

# Review: ACE inhibitors reduce mortality and cardiovascular endpoints in stable coronary artery disease

Danchin N, Cucherat M, Thuillez C, et al. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: an overview of long-term randomized controlled trials. Arch Intern Med. 2006;166:787-96.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆ Cardiology ★★★★★☆☆

## QUESTION

Are angiotensin-converting enzyme (ACE) inhibitors effective in patients with coronary artery disease (CAD) and no signs of heart failure or severe left ventricular systolic dysfunction (LVSD)?

## METHODS

**Data sources:** MEDLINE (1990 to 2004), EMBASE/Excerpta Medica (through 2004), Cochrane Controlled Trials Register (through 2004), cardiology meeting presentations from 2003 and 2004, and references of relevant articles.

**Study selection and assessment:** Randomized placebo-controlled trials (RCTs) with ≥ 2-year follow-up that evaluated the effect of ACE inhibitors on all-cause mortality, cardiovascular mortality, or myocardial infarction (MI) in patients with CAD and no signs of heart failure or LVSD (LV ejection fraction < 0.35). 7 RCTs (*n* = 33 960, mean age range 58 to 66 y) with a follow-up range of 2 to 5 years (mean 4.4 y) met the selection criteria. Quality assessment was based on allocation concealment and blinding of patients, clinicians, and outcome assessors.

**Outcomes:** All-cause mortality, cardiovascular mortality, and MI. Secondary outcomes were stroke, cardiac arrest, hospitalization for unstable angina, hospitalization for heart fail-

ure, revascularization, and onset of diabetes mellitus.

## MAIN RESULTS

5 ACE inhibitors were evaluated: ramipril, quinapril, enalapril, perindopril, andtrandolapril. Meta-analysis using fixed effects showed that ACE inhibitors reduced all-cause mortality, cardiovascular mortality, MI, stroke, hospitalization because of heart failure, revascularization, cardiac arrest, and onset of diabetes (Table). Reduction in hospitalization because of unstable angina did not reach statistical significance (Table).

## CONCLUSION

In patients with coronary artery disease and no signs of heart failure or severe left ventricular systolic dysfunction, angiotensin-converting enzyme inhibitors reduce all-cause and cardiovascular mortality, myocardial infarction, stroke, and other cardiovascular endpoints more than placebo.

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### Angiotensin-converting enzyme (ACE) inhibitors vs placebo for stable coronary artery disease\*

Outcomes at mean 4.4 y	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		ACE inhibitors	Placebo		
All-cause mortality	7 (33 960)	7.2%	8.2%	13% (6.5 to 20)	94 (63 to 189)
Cardiovascular mortality	7 (33 960)	3.9%	4.8%	18% (9.6 to 26)	115 (81 to 218)
Myocardial infarction	7 (33 960)	6.1%	7.4%	17% (10 to 24)	80 (58 to 132)
Stroke	6 (32 210)	2.2%	2.8%	23% (12 to 33)	159 (108 to 306)
Cardiac arrest	7 (33 960)	0.3%	0.5%	42% (16 to 59)	478 (340 to 1256)
Hospitalization for unstable angina	4 (23 882)	6.5%	6.7%	2.8% (-6.5 to 10)	Not significant
Hospitalization for heart failure	5 (31 750)	2.1%	2.7%	24% (12 to 33)	158 (111 to 317)
Revascularization	6 (33 500)	15.6%	16.7%	6.8% (1.7 to 11)	89 (55 to 359)
Onset of diabetes mellitus	2 (21 515)	4.9%	6.3%	22% (11 to 31)	73 (52 to 141)

\*Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from odds ratios in article using a fixed-effects model.

## COMMENTARY

An unexpected observation from initial, large RCTs of ACE inhibitors was a substantial reduction in MI, which seemed to be unrelated to the effects on systolic function. The angiotensin system plays an active vasculopathic role contributing to the development and progression of atherosclerosis (1), and subsequent RCTs have investigated the role of ACE inhibitors in the secondary prevention of CAD events. Since these agents are effective in reducing blood pressure (BP) as well as protecting the arterial wall, the responsible mechanisms of action in reducing CAD events may be difficult to ascertain.

Danchin and colleagues investigated the protective role of ACE inhibitors in the prevention of CAD events in patients with CAD and no LVSD. The authors' investigation included assessing differences in baseline risk, effect on BP reduction, individual pharmacologic properties of the ACE inhibitors, and dosage. They noted that the 50% inhibitory level for plasma ACE was higher than the dosage used in many of the trials, and commented further that the 2 RCTs with definitely positive results used the highest doses of ACE inhibitor. However, these higher doses would also probably lower BP more than the lower doses, and the beneficial effect may have been due simply to BP reduction and not to vascular protection.

Subtle but important differences in risk status among the patient

populations may also exist and may be difficult to ascertain and adjust for in statistical models. For example, despite apparent similarity in risk status of patients in the negative PEACE trial and the positive HOPE and EUROPA trials, the placebo group in the PEACE trial had a lower event rate than the active treatment group in the HOPE trial. It may be that the cumulative effects of the multiple vasculoprotective agents used (e.g., statins, β-blockers, and aspirin) ultimately result in an asymptote of vascular stability that can no longer be improved with introduction of new agents.

The details of the studies provided no clear answers to explain the inconsistencies observed among the different studies. The role of the angiotensin system contributing to vascular pathologic conditions is clear, however. Certainly more study is needed to confirm that ACE inhibitors confer vascular protection. Despite lack of clarity on the underlying mechanism(s), the evidence concerning the benefits of ACE inhibitors for patients with acute coronary events is mounting, regardless of whether they have heart failure or LVSD.

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## Reference

1. Ferrario CM, Strawn WB. Am J Cardiol. 2006;98:121-8.