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Using aspirin and ACE inhibitors in combination: Why the hullabaloo?

■ ABSTRACT

Observational studies indicate that aspirin may counteract the beneficial effect of angiotensin-converting enzyme (ACE) inhibitors, but the data are not yet sufficient for making firm recommendations. We review the available data and offer tentative conclusions.

■ KEY POINTS

Aspirin blocks production of prostaglandins, potentially counteracting or reducing the beneficial effects of ACE inhibitors.

Evidence of an adverse interaction between aspirin and ACE inhibitors comes from retrospective analyses of studies that were not designed to examine this issue.

For patients with heart failure who take an ACE inhibitor and aspirin, it may be appropriate to limit the aspirin dosage in long-term therapy to less than 100 mg/day, since larger doses have not been proven more effective.

S HOULD WE AVOID giving aspirin and angiotensin-converting enzyme (ACE) inhibitors concomitantly? Both are often used in combination in patients with coronary artery disease, especially if it is complicated by heart failure. Yet investigators have raised concerns about a possible adverse interaction between aspirin and ACE inhibitors in patients with heart failure,[1,2] and perhaps even in patients without heart failure.

Given the utility of both these drugs in treating heart disease, theories about a potential negative interaction have created quite a hullabaloo. This is especially true since some of the data pointing toward a negative interaction are seemingly strong, but based on retrospective analyses of studies designed to examine other issues.

In this review, we examine the basis for this concern and discuss the implications of current data for clinical practice.

■ ASPIRIN AND ACE INHIBITORS ARE BENEFICIAL BY THEMSELVES

After an acute myocardial infarction (MI), aspirin reduces short-term mortality by approximately 25%.[3] Its continued use after the acute phase of an MI may reduce the incidence of a recurrence and of death from vascular events.[4]

ACE inhibitors reduce the mortality rate both in the short term and in the long term after an MI in patients with clinical heart failure or depressed left ventricular function.[5,6] They also reduce the mortality rate by a small but statistically significant amount when they are started early after an MI and continued for several weeks in patients not selected by left

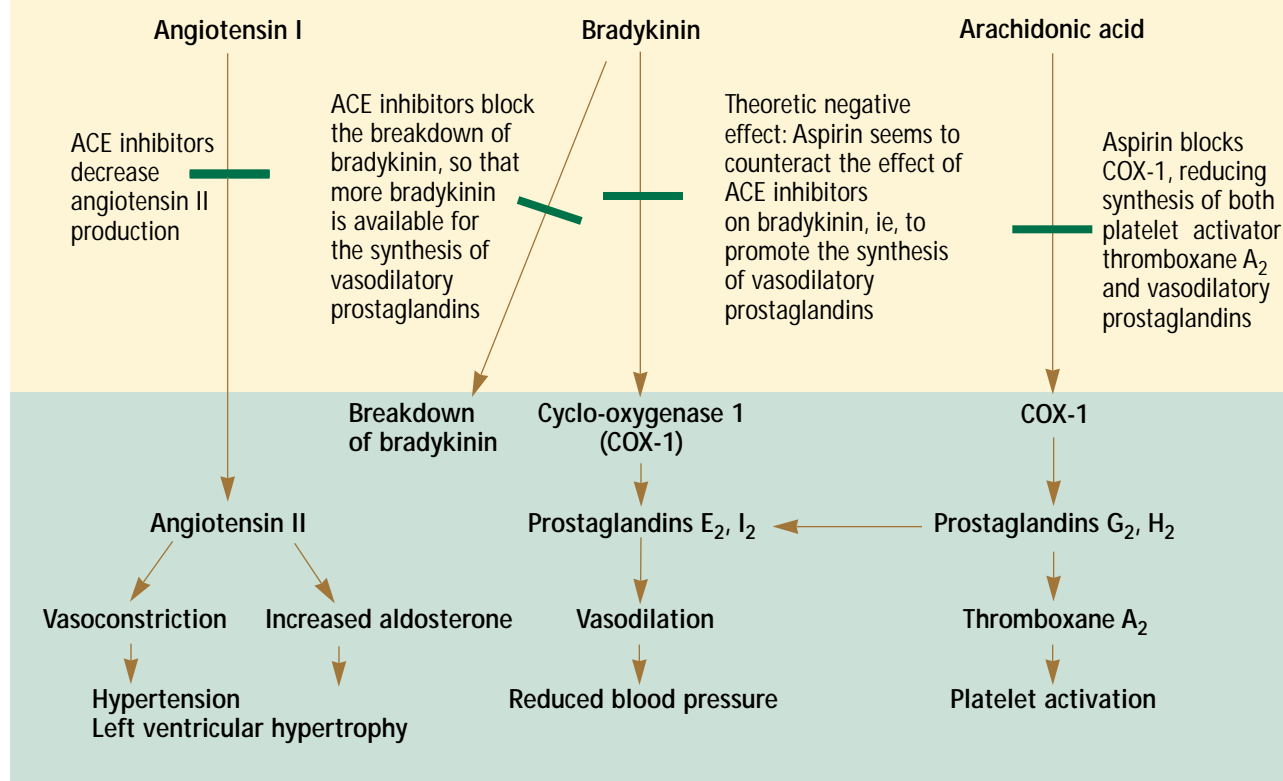## If aspirin counteracts ACE inhibitors, what is the mechanism?

FIGURE 1. Theoretical interaction between aspirin and angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors decrease angiotensin II production and inhibit breakdown of bradykinin. Bradykinin stimulates vasodilator prostaglandins via a cyclo-oxygenase–dependent pathway. Aspirin inhibits cyclo-oxygenase-1 (COX-1), thereby reducing synthesis of vasodilatory prostaglandins.

ventricular function.[7,8]

In addition, the ACE inhibitor ramipril was recently shown to reduce death and vascular events in patients who either had known vascular disease or were at high risk for vascular events.[9]

■ MECHANISMS OF POTENTIAL INTERACTION

Aspirin is believed to reduce death and reinfarction in MI patients by reducing platelet activation. Platelets produce the vasodilatory prostaglandins PGE_2 and PGI_2 and the platelet activator thromboxane A_2, with the cyclo-oxygenase enzyme type-1 (COX-1) as a common pathway.[10] Aspirin irreversibly inhibits COX-1, simultaneously decreasing production of PGE_2, PGI_2, and thromboxane A_2. The vascular endothelium also produces PGE_2 and PGI_2, and aspirin inhibits this production as well (FIGURE 1).

ACE inhibitors probably produce their favorable effects through several mechanisms. They reduce plasma levels of the vasoconstrictor angiotensin II by blocking its conversion from its precursor, angiotensin I. They also inhibit breakdown of the potent vasodilator bradykinin,[11] which stimulates prostaglandin synthesis. Research suggests that the increase in bradykinin is the predominant mechanism responsible for the antihypertensive effect of ACE inhibitors.[12,13] Any reduction in the ability to produce vasodilatory prostaglandins—as occurs with aspirin therapy—may also reduce ACE inhibitor activity (FIGURE 1).

Prostaglandins may be a compensatory response to heart failure

Vasodilatory prostaglandins are important in heart failure.[14] A landmark study[15] found that patients with severe heart failure had plasma levels of the vasodilatory prostaglandins PGI_2 and PGE_2 that were 3 to 10 times higher than in healthy subjects. These elevations were thought to be a compensatory response to elevated levels of vasoconstrictors such as angiotensin II, norepinephrine, and vasopressin. When given indomethacin (an inhibitor of prostaglandin synthesis), patients with the most severe heart failure had significant hemodynamic worsening (a lower cardiac index and a higher pulmonary artery wedge pressure) as assessed by right heart catheterization.

At the time of this study, none of the major trials of ACE inhibitors had been conducted, and there were few data supporting the use of aspirin. However, the study observations gave rise to further investigation as the neurohormonal hypothesis of heart failure was being developed.

Subsequent physiologic studies looked directly at the concomitant use of aspirin and ACE inhibitors in patients with heart failure. Hall et al[16] observed the acute hemodynamic effects of enalapril 10 mg in 18 patients with heart failure before and after giving them aspirin 350 mg. Enalapril without aspirin had significant beneficial hemodynamic effects, decreasing systemic vascular resistance, left ventricular filling pressure, and total pulmonary resistance while increasing cardiac output. Aspirin abolished all of these changes. However, similar studies yielded inconsistent results, perhaps because they used different aspirin doses or the duration of treatment with ACE inhibitors was different.[17–19]

Further complicating the issue, some studies suggested another mechanism of interaction.[19,20] ACE inhibitors also inhibit platelet activation, mainly by reducing thromboxane A_2. The reductions seen in ischemic events with the use of ACE inhibitors in multiple trials would be consistent with this process.[6,9,21–23] If this mechanism really does mediate a reduction in ischemic events, then one would expect that aspirin would be less beneficial in patients taking ACE inhibitors because the ACE inhibitor would already be inhibiting platelet activation.

■ EVIDENCE FROM CLINICAL TRIALS

Trials in heart failure

The SOLVD trial (Studies of Left Ventricular Dysfunction)[22,23] randomized patients with left ventricular dysfunction to receive either the ACE inhibitor enalapril or placebo. The results: patients who received enalapril had significantly lower rates of death, congestive heart failure, and MI.

However, a retrospective analysis of the SOLVD data[2] showed something interesting: although antiplatelet agents (almost exclusively aspirin) were independently associated with reduced mortality, the addition of enalapril did not decrease the mortality rate in patients receiving antiplatelet agents, and conversely neither did the addition of aspirin in patients receiving enalapril.

This analysis supported the hypothesis of a complex interaction between aspirin and ACE inhibitors in heart failure patients, as anticipated by the hemodynamic studies. However:

The SAVE trial (Survival and Ventricular Enlargement),[6] in patients with left ventricular dysfunction, did not reveal such an interaction.

The AIRE trial (Acute Infarction Ramipril Efficacy)[5] showed less benefit from an ACE inhibitor in patients receiving aspirin vs not receiving aspirin, but the trend was not statistically significant.

All in all, most of the hemodynamic data and some of the retrospective clinical data support the argument that a clinically important interaction exists between aspirin and ACE inhibitors in patients with heart failure.

Studies in ischemic heart disease

Almost all studies of ACE inhibitors in ischemic heart disease showed beneficial effects. Some, however, suggested a clinically significant adverse interaction between aspirin and ACE inhibitors.

CONSENSUS II (the second Cooperative New Scandinavian Enalapril Survival Study)[24] was designed to examine the

Most evidence so far is from observational studies

effect of ACE inhibitors given early after an acute MI but was stopped early because of a lack of benefit and of possible harm from this therapy, which included intravenous enalaprilat.

Nguyen et al[25] examined the data retrospectively using logistic regression analysis and found evidence of an interaction between enalapril and aspirin. At the end of the study, among patients not receiving aspirin, the odds ratio for mortality was 0.86 (95% CI 0.63–1.16) in the enalapril group, meaning there was a trend toward enalapril being better than placebo, although it was not statistically significant. However, among patients receiving aspirin, the odds ratio for mortality in the enalapril group was 1.23 (95% CI 0.99–1.53), meaning that there was a trend toward placebo being better than enalapril if the patients were taking aspirin. The *P* value for the interaction between enalapril and aspirin was .047.

GUSTO-1 (the Global Utilization of Streptokinase and TPA for Occluded Arteries) compared various thrombolytic regimens in more than 40,000 patients with acute MI. We retrospectively analyzed the GUSTO-1 data on the effect of aspirin, ACE inhibitors, and their combination on the outcome of patients alive at 30 days who did not have congestive heart failure.[26] As expected, significant differences in baseline characteristics were observed between patients who were and were not discharged on ACE inhibitor therapy. After adjusting for these differences by regression analysis, we found aspirin to be independently associated with a lower 1-year mortality rate, while ACE inhibitors did not have a statistically significant effect.

However, patients receiving both aspirin and an ACE inhibitor had a *higher* mortality rate, even after we excluded patients who were at higher risk for left ventricular dysfunction.[26] A weakness of this study was that left ventricular functional status was unknown for most patients.

EPILOG (the Evaluation of PTCA to Improve Long-term Outcome by c7E3 GPIIb/IIIa Receptor Blockade), on the other hand, did measure left ventricular function. And when we analyzed the EPILOG data retrospectively, we got similar results even after adjusting for ventricular function.[26]

A retrospective analysis of another trial, however, did find aspirin to be effective in patients with coronary artery disease treated with ACE inhibitors. In the **Benzafibrate Infarction Prevention (BIP) trial**, 1,247 patients were taking ACE inhibitors, and their records were retrospectively examined with respect to aspirin use.[27] (As in the GUSTO-I and EPILOG trials, neither aspirin nor ACE inhibitors were randomized.) At 5 years, the mortality rate was 19% in patients taking aspirin plus an ACE inhibitor vs 27% in patients taking an ACE inhibitor without aspirin (*P* < .001). The benefit extended to patients with heart failure: 24% vs 34%; *P* = .001. Since only patients taking ACE inhibitors were studied, it was unknown whether the magnitude of effect of aspirin was similar for those who were and were not on ACE inhibitors.

Limitations of clinical data

A limitation of all these studies is that the decisions to use aspirin or ACE inhibitors or both were not randomized: ie, patients were not assigned to a combination of both drugs by random chance. Because these drugs are prescribed for a variety of indications that often cannot be adequately captured on clinical trial case report forms, serious confounding factors cannot be excluded.

■ CAUTIOUS CONCLUSIONS, RECOMMENDATIONS

Current data indicate that aspirin can and probably does interfere with the production of vasodilatory prostaglandins in patients with heart failure. Since ACE inhibitors rely in part on these prostaglandins to lower blood pressure, aspirin likely attenuates the antihypertensive potential of ACE inhibitors.

On the other hand, because current evidence of an adverse interaction between ACE inhibitors and aspirin is based entirely on observational analyses in which confounding factors may not have been entirely accounted for, it is premature to make any definitive recommendations. Prospective randomized trials need to be done to answer this very important question with far-reaching public health ramifications.

Use lower daily doses for long-term aspirin therapy

With these caveats in mind, we offer the following recommendations.

Recommendations for patients with heart failure

Limit the dosage of long-term aspirin therapy. Although ACE inhibitors and aspirin remain first-line therapy for patients with ischemic cardiomyopathy, we suggest limiting the dosage of long-term aspirin therapy to 100 mg/day or less. Lower aspirin doses may mitigate the adverse interaction.[17] In any case, we have no clear evidence that larger doses are more effective for secondary prevention.[4] The lower dose is certainly reasonable, especially if patients have poorly controlled hypertension or severe heart failure.

Do not prescribe aspirin long-term to patients without coronary disease who have heart failure and are taking an ACE inhibitor, because there is no evidence of benefit.

Consider alternative antiplatelet agents such as clopidogrel if a lower dose of aspirin was not effective (ie, if a patient had an ischemic event while on aspirin therapy).

Avoid nonsteroidal anti-inflammatory drugs, which may have some of the same effects as aspirin, in patients with ischemic and nonischemic cardiomyopathy, especially if they are taking ACE inhibitors. Further investigation into this potential interaction for patients with ischemic heart disease without heart failure should be undertaken.

COX-2 inhibitors may be a reasonable alternative to traditional nonsteroidal anti-inflammatory drugs for heart failure patients.

Given that the platelets do not express COX-2, and given that COX-2 is usually not detectable before acute inflammation, it is in theory possible that COX-2 antagonists would not interact with ACE inhibitors to a similar degree as traditional nonsteroidal anti-inflammatory drugs.[28]

Nonetheless, no one knows whether an adverse interaction between COX-2 antagonists and ACE inhibitors exists in patients with heart failure or coronary disease. Therefore, prudence would dictate that, until more is known, these two types of agents should probably not be used together.

Recommendations for patients with ischemic heart disease

Whether to use aspirin and ACE inhibitors together in all patients with ischemic heart disease is much less clear. We have some evidence that the benefits of aspirin may not be as great in patients treated with ACE inhibitors, but the net effect from the combination is not clear. While retrospective studies suggest that the net effect may be negative, more recent studies suggest the opposite. Therefore, a recommendation to change current practice— ie, using both ACE inhibitors and aspirin together without worrying about a possible interaction—would be premature. However, as data from comparisons between ACE inhibitors and angiotensin II-receptor blockers in different populations become available, the issue of this interaction may become less vital, since effective alternatives to both aspirin and ACE inhibitors may be available.

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