: A comprehensive search of PUBMED, EMBASE, ISI Web of Science, MEDLINE and the Cochrane Register of Controlled Trials before July 2022 was conducted to identify all RCTs on ACEIs that recorded CR as an outcome. Review Manager 5.3 was used to analyze the data.

Results: Five RCTs including 26,383 patients with MI were identified; 71 of the 13,159 patients receiving ACEIs and 107 of the 13,224 control patients were verified to have CR. ACEI therapy started within 24 hours after the onset of acute MI significantly decreased the risk of CR, by 33% (RR: 0.67, 95% CI: 0.50–0.90, P=0.008).

Conclusions: Early administration of ACEIs (within 24 hours after the onset of acute MI) decreased the incidence of CR in patients with acute MI.

Keywords: angiotensin-converting enzyme inhibitors; cardiac rupture; myocardial infarction; RCTs; meta-analysis

Introduction

Cardiac rupture (CR) is a leading cause of early death after acute myocardial infarction (MI). In the pre-reperfusion era, the incidence of CR after acute MI was as high as 6% [1]. With the rapid development of drug treatment and reperfusion strategies, the outcomes in patients with MI have greatly improved, and the incidence of CR has declined to approximately 2% [2–4]. However, the hospital mortality of CR remains extremely high, at 75%–91% [5, 6]. Because of its dangerous onset, difficult diagnosis and poor prognosis, effective precautions and treatment measures remain lacking in clinical settings.
In patients with MI, progressive left ventricular dilation, that is, ventricular remodeling, is associated with elevated incidence of morbidity and mortality [7]. A series of clinical trials have demonstrated that angiotensin-converting enzyme inhibitors (ACEIs) are effective in prolonging survival after acute MI [8–11]. Large studies have shown that early administration of ACEIs (within 24 hours after the onset of acute MI) decreases morbidity of heart failure, total mortality and sudden cardiac death [12, 13]. ACEIs suppress the activation of the cardiac renin-angiotensin-aldosterone system, and attenuate cardiac structural and functional changes [14]. Moreover, ACEIs inhibit plasma matrix metalloproteinase activity and prevent left ventricular remodeling in patients with acute MI [15], thus further decreasing mortality. Nevertheless, whether ACEI treatment started within 24 hours after the onset of acute MI is beneficial in decreasing the occurrence of CR was unknown.

The objective of this meta-analysis was to explore whether the early use of ACEIs might prevent CR, and to estimate the effectiveness of ACEIs in decreasing the incidence of CR in patients with acute MI.

**Methods**

**Search Strategy**

A comprehensive search was conducted to identify all human randomized controlled trials (RCTs) on ACEIs that recorded CR as an outcome. PUBMED, EMBASE, ISI Web of Science, MEDLINE and The Cochrane Register of Controlled Trials were searched by two independent investigators for relevant human RCTs published before July 2022. The exact search terms were 

[(Angiotensin Converting Enzyme Inhibitors) OR (Enzyme Inhibitors, Angiotensin-Converting) OR (Inhibitors, Angiotensin-Converting Enzyme) OR (Inhibitors, Angiotensin Converting Enzyme) OR (Angiotensin-Converting Enzyme Antagonists) OR (Angiotensin Converting Enzyme Antagonists) OR (Enzyme Antagonists, Angiotensin-Converting) OR (Inhibitors, ACE) OR (ACE Inhibitors) OR (Angiotensin Converting Enzyme Inhibitor) OR (ACE Inhibitor) OR (Inhibitor, ACE) OR (Angiotensin-Converting Enzyme Inhibitor) OR (Enzyme Inhibitor, Angiotensin-Converting) OR (Inhibitor, Angiotensin-Converting Enzyme) OR (Antagonists, Angiotensin-Converting Enzyme) OR (Antagonists, Angiotensin Converting Enzyme) OR (Lisinopril) OR (Cilazapril) OR (Enalapril) OR (Captopril) OR (Fosinopril) OR (Zofenopril) OR (Enalaprilat) AND (Myocardial Infarction) OR (Infarction, Myocardial) OR (Infarctions, Myocardial) OR (Myocardial Infarctions) OR (Cardiovascular Stroke) OR (Cardiovascular Strokes) OR (Stroke, Cardiovascular) OR (Strokes, Cardiovascular) OR (Myocardial Infarct) OR (Infarct, Myocardial) OR (Infarcts, Myocardial) OR (Myocardial Infarcts) OR (Heart Attack) OR (Heart Attacks)] and 

[(Angiotensin Converting Enzyme Inhibitors) OR (Enzyme Inhibitors, Angiotensin-Converting) OR (Inhibitors, Angiotensin-Converting Enzyme) OR (Inhibitors, Angiotensin Converting Enzyme) OR (Angiotensin-Converting Enzyme Antagonists) OR (Angiotensin Converting Enzyme Antagonists) OR (Enzyme Antagonists, Angiotensin-Converting) OR (Inhibitors, ACE) OR (ACE Inhibitors) OR (Angiotensin Converting Enzyme Inhibitor) OR (ACE Inhibitor) OR (Inhibitor, ACE) OR (Angiotensin-Converting Enzyme Inhibitor) OR (Enzyme Inhibitor, Angiotensin-Converting) OR (Inhibitor, Angiotensin-Converting Enzyme) OR (Antagonists, Angiotensin-Converting Enzyme) OR (Antagonists, Angiotensin Converting Enzyme) OR (Lisinopril) OR (Cilazapril) OR (Enalapril) OR (Captopril) OR (Fosinopril) OR (Zofenopril) OR (Enalaprilat) AND (Heart Rupture) OR (Heart Ruptures) OR (Cardiac Rupture) OR (Cardiac Ruptures) OR (Ventricular Free Wall Rupture) OR (Free Wall Rupture, Heart) OR (Cardiac Free Wall Rupture)].

Furthermore, the references of selected studies, relevant manuscripts and systematic reviews were further retrieved. The literature search was not limited to English language publications.

**Study Selection and Data Extraction**

Two reviewers evaluated all retrieved titles and abstracts to identify potentially relevant articles. They then re-evaluated the results and tables of these possibly related studies to identify whether
CR was reported. Finally, RCTs assessing the effects of ACEIs on CR in patients with MI were included. Studies were selected if they met the following criteria: 1) RCTs; 2) more than 100 participants; 3) administration of ACEIs within 24 hours after acute MI; and 4) collection of data on CR during follow-up. Any discordance between reviewers was resolved by consensus.

Two investigators independently completed the data extraction. Discordance between investigators was resolved by discussion with a third investigator. The following information was recorded: study design, participants, quality indicators, clinical baseline characteristics, intervention strategy and clinical outcomes.

Quality Assessment

We used the method recommended by the Cochrane Collaboration to evaluate the quality of RCTs, which included primarily the following six aspects: 1) sequence generation for allocation; 2) allocation concealment; 3) blinding of participants, personnel and outcome assessors; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other sources of bias.

Data Analysis

Review Manager 5.3 (Cochrane Center, Denmark) was used to analyze the data. The effects of treatment are presented as risk ratios (RR) and 95% confidence intervals (95% CI). The pooled RR was calculated with the fixed-effects model. The chi-square test was used to assess heterogeneity among studies. We considered $P > 50\%$ to indicate significant heterogeneity [16].

Results

Study Search and Selection

We identified a total of 710 RCTs on ACEIs for MI in the PUBMED, EMBASE, ISI Web of Science, MEDLINE and Cochrane databases, 109 of which were considered potentially relevant studies. Five RCTs met the inclusion criteria and were included in the meta-analysis [12, 13, 17–19]. The flow diagram of study selection is shown in Figure 1.

Studies Inclusion

The study included five RCTs in 26,383 participants, of whom 13,159 were treated with ACEIs, and 13,224 received a control treatment (Table 1). In terms of ACEI administration strategies, all five RCTs administered ACEIs at an early stage. Four RCTs administered oral ACEIs within 24 hours after the onset of acute MI, and one RCT used intravenous administration followed by oral ACEIs, within 24 hours after the onset of MI. The treatment duration ranged from 3 weeks to 12 months. The design of the included studies is summarized in Table 1. Quality assessment results are detailed in Table 2.

Baseline characteristics of the included RCTs are demonstrated in Table 3. None of the five studies stated whether patients received primary percutaneous coronary intervention (PCI). Furthermore, participants did not receive any reperfusion therapy in the SMILE study, whereas more than 50% of the participants received thrombolytic therapy in four studies. No significant difference was observed in sex (male percentage, 76.0% vs. 75.8%) and age (years, 63.28 vs. 62.78) (except GISSI-3 had no specific age) between the ACEI group and control group. The detailed baseline characteristics of patients are shown in Supplementary Table 1.

Main Outcomes

Overall, the use of ACEIs, compared with control treatment, decreased the occurrence of CR (RR: 0.67, 95% CI: 0.50–0.90, $P=0.008$). A total of 107 cases of CR were recorded among 13,224 patients.
<table>
<thead>
<tr>
<th>Author/Study, Date</th>
<th>Design</th>
<th>Placebo-Controlled</th>
<th>Drug</th>
<th>Subjects (E/C)</th>
<th>Participants</th>
<th>Exclusion criteria</th>
<th>Early administration Time</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedberg (CONSENSUS II), 1992</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Enalaprilat and Enalapril</td>
<td>3044/3046</td>
<td>AML, chest pain of acute onset within 24 hours, BP &gt; 100/60 mmHg</td>
<td>A need for vasopressor agents for blood-pressure support; hemodynamically severe valvular stenosis; untreated third-degree atrioventricular block; a history of angioedema or sensitivity to ACEIs or the use of such drugs within one week before the infarction; clinically severe renal, hepatic, or hematologic disorders; a history of cerebral transient ischemic attacks related to a reduction in blood pressure within the preceding six months; a clear indication for treatment with ACEIs; life-threatening conditions other than MI; or comply poorly with treatment.</td>
<td>Enalapril therapy was started within 24 hours of the onset of acute MI.</td>
<td>Treatment was started with an intravenous infusion of 1 mg of enalaprilat diluted in 100 mL of 0.9 percent saline or an infusion of placebo; it was administered over a two-hour period. Six hours after the infusion was completed, therapy was continued with oral enalapril or placebo. The recommended doses were 2.5 mg twice a day on the second day, 5 mg twice a day on the third day, 10 mg daily on the fourth day, and 20 mg daily on the fifth day and thereafter.</td>
</tr>
<tr>
<td>Foy (PRACTICAL), 1994</td>
<td>Single center</td>
<td>Yes</td>
<td>Captopril</td>
<td>75/75</td>
<td>AMI, within 24 hours of the onset of chest pain</td>
<td>Persistent hypotension with systolic blood pressure &lt; 90 mmHg; a history of sensitivity to ACEIs or the use of ACEIs within 1 week of the infarction; hemodynamically significant valvular stenosis; clinically severe renal or hepatic disorders; a clear indication for treatment with an ACEI; have no informed consent; or comply poorly with treatment.</td>
<td>Captopril therapy was started within 24 hours of the onset of acute MI.</td>
<td>The patients were randomly assigned to receive oral captopril 6.25 mg at 2-hour intervals for 3 doses, followed by 25 mg 3 times daily begun 6 hours after initial dose. Randomized therapy was continued for a total of 12 months.</td>
</tr>
<tr>
<td>Foy (PRACTICAL), 1994*</td>
<td>Single center</td>
<td>Yes</td>
<td>Enalapril</td>
<td>75/75</td>
<td>AMI, within 24 hours of the onset of chest pain</td>
<td>Persistent hypotension with systolic blood pressure &lt; 90 mmHg; a history of sensitivity to ACEIs or the use of ACEIs within 1 week of the infarction; hemodynamically significant valvular stenosis; clinically severe renal or hepatic disorders; a clear indication for treatment with an ACEI; have no informed consent; or comply poorly with treatment.</td>
<td>Enalapril was started within 24 hours of the onset of acute MI.</td>
<td>Randomization to receive oral enalapril 1.25 mg at 2 hourly intervals for 3 doses, followed by 5 mg 3 times daily begun 6 hours after initial dose. Randomized therapy was continued for a total of 12 months.</td>
</tr>
<tr>
<td>Ambrosioni (SMILE), 1995</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Zofenopril</td>
<td>772/784</td>
<td>18 to 80 years old, acute anterior MI, within 24 hours of the onset of chest pain, who were not eligible for thrombolytic therapy</td>
<td>Cardiogenic shock (Killip class 4) on admission; a systolic blood pressure &lt; 100 mmHg (measured with the patient supine) on admission; a serum creatinine concentration &gt; 2.5 mg per deciliter (221 μmol per liter); a history of congestive heart failure; being treated with ACEIs; had contraindications to the use of ACEIs; or were unable or unwilling to give informed consent.</td>
<td>Zofenopril was started within 24 hours after the onset of acute anterior MI.</td>
<td>The patients were randomly assigned to receive oral zofenopril or placebo. The initial dose of medication was 7.5 mg. The dose was repeated after 12 hours and progressively doubled until the final target dose of 30 mg twice daily was reached. The treatment period was 6 weeks.</td>
</tr>
<tr>
<td>Author/Study, Date</td>
<td>Design</td>
<td>Placebo-Controlled</td>
<td>Drug</td>
<td>Subjects (E/C)</td>
<td>Participants</td>
<td>Exclusion criteria</td>
<td>Early administration Time</td>
<td>Interventions</td>
</tr>
<tr>
<td>--------------------</td>
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</tr>
<tr>
<td>French, 1999</td>
<td>Single center</td>
<td>Yes</td>
<td>Captopril</td>
<td>243/250</td>
<td>Aged ≤ 75 years with first infarctions, presenting within 4 hours of the onset of ≥ 30 minutes chest pain, who received streptokinase</td>
<td>Authors' previously reported contraindications against streptokinase; patients with prior MI who were receiving an ACEI and those with systolic blood pressure of &lt; 90 mmHg 6 hours after thrombolysis.</td>
<td>Captopril was started within 4 hours of symptom (first infarction) onset.</td>
<td>Randomization to receive 6.25 mg captopril or matching placebo occurred 2 h after streptokinase was commenced if the systolic BP was ≥ 90 mmHg. Dosing was increased, starting 2 h after randomization, as follows: 12.5 mg (3 doses), 25 mg (3 doses), then 50 mg 3 times daily for 3 weeks.</td>
</tr>
<tr>
<td>Pedrazzini (GISSI-3), 2007</td>
<td>Multicenter</td>
<td>No</td>
<td>Lisinopril</td>
<td>8950/8994</td>
<td>MI, within 24 hours of chest pain onset and had no clear contraindications to the study treatments</td>
<td>Severe heart failure requiring any of the study treatments; Killip class 4; high risk of further serious hemodynamic deterioration after treatment with vasodilators (systolic blood pressure ≤ 100 mmHg); specific contraindications to the study drugs – namely, a history of clinically relevant renal failure (serum creatinine &gt; 177 μmol/L, proteinuria &gt; 500 mg per 24 hours, or both), history of bilateral stenosis of the renal arteries; documented allergy to one of the study drugs; other life-threatening disorders (e.g., tumors, serious respiratory diseases); or previous randomization within the trial.</td>
<td>Lisinopril was started within 24 hours from acute MI symptoms.</td>
<td>Patients were randomly assigned oral lisinopril (5 mg at randomization, 5 mg after 24 h, 10 mg after 48 h, then 10 mg daily for 6 weeks) or open control.</td>
</tr>
</tbody>
</table>

*Also came from the “Foy (PRACTICAL), 1994” study but with different ACEIs.
with MI (0.809%) who received control therapy, whereas 71 cases of CR were recorded among 13,159 patients with MI (0.540%) treated with ACEIs. Heterogeneity was not found across studies ($I^2 = 0\%$), and a fixed-effects model was selected to describe the data. Pooled CR data are shown in Figure 2.

Discussion

This meta-analysis based on five RCTs in more than 26,000 patients explored the relationship between early administration of ACEIs and CR in patients with acute MI, thus suggesting that ACEIs were effective in preventing the development of CR. This is the first meta-analysis confirming that ACEIs decreased the occurrence of CR, thus suggesting that ACEIs had beneficial effects on the repair and healing of the infarcted myocardium after MI.

The use of ACEIs to decrease mortality after MI is not a new finding. Many studies have demonstrated that early or late treatment with ACEIs decreases mortality in patients with acute MI [8–10, 20]. The causes of death after MI are usually divided into cardiovascular death and non-cardiovascular death. Death due to progressive heart failure and sudden death are the most common causes of death. In a meta-analysis including 15,104 patients with MI treated with placebo or ACEIs, 1105 deaths occurred in the ACEI group, and 1251 deaths occurred in the placebo group. Overall, ACEI therapy significantly decreased the risk of death (OR: 0.83; 95% CI: 0.71–0.97), cardiovascular death (OR: 0.82; 95% CI: 0.69–0.97) and sudden cardiac death (OR: 0.80; 95% CI: 0.70–0.92) [21]. Køber et al. and Preffer et al. have found that using ACEIs for 3 days after MI clearly decreases death due to heart failure (ACEI group vs. placebo group: 82 vs. 103 and 38 vs. 58) [8, 22]. In our meta-analysis, because of the specific inclusion criteria, the pooled RR of mortality, sudden death and heart failure with ACEI treatment was 0.92 (95% CI: 0.75–1.13), 0.92 (95% CI: 0.69–1.22) and 1.04 (95% CI: 0.90–1.21), respectively. These results did not represent the real effects of ACEIs.

Valid precautions and treatment measures are lacking for CR, a catastrophic complication of acute MI, given its difficult diagnosis and poor prognosis. In this context, whether early administration of ACEIs might be effective for CR is worthy of further exploration. Several clinical cohort studies have shown that patients with CR had lower rates of ACEI use than those without CR after MI. Chang et al. have found that patients with ST-elevation MI receiving ACEIs had a lower risk of ventricular free wall rupture than those not receiving ACEIs (adjusted OR = 0.32, P = 0.014) [2]. A systematic review has indicated that the use of ACEIs decreased the risk of CR in patients with acute MI, and ACEIs were a protective factor against MI [23]. Moreover, some early RCTs examining CR have also suggested that early use of ACEIs decreased the incidence of CR after MI. In CONSENSUS II, 25 CR cases were observed in the ACEI group (n = 3, 044), whereas 27 CR cases were observed in the placebo group (n = 3, 046) [17]. In the GISSI-3 trial, 33 of the 8950 patients with MI receiving ACEIs and 55 of the 8994 patients with MI receiving control treatment were verified to have myocardial rupture (OR:

<table>
<thead>
<tr>
<th>Author/Study, Date</th>
<th>Adequate sequence generation of allocation</th>
<th>Allocation concealment</th>
<th>Blindness of participants, personnel, and outcome assessors</th>
<th>Complete outcome data</th>
<th>Free of selective outcome reporting</th>
<th>Free of other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedberg (CONSENSUS II), 1992</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Foy (PRACTICAL), 1994</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Ambrosioni (SMILE), 1995</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>French, 1999</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Pedrazzini (GISSI-3), 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

*Also came from the “Foy (PRACTICAL), 1994” study, but with different ACEIs.
Overall, 81% (71/88) of patients with CR were diagnosed by autopsy. The SMILE study has reported that patients receiving ACEIs had a lower risk of dying from CR than patients receiving the placebo (OR: 0.19; 95% CI: 0.10–0.41) [12]. French et al. have reported CR in 0.4% of patients receiving ACEIs (n=243) and 1.2% of patients receiving placebo (n=250) [19]. In the PRACTICAL trial, four patients in the ACEI group (n=150) and six patients in the placebo group (n=75) had post-infarction rupture during the first 90-day study period (including death due to left ventricular failure) [18]. In our meta-analysis of five pooled RCTs, the pooled RR of CR with ACEI use was 0.67 (95% CI: 0.50–0.90, P=0.008). Early administration of ACEIs (within 24 hours after the onset of acute MI) had a significant protective effect against CR after MI.

The mechanisms through which ACEIs prevent CR have not been fully delineated. ACEIs may decrease the likelihood of cardiac death through several potential mechanisms, such as pump failure or myocardial rupture. ACEIs have beneficial effects on the hemodynamic and neurohumoral profile, decrease ventricular dilation and remodeling, and also modulate adrenergic tone [13]. ACEIs also have substantial sympatholytic activity [24]. The increased sympathetic activation in patients with MI is associated with elevated blood pressure, heart rate and ventricular contraction, and diminished myocardial perfusion, cardiomyocytes and tensile strength of the infarct myocardium [25]. Treatment with ACEIs may decrease circulating norepinephrine and angiotensin II, which are facilitators of adrenergic neurotransmission [24]. Prostacyclin synthesis may also increase with ACEI treatment, thus decreasing local norepinephrine release [26]. Moreover, improvements in the hemodynamic state suppress sympathetic activity and decrease sympathetically mediated vasoconstriction. All the above findings indicate that ACEIs are conducive to decreasing the incidence of CR. Furthermore, the administration of ACEIs favorably affects the ventricular remodeling process [27] and may decrease the risk of ventricular rupture [13]. Ventricular remodeling alters the function and distribution of cardiac myocytes [28], thus leading to dilatation, hypertrophy and decreased contractility, all of which are associated with poor prognosis and

Table 3  Characteristics of the Included RCTs.

<table>
<thead>
<tr>
<th>Author/Study, Date</th>
<th>Follow-up</th>
<th>Mortality</th>
<th>Reperfusion</th>
<th>Diagnosis of CR</th>
<th>Prevalence of CR (E/C)</th>
<th>Prevalence of Sudden Death (E/C)</th>
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<tbody>
<tr>
<td>Swedberg (CONSENSUS II), 1992</td>
<td>6 months</td>
<td>10.2% / 9.4%</td>
<td>Thrombolysis (56%)</td>
<td>Not mentioned</td>
<td>10.2% / 9.4%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Foy (PRACTICAL), 1994</td>
<td>3 months</td>
<td>12.0% / 9.3%</td>
<td>Thrombolysis (71%)</td>
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<td>12.0% / 9.3%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Foy (PRACTICAL), 1994*</td>
<td>3 months</td>
<td>1.3% / 1.3%</td>
<td>Thrombolysis (74%)</td>
<td>Not mentioned</td>
<td>1.3% / 1.3%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Ambrosioni (SMILE), 1995</td>
<td>6 weeks</td>
<td>6.5% / 8.3%</td>
<td>Thrombolysis (100%)</td>
<td>Not mentioned</td>
<td>6.5% / 8.3%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>French, 1999</td>
<td>1 month</td>
<td>2.1% / 4.4%</td>
<td>Thrombolysis (72%)</td>
<td>In-hospital</td>
<td>2.1% / 4.4%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Pedrazzini (GISSI-3), 2007</td>
<td>In-hospital</td>
<td>5.2% / 5.7%</td>
<td>Thrombolysis (59%)</td>
<td>Autopsy (71/88, 81%), echocardiographic, or surgical evidence</td>
<td>5.2% / 5.7%</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>

*Also came from the “Foy (PRACTICAL), 1994” study, but with different ACEIs.
increased CR [29, 30]. Moreover, animal studies have shown that ACEIs inhibited RAS by blocking the release of monocytes and neutrophils from the spleen, thereby inhibiting systemic and local inflammatory responses; suppressing the activation of matrix metalloproteinases and collagen synthesis; and further preventing heart rupture during the acute phase of MI [31, 32].

The optimal time, mode and duration of ACEI use in patients with acute MI have long been controversial. Different trials have used varying strategies. Our meta-analysis, including five RCTs, evaluated early administration (within 24 hours after the onset of chest pain) of only oral ACEIs (except CONSENSUS II) in patients with acute MI. This strategy decreased the risk of CR, thereby suggesting that early oral ACEI administration is an optimal schedule to decrease the incidence of CR in patients with MI. Because most prior clinical studies have used only oral ACEI treatment, the effects of combining early intravenous infusion of ACEIs followed by oral ACEIs must be further explored.

In this meta-analysis, 60% of the total population received thrombolytic therapy. However, use of primary PCI was not described. The early use of ACEIs may somewhat decrease the incidence of CR in patients with MI who receive thrombolytic therapy. However, the effects of ACEIs on CR in patients with MI who received primary PCI were unclear. Primary PCI is the gold standard therapy for acute MI in developed countries. Puerto et al. have found that the incidence of CR did not decrease significantly in the thrombolysis era but did decrease significantly in the era of primary PCI [33]. From 1977 to 2011, with the rapid development of primary PCI (from 0.2% to 66.6%), the occurrence of CR continually decreased (from 3.3% to 1.7%) [34]. The benefit of ACEIs in decreasing CR may be invalid in the era of primary PCI. However, according to statistics, the use of primary PCI remains very low in developing countries, and 65% of patients with ST-elevation MI in Indonesia did not receive primary PCI [35]. In an observational study of patients with non-ST elevation MI, all of whom were successfully treated with PCI, the use of ACEIs has been significantly associated with a diminished risk of 4-year all-cause mortality [36]. ACEI treatment might have some benefits regarding CR after MI in the era of primary PCI. Further exploration of the efficacy of ACEIs against CR in patients undergoing primary PCI will be essential.

### Limitations

This meta-analysis had several limitations. First, the number of included randomized trials was limited, and some studies had limited patients. Second, GISSI-3 was an open-label trial, and subjective bias might exist in the results. Third, autopsy, the gold standard for diagnosis of CR, was performed in a minority of cases, and most included studies did not report the rate of autopsy. Therefore, the rate of CR might be underestimated. Fourth, the relevance of the findings of trials conducted approximately 10 years ago to contemporary patients may

### Table 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ACEI</th>
<th>Control</th>
<th>Risk ratio M-H, fixed, 95% CI</th>
<th>Total events</th>
<th>Total Weight</th>
<th>M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrosioni (SMILE), 1995</td>
<td>8</td>
<td>772</td>
<td>10 784 9.3%</td>
<td>0.81 [0.32, 2.05]</td>
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<tr>
<td>Foy (PRACTICAL), 1994</td>
<td>4</td>
<td>75</td>
<td>6 75 5.6%</td>
<td>0.67 [0.20, 2.27]</td>
<td></td>
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</tr>
<tr>
<td>Foy (PRACTICAL), 1994*</td>
<td>0</td>
<td>75</td>
<td>6 75 6.1%</td>
<td>0.08 [0.00, 1.34]</td>
<td></td>
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</tr>
<tr>
<td>French, 1999</td>
<td>1</td>
<td>243</td>
<td>3 250 2.8%</td>
<td>0.34 [0.04, 3.27]</td>
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<td></td>
</tr>
<tr>
<td>Pedrazzini (GISSI-3), 2007</td>
<td>33</td>
<td>8950</td>
<td>55 8994 51.2%</td>
<td>0.60 [0.39, 0.93]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swedberg (CONSENSUS II), 1992</td>
<td>25</td>
<td>3044</td>
<td>27 3046 25.2%</td>
<td>0.93 [0.54, 1.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>13,159</td>
<td>13,224</td>
<td>100.0%</td>
<td>0.67 [0.50, 0.90]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2** Pooled CR Data.

*Also came from the “Foy (PRACTICAL), 1994” study, but with different ACEIs.
be questionable. Primary PCI is known to be an effective method to decrease mortality in patients with acute MI. To some extent, the results are not applicable to a population of patients with acute MI treated with primary PCI. However, given the limited access to primary PCI in many regions, the early treatment of acute MI with ACEIs remains of great clinical relevance.

Conclusion

On the basis of five RCTs, a clinically meaningful decrease in CR was observed in patients with acute MI with early use of ACEIs. This meta-analysis suggested that ACEIs had beneficial effects on the repair and healing of infarcted myocardium after MI. Early administration of oral ACEIs or combined treatment with intravenously infused ACEIs may be an appropriate treatment measure for patients with acute MI. More studies remain necessary to confirm this conclusion and explore the potential mechanisms.

Compliance with Ethical Standards

Funding

This study was supported by the National Natural Science Foundation of China (81970292, 82270258 and 82100260), Natural Science Foundation of Beijing, China (7222046 and 7191002), Interdisciplinary Cooperation Project of Beijing Nova Program (Z211100002121165), and National Key Research & Development Program of China (2020YFC2004800).

Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

REFERENCES


Supplementary Materials: Supplementary material is available at the following link https://cvia-journal.org/wp-content/uploads/2023/06/Supplementary_Table_1_CVIA_331.pdf.