Does Aspirin Attenuate the Beneficial Effects of Angiotensin-Converting Enzyme Inhibition in Heart Failure?

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Ischemic heart disease is the most common underlying cause of congestive heart failure, and thus aspirin (acetylsalicylic acid [ASA]) and angiotensin-converting enzyme (ACE) inhibitors are commonly used together for treatment in this setting. The issue of possible attenuation of the effect of ACE inhibitors by ASA has been an area of intense debate. Currently, it is perceived that a significant part of the beneficial effect of ACE inhibitors is related to augmentation of bradykinin levels, which among other effects stimulate the release of prostacyclin. Aspirin, on the other hand, inhibits the production of prostacyclin by blocking cyclooxygenase. Prostaglandins play an important endogenous vasodilatory role and counteract the enhanced peripheral vasoconstriction state in congestive heart failure. Thus, the counteracting effect of ASA on the augmentation of prostacyclin synthesis by ACE inhibitors could result in a potential reduction of the beneficial effects of the ACE inhibitor’s and could be of great importance. This article reviews reports from large clinical trials pertaining to this issue and relates their findings to the currently available theoretical bases for support of the counteracting effect of ASA on augmentation of prostacyclin synthesis by ACE inhibitors. The clinical implications of such an interaction are discussed.

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Angiotensin-converting enzyme (ACE) inhibitors have been one of the most important advances in the treatment of congestive heart failure (CHF). They have been demonstrated to produce beneficial hemodynamic, symptomatic, and prognostic effects in patients with CHF and to improve both the function and the survival of these patients. As a group, ACE inhibitors have been clearly documented to be similar in their effect on conversion of angiotensin I to angiotensin II and have a similar therapeutic profile in the treatment of CHF. However, it appears that the benefit of ACE inhibition cannot be entirely explained by the inhibition of the formation of angiotensin II. It has been found that although even very small doses of ACE inhibitor can completely inhibit ACE and angiotensin II production initially, progressively larger doses are required to maintain ACE inhibition. Also, ACE inhibitors appear to produce persistent benefits, even though circulating levels of angiotensin II (initially suppressed) gradually return to those seen before treatment.

Angiotensin-converting enzyme is also identical to kininase II, and as such degrades kinins. Therefore, ACE inhibitors reduce the degradation of bradykinin, a potent vasodilator, which among other mechanisms acts through the enhancement of synthesis of vasodilatory prostaglandins. It is thought that this mechanism is responsible for a significant portion of the beneficial cardiac effects of ACE inhibitors.

The important role of aspirin (acetylsalicylic acid [ASA]) in the prevention of occlusive vascular disease has been clearly established, and its use in the treatment and prevention of coronary artery disease is of primary importance. Aspirin exerts its inhibitory effect on platelet aggregation through the blockade of the enzyme cyclooxygenase and thus inhibits the production of prostaglandins. This effect of attenuation of prostaglandin synthesis by ASA is the opposite of the effect exerted by ACE inhibitors.
Considering the fact that ischemic heart disease is the most common underlying cause of CHF, the concomitant use of these 2 fundamental agents, ASA and ACE inhibitors, is very common. Thus, the counteracting effect of ASA on the augmentation of prostacyclin synthesis by ACE inhibitors could result in a potential reduction of the beneficial effects of ACE inhibitors and could be of great importance.

In this article, we review reports from large clinical trials whose findings pertain to the counteracting effect of ASA on the augmentation of prostacyclin synthesis by ACE inhibitors and relate those findings to the currently available theoretical bases for support of such an interaction.

THEORETICAL BASES FOR ATTENUATION OF EFFECTS OF ACE INHIBITION BY ASA

Prostaglandins serve as an important endogenous vasodilator mechanism in circulatory homeostasis and are thought to constitute an important counter-regulatory pathway to the enhanced peripheral vasoconstriction state of heart failure. Dzau et al observed that mean circulating levels of vasodilating prostaglandins were 3 to 10 times higher in patients with CHF (severe CHF with hyponatremia) than in normal individuals, and that their plasma levels correlated with the degree of activation of the renin angiotensin system. Thus, one could expect that the response to inhibition of the prostaglandin synthetic pathway might be different in patients with coronary disease and preserved left ventricular function as opposed to those with significant ventricular dysfunction. Administration of indomethacin (which also inhibits cyclooxygenase) to patients with heart failure results in vasoconstriction and a fall in cardiac output, renal blood flow, and glomerular filtration rate. Effects are more prominent in patients with hyponatremia.

The contribution of bradykinin to the effect of ACE inhibition has been the subject of debate. It is possible that the inhibitory effect of ACE inhibitors on the degradation of bradykinin is responsible for a significant portion of the beneficial cardiac effects of ACE inhibitors. Bradykinin is a potent vasodilator that, among other vasodilating substances, enhances the release of prostacyclin. This could be a significant mechanism of action of ACE inhibitors, counteracting the neurohumoral changes occurring in patients with heart failure, and thus the concomitant use of prostaglandin synthesis inhibitors could attenuate the beneficial effects of ACE inhibition. Several long-term studies address the possibility of such an interaction.

Townsend et al showed that single doses of indomethacin attenuated the increase in cardiac output and renal blood flow in response to captopril therapy, but did not attenuate the increase in forearm or calf blood flow. Hall et al noted that a single dose of ASA, 350 mg, attenuated the decrease in systemic vascular resistance, left ventricular filling pressure, and total pulmonary resistance as well as the increase in cardiac output elicited by enalapril maleate therapy. Nashimura et al showed that indomethacin therapy attenuated the peripheral hemodynamic effects of captopril therapy in patients with heart failure. These findings were not confirmed by studies of van Wijngaarden et al, who found that even though the combination of ASA and captopril reduced the levels of prostaglandins, there was no discernible difference in the hemodynamic effects of captopril therapy alone or with ASA. The fact that a lower dose of ASA (<300 mg) was used in this study might explain the discrepancy, as other authors who used low doses of ASA (<300 mg) also did not find a significant hemodynamic interaction. Low doses of ASA have been shown to inhibit thromboxane synthesis, but higher doses of ASA (>325 mg) are required to inhibit synthesis of vasodilating prostaglandins. Therefore, a higher dose of ASA would be necessary to inhibit the presumed vasodilating prostaglandin-mediated hemodynamic effect of ACE inhibitors. Thus, prostaglandin synthesis would not be inhibited by lower doses of ASA (80-100 mg), which would still exert the intended antiplatelet action through blockade of thromboxane synthesis.

On the other hand, Evans et al found that ASA, 325 mg, had no adverse effects on hemodynamic, neurohumoral, or renal function in heart failure. Furthermore, ASA had no adverse effect on the acute response to enalapril therapy.

Spaulding et al showed that enalapril therapy reduced systemic vascular resistance more effectively when given in combination with ticlopidine hydrochloride, a potent antiplatelet agent not affecting prostaglandin synthesis, than when combined with ASA. The authors suggested that in patients with well-established indications for ACE inhibitors and platelet inhibition, alternative antiplatelet agents to ASA might be of greater efficacy.

The currently available data on the acute hemodynamic effect of antagonism of ACE inhibitors by ASA remain conflicting and must be interpreted with caution, especially with regard to the long-term concomitant administration of ASA and ACE inhibitors.

EVIDENCE FROM LARGE CLINICAL TRIALS

The issue of possible attenuation of the effect of ACE inhibitors in heart failure by ASA became a topic of intense debate following the reports of the possibility of such an interaction from the Studies of Left Ventricular Dysfunction (SOLVD). These results showed that in contrast to the overall effect, enalapril therapy had no beneficial effect on mortality among those taking ASA. Other trials also reported a tendency toward reduced benefit from ACE inhibition among patients taking ASA, although the existing data are still controversial and inconclusive.

Nguyen et al conducted a retrospective subgroup analysis of data from the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) and showed that the enalapril-ASA interaction was a significant predictor of mortality at the end of the study, and thus concluded that the effect of enalapril therapy was less favorable among pa-
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*APA indicates antiplatelet agent; MI, myocardial infarction.

Patients taking ASA than among patients not taking ASA at baseline. At the same time, the authors did not find a significant interaction with regard to nonfatal major events. The finding of long-term enalapril-ASA antagonism seems to be consistent with the main effect of enalapril therapy, ie, the reduction of progression to CHF. The retrospective character of this study does impose significant limitations on the interpretation of the data. Also, as the authors of this study comment, it is possible that the non-ASA group consisted of a sicker population. Angiotensin-converting enzyme inhibitors have been shown to be more effective in patients with more advanced heart failure.32,33 Other authors argue that the patients receiving ASA were more likely to have had previous coronary disease and, more importantly, carotid disease, thus putting these patients at an increased risk for cerebral effects of acute blood reduction in the early acute infarct period.34

On the other hand, Isnard et al35 studied 317 patients with left ventricular dysfunction (left ventricular ejection fraction <35%) and found that over a mean period of 5.7 years ASA therapy exerted favorable effects on long-term prognosis for these patients with ischemic left ventricular systolic dysfunction, whether they were treated with ACE inhibitors or not.35

Despite this, it is also worth noting that while ASA therapy has been shown to improve both short- and long-term prognosis for patients with coronary artery disease and well-preserved left ventricular function,1-13 its role in high-risk patients with significant ventricular damage is uncertain and remains an area of debate. This is evidenced in the reports of the Aspirin Myocardial Infarction Study (AMIS)36 and Persantine-Aspirin Reinfarction Study II (PARIS II)37 trials on the influence of baseline characteristics on the outcomes. The AMIS trial, one of the largest in terms of number of patients studied, number of years conducted, and duration of trial-agent exposure, showed a trend toward increased mortality with ASA therapy in most subgroups studied.36 The PARIS trial showed an overall trend toward benefit with ASA therapy, but showed an opposite trend among patients with heart failure or major ventricular dysfunction.37 Similarly, the data from Swedish Angina Pectoris Aspirin Trial (SAPAT) supported the long-term use of ASA in patients with coronary artery disease and well-preserved ventricular function, but at the same time showed that ASA therapy could possibly be harmful in patients with major ventricular damage.12 On the other hand, Oosterla et al38 after conducting a post hoc analysis of the Captopril and Thrombolysis Study (CATS), found that ASA therapy did not attenuate the acute and long-term effects of ACE inhibition after acute myocardial infarction, but rather independently reduces left ventricular dilation after myocardial infarction (Table).29,38

These results provide interesting and provocative data not only with regard to a possible negative interaction between ACE inhibitors and ASA, but also with regard to the role of ASA therapy in heart failure in general. It is important to realize that until further studies clarify these issues, the evidence for harm or benefit from ASA therapy in patients with heart failure remains inconclusive.

**The Role of Pulmonary Factors in the Effect of ACE Inhibitor Efficacy and Their Counteraction by ASA Therapy**

Pulmonary factors appear to be important determinants of exercise intolerance in patients with heart fail-
It has been described that patients with chronic severe cardiomyopathy tend to have predominantly restrictive lung disease. The reduction in pulmonary diffusing capacity for carbon monoxide (DLCO) has also been well documented in patients with chronic heart failure. It appears that reduced alveolar-capillary membrane diffusing capacity is the major component of impaired pulmonary gas transfer, and this has been shown to correlate well with the maximal exercise capacity and the functional status of patients.

Angiotensin-converting enzyme is highly concentrated on the luminal surface of the lung blood vessels. As a consequence, pulmonary circulation is the major conversion site of angiotensin I to angiotensin II, as well as being a site for the inactivation of circulating bradykinin during its passage through the lung. As mentioned earlier in this article, bradykinin is a potent vasodilator that enhances the release of prostacyclin and other vasodilating substances. Angiotensin-converting enzyme inhibitors reduce the exposure of the lung vessels to angiotensin II and simultaneously potentiate the influence of bradykinin and vasodilating prostaglandins within the lungs. As commented earlier, bradykinins are assumed to play a significant part in the mechanism of action of ACE inhibitors in heart failure.

Guazzi et al showed that enalapril therapy improved DLCO and lung volumes (forced expiratory volume in 1 second and maximal voluntary ventilation), which were reduced in patients with heart failure compared with control subjects. Changes in DLCO were counteracted by ASA therapy (325 mg/d). The authors concluded that ACE inhibition exerts a modulatory influence on pulmonary function, which at least in part is mediated through prostaglandins, whose primary feature is an improvement in alveolar-capillary membrane diffusing capacity and functional capacity.

In another study, Guazzi et al confirmed the above findings and also reported that enalapril therapy caused an improvement in peak exercise oxygen uptake that was counteracted by ASA therapy. In the same study, it was shown that losartan potassium, an angiotensin receptor (AT1) blocker, resulted in a comparable improvement in VO_2,max and exercise tolerance in patients with heart failure. Losartan, however, does not affect DLCO significantly, and its effect was not counteracted by ASA therapy. The authors concluded that AT1 receptor blockers may represent an alternative to or even an advance beyond ACE inhibitors for the treatment of heart failure because of their similar efficacy and lack of counteraction with ASA therapy.

It appears that decreased alveolar membrane diffusing capacity is a major reason for impaired pulmonary gas transfer in patients with heart failure, and this appears to correlate with maximum exercise capacity and the functional status of patients. Prostaglandin-mediated functional improvement of the alveolar-capillary membrane appears to contribute to the beneficial effect of ACE inhibition in heart failure and may be negated by ASA administration.

**CONCLUSION**

The data that support the evidence for a negative interaction between ASA and ACE inhibitors in patients with heart failure are still not adequate. The clinical trials that report such an interaction were not specifically designed to analyze this issue, but rather were conducted as retrospective analyses of data from existing trials. Existing data documenting the interaction of hemodynamic and pulmonary effects of ACE inhibitors by ASA and the reports from clinical trials do not provide sufficient data to clarify this issue. Until more definite data become available, it might be prudent to lower the dose of ASA to 80 to 100 mg in patients with heart failure who are concurrently treated with ACE inhibitors. Alternatively, either an effective antiplatelet agent, such as clopidogrel bisulfate or ticlopidine hydrochloride, could be used in combination with ACE inhibitors or, in the course of therapy, ACE inhibitors could be titrated upward to overcome the potential attenuation of full-dose ASA therapy (≥325 mg/d). The use of an AT1 blocker in place of an ACE inhibitor may also represent an alternative treatment.

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