

Review: Concomitant aspirin use does not reduce the effectiveness of ACE inhibitors

Teo KK, Yusuf S, Pfeffer M, et al. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet*. 2002;360:1037-43.

QUESTION

In patients with coronary artery disease, left ventricular dysfunction, or heart failure at high risk for cardiovascular events, does the concomitant use of aspirin reduce the benefits of angiotensin-converting enzyme (ACE) inhibitor treatment?

DATA SOURCES

{Studies were identified by searching MEDLINE, scanning bibliographies of review articles, and contacting researchers and colleagues in the pharmaceutical industry.}*

STUDY SELECTION

Studies were selected if they were randomized controlled trials comparing ACE inhibitors with placebo and included > 1000 patients.

DATA EXTRACTION

Individual patient data were extracted on baseline characteristics including receipt of aspirin, prognostic factors, ACE inhibitor regimen, and follow-up. Clinical outcomes were death, myocardial infarction or reinfarction, hospital admission for congestive heart failure, stroke, and revascularization. The main outcome was a composite of all these major cardiovascular events.

MAIN RESULTS

6 randomized, double-blind, placebo-controlled trials (22 060 patients) were included. 14 410 patients received aspirin at baseline, and 7650 did not. A post hoc analysis of 2 trials (Studies of Left Ventricular Dysfunction [SOLVD] treatment and prevention trials) generated the hypothesis that aspirin might reduce the benefits of ACE inhibitors. The hypothesis was tested in 3 post-MI trials and the Heart Outcomes and Evaluation (HOPE) trial. Overall, ACE inhibitor treatment reduced the combined outcome of major vascular events with no difference between groups taking and not taking aspirin (relative risk reduction 20% vs 29%, $P = 0.07$). The benefit of ACE

inhibitors and lack of difference between baseline aspirin use and nonuse was seen in all trials (Table).

CONCLUSION

In patients with coronary artery disease, left ventricular dysfunction, or heart failure at high risk for cardiovascular events, concomitant use of aspirin does not reduce the benefits of angiotensin-converting enzyme inhibitor treatment.

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*Flather MD, Yusuf S, Køber L, et al. *Lancet*. 2000;355:1575-81.

Benefit of ACE-inhibitor therapy in high-risk patients taking aspirin vs no aspirin on a composite of major vascular events†

Trial	Odds ratio (99% CI)	
	Aspirin	No aspirin
Studies of left ventricular dysfunction	0.78 (0.64 to 0.96)	0.69 (0.58 to 0.83)
Post-MI trials	0.79 (0.65 to 0.95)	0.67 (0.49 to 0.92)
Heart Outcomes Prevention and Evaluation	0.81 (0.71 to 0.93)	0.75 (0.60 to 0.95)
All trials	0.80 (0.73 to 0.88)	0.71 (0.62 to 0.81)

†MI = myocardial infarction. Vascular events were death, MI or reinfarction, hospital admission for congestive heart failure, stroke, and revascularization. Mean follow-up ranged from 15 to 54 months. CI defined in Glossary.

COMMENTARY

Aspirin and ACE inhibitors are purported to exert favorable effects on the course of heart disease through independent mechanisms: aspirin by reducing thrombotic events and ACE inhibitors by slowing structural remodeling in the vasculature and heart. However, other actions may overlap, such as anti-inflammatory effects and their ability to prevent myocardial infarction. Therefore, the effects of aspirin and ACE inhibitors should be at least in part additive, but concern has been raised about interference of aspirin with the pharmacologic action of ACE inhibitors. Since ACE inhibitors stimulate production of prostaglandin and other vasodilators that may slow structural remodeling, aspirin might interfere with this favorable effect. Reduced effectiveness could therefore be a true pharmacologic interaction or, alternatively, the result of a partial clinical benefit of aspirin that overlaps the clinical benefit of ACE inhibitors.

The review by Teo and colleagues analyzed large-scale trials that allowed patients to use aspirin and has confirmed long-term clinical efficacy of ACE inhibitors in patients receiving aspirin. Although a

significant interaction of aspirin on efficacy could not be identified, the marginally significant P value leaves open the possibility of some clinically significant interaction. Nonetheless, the data support the widely held belief that even if aspirin reduces the apparent clinical effectiveness of ACE inhibitors, its influence is minor at best and should not discourage use of the 2 drugs together. Such a post hoc review can never achieve the strength of a prospective randomized trial, but the data should reduce any concern about dual efficacy. The appropriate study would compare not only outcome results, which are influenced by the independent clinical outcome effects of the drugs, but also explore the mechanism of ACE inhibitors (echocardiography results, vascular wall thickness, and arterial compliance) to determine if aspirin inhibits the drug's favorable action on structure. Until such a study is done, at present the drugs can be used comfortably together.

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