The Efficacy of Renin Angiotensin System Inhibitors (Rasi) in Patients with Coronary Artery Disease without Heart Failure: Systematic Review and Meta-Analysis

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Abstract

The benefit is much less clear for stable disease than for acute coronary syndromes. Patients who have hypertension, diabetes mellitus, a left ventricular ejection fraction of 40% or less, or chronic kidney disease; the aim of this systematic review and meta-analysis was renin angiotensin system inhibitors in patients with coronary artery disease. MEDLINE, PubMed, Cochrane Library, Embase, ISI, google scholar were used as electronic databases to perform a systematic search for relevant articles published in the dental literature between unit 2019. A commercially available software program (Endnote X9) was used for electronic title management. Searches were performed with keywords, “angiotensin system inhibitors”, “coronary artery disease”,” heart failure”,” RASi”. All the included studies reported the effect of RAS inhibitors on mortality. Use of RAS inhibitors was associated with reduced mortality in the pooled analysis of OCSs with PS analysis (RR [95% CI] = 0.90). Patients with stable coronary artery disease without heart failure, the current body of evidence from randomized trials shows a significant benefit of RASi for the reduction of cardiovascular events and all-cause mortality only in comparison with placebo but not with active controls.

Keywords: Renin Angiotensin System, Coronary Artery Disease, Heart Failure.

Introduction

Renin angiotensin system inhibitors (RASi) have been documented to reduce the risk of cardiovascular events and overall mortality when compared with placebo in patients with coronary artery disease and even in those without apparent heart failure (1). Because the mean systolic blood pressure on entry in these trials was lower than 140 mm Hg and the end of trial difference in blood pressure between the two treatment strategy was minimal, the favorable effect of RASi on outcomes has been dubbed as a “blood pressure independent effect”—a vasculo protective properties of these drugs (2). Angiotensin-converting-enzyme (ACE) inhibitors are effective in reducing the risk of heart failure, myocardial infarction, and death from cardiovascular causes in patients with left ventricular systolic dysfunction or heart failure (3). Similar results with no benefit of RASi were seen in the Quinapril Ischemic Event Trial (QUIET), Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study, and Ischemia Management With Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme (IMAGINE) trial (4). The benefit is much less clear for stable disease than for acute coronary syndromes. Patients who have hypertension, diabetes mellitus, a left ventricular ejection fraction of 40% or less, or chronic kidney disease (5); The aim of this systematic review and meta-analysis was renin angiotensin system inhibitors in patients with coronary artery disease.

Method

This systematic review was structured and conducted according to the preferred reporting items of the PRISMA statement. Systematic evaluation of six selected studies was performed in order to prepare the study protocol. Data extraction forms were constructed after the initial results of the search.

Search strategy

MEDLINE, PubMed, Cochrane Library, Embase, ISI, Google scholar were used as electronic databases to perform a systematic search for relevant articles published in the dental literature between unit 2019. A commercially available software program (Endnote X9) was used for electronic title management. Searches were performed with keywords, “angiotensin system inhibitors”, “coronary artery disease”,” heart failure”,” RASi”.

Study inclusion and exclusion criteria

The following inclusion criteria were applied:

1. Trials with mean baseline systolic blood pressure 140 mm Hg or less versus more than 140 mm Hg.
2. Full text available.
3. Trials enrolling patients with recent myocardial infarction.
4. Trials using angiotensin converting enzyme inhibitors compared with those using angiotensin receptor blockers as the treatment.
5. Evaluate whether the benefit of RASi is restricted to patients with recent myocardial infarction.

Quality assessment of selected studies

A quality assessment of all selected full-text articles was performed according to the Cochrane collaborations' tool. Quality assessment was performed in two different phases. In particular, during phase I quality assessment was based on the published full-text article performed independently by both authors. In phase II, disagreements were resolved by discussion.

Data Extraction and method of analysis

Analysis to evaluate the relation of the following potential effect modifiers to the risk of outcomes with RASi: end of trial systolic blood pressure difference between treatment arms, percentage of patients with hypertension, percentage of patients with diabetes, and percentage of patients on statins.

Heterogeneity between RCT's, meta-analysis (weighted mean difference and 95% confidence

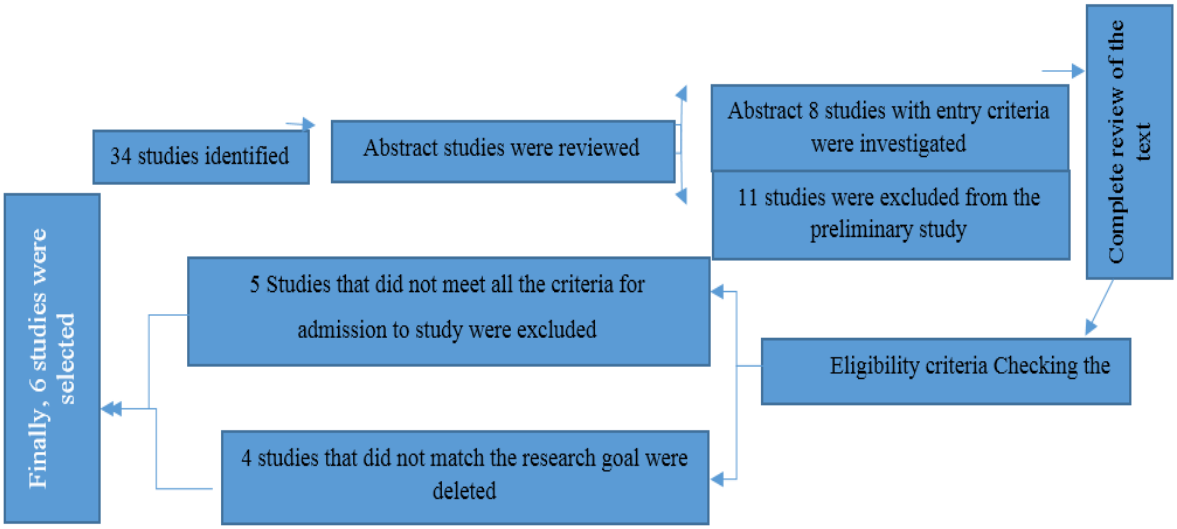

Figure-1: Study Attrition Diagram

Baseline patient characteristics of included studies are summarized in Table 1. Patients have advanced age (median, 76.1 years) and comorbidities such as coronary artery disease (41–68 %), diabetes (33%), and atrial fibrillation (37%).

All the included studies reported the effect of RAS inhibitors on mortality. Use of RAS inhibitors was associated with reduced mortality in the pooled analysis of OCSs with PS analysis (RR [95% CI] = 0.90).

Table-1: Characteristics of studies included in systematic review

Study	Design	Treatment group /no. of patients	Control group/no. of patients	Mean age (years)	Entry EF	Follow-up	End points	RAS inhibitors	PS analysis	Overall population Treatment/control (n)	PS-analysis population Treatment/control (n)
Patel et al (6)	Prospective OCS	58/120	73/120	76	≥0.50	5	ACD, HF admission	ACE-I	+	165/193	120/120
Lund et al (7)	Prospective OCS	185/296	190/296	80	≥0.40	6	ACD	ARB	+	303/3500	296/296
Mujib et al (8)	Prospective OCS	930/1337	951/1337	81	≥0.40	2.4	ACD, HF admission	ACE-I or ARB	+	3673/12,543	3329/3329
Philbin et al (9)	Prospective OCS	23/190	30/160	75	≥0.40	6 month	ACD, HF admission	ACE-I	-	190/160	NA
Ahmed et al (9)	Prospective OCS	NR/62	NR/176	78	≥0.40	4	ACD	ACE-I	-	62/176	NA
Pitt et al (10)	RCT	244/1514	237/1509	67	≥0.40	3	ACD, HF admission	ARB	-	424/426	NA

Table-2: Heterogeneity chi-squared

study	[95% Conf. Interval]		% Weight
Patel et al (6)	-194.996	196.996	7.41
Lund et al (7)	-172.437	176.437	9.35
Mujib et al (8)	-102.838	108.838	25.40
Philbin et al (9)	-148.877	156.877	12.17
Ahmed et al (9)	-190.996	200.996	7.41
Pitt et al (10)	-80.238	92.238	38.26
I-V pooled ES	-49.166	57.518	100.00

Heterogeneity chi-squared = 0.00 (d.f. = 5) p = 1.000

I-squared (variation in ES attributable to heterogeneity) = 0.0%

Test of ES=0: z= 0.15 p = 0.878

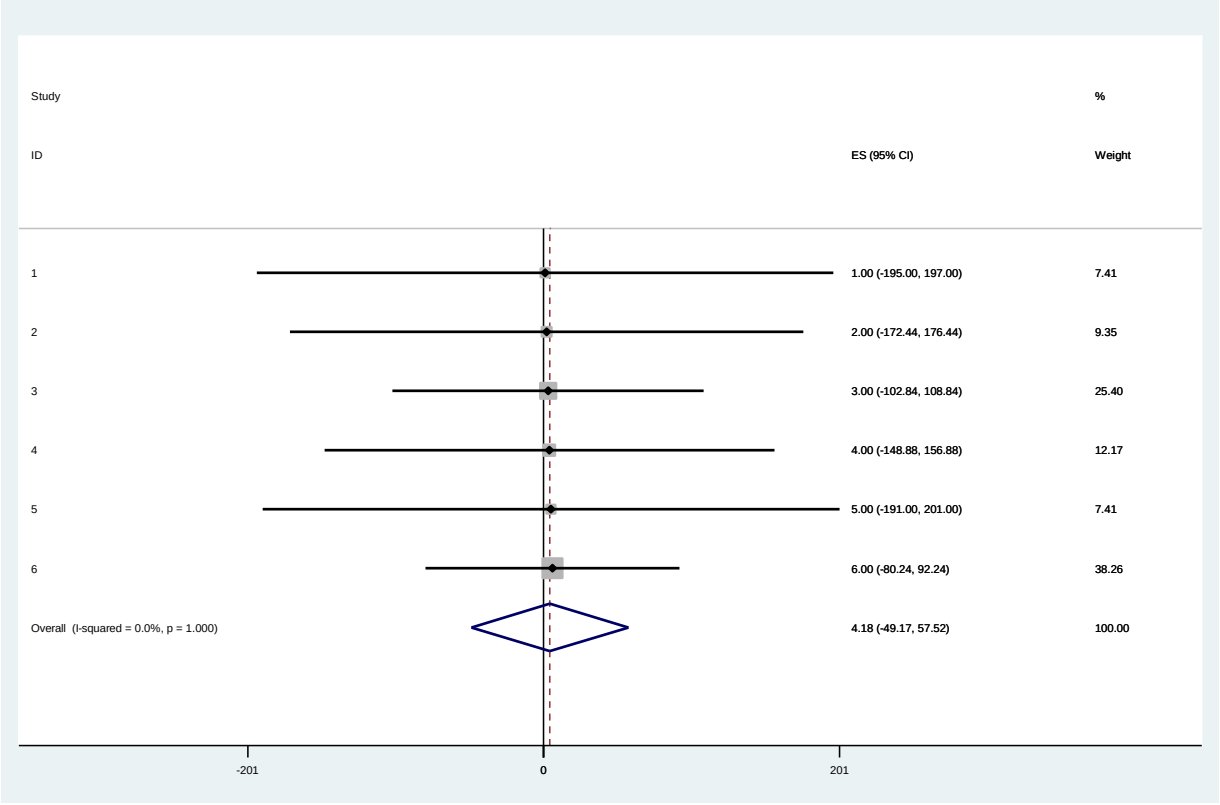

Figure-2: A meta-analysis forest plot including its various components

Discussion

RASi reduced the risk of cardiovascular events and all-cause mortality when compared with placebo, similar to the results seen in HOPE and EUROPA. However, even in the placebo controlled trials, Bayesian meta-regression analysis showed that the baseline risk (as measured by control event rate) explained the heterogeneity of treatment effect such that RASi was only beneficial in trials with a higher baseline risk and not those with a lower baseline risk (2, 20, 21). Thus the universal endorsement of RASi for all patients with stable coronary artery disease is not supported by even placebo controlled trials, and might apply only to patients with higher baseline risk (11). RASi did not reduce the risk of cardiovascular events or mortality when compared with active controls (12). Results were consistent between trials of angiotensin converting enzyme inhibitors and those of angiotensin receptor blockers when compared with active controls. There was no outcome for which a higher percentage of participants with either enrolled hypertension or diabetes conferred a statistically significant advantage of RASi over active controls. RASi showed a consistent reduction in incident diabetes when compared with placebo or active controls.

Placebo The lack of advantage of RASi over active controls for cardiovascular events could be due to three reasons. Firstly, the active controls are as good as RASi, and the effect is mediated mainly by a reduction in blood pressure. Secondly, the enrolled cohort (unlike patients with heart failure or renovascular hypertension) might not have had an

activated renin-angiotensin-aldosterone system, resulting in less benefit.

Even among placebo controlled trials, RASi was no better than placebo in trials with lower baseline risk. This lack of benefit could have implications for patients with stable coronary artery disease with aggressive management of risk factors such as hypertension and hypercholesterolemia (with high intensity statins) and consequent lower baseline residual risk (13-19).

Conclusions

In patients with stable coronary artery disease without heart failure, the current body of evidence from randomized trials shows a significant benefit of RASi for the reduction of cardiovascular events and all-cause mortality only in comparison with placebo but not with active controls.

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