

Acetylsalicylic Acid and Angiotensin-Converting Enzyme Inhibitors in Heart Failure: A Serious Hemodynamic Interaction? A Systematic Critique

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ABSTRACT

The potential interaction between acetylsalicylic acid and angiotensin-converting enzyme inhibitors in patients with heart failure has received considerable attention lately. Opposing effects on prostaglandin synthesis and metabolism form the theoretical basis of an interaction. A review of the available literature revealed conflicting data from animal studies, human pharmacological studies, and clinical outcome studies. This paper illustrates a possible approach to examining complex and contradictory evidence, through systematic review and critique of the relevant studies. In summary, no substantial clinical evidence could be found that acetylsalicylic acid diminishes the benefits of angiotensin-converting enzyme inhibitors in heart failure.

Key words: angiotensin-converting enzyme inhibitors, captopril, enalapril, drug interaction, acetylsalicylic acid, ASA, Aspirin, heart failure

RÉSUMÉ

L'interaction potentielle entre l'acide acétylsalicylique et les inhibiteurs de l'enzyme de conversion de l'angiotensine chez les insuffisants cardiaques a retenu beaucoup l'attention dernièrement. Des effets opposés sur la synthèse et le métabolisme des prostaglandines constituent le fondement théorique de cette interaction. L'examen de la documentation, notamment d'études chez l'animal, d'études pharmacologiques chez l'humain et d'études d'effets cliniques, ont mis au jour des données contradictoires. Cet article présente une façon d'analyser ces données contradictoires et complexes, au moyen d'un examen et d'une critique systématiques des études pertinentes. En résumé, il n'existe aucune donnée clinique substantielle qui montre que l'acide acétylsalicylique diminue les effets favorables des inhibiteurs de l'enzyme de conversion de l'angiotensine dans l'insuffisance cardiaque.

Mots clés : inhibiteurs de l'enzyme de conversion de l'angiotensine, captopril, énalapril, interaction médicamenteuse, acide acétylsalicylique, ASA, Aspirin, insuffisance cardiaque

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INTRODUCTION

The safety of acetylsalicylic acid (ASA) in patients receiving angiotensin-converting enzyme (ACE) inhibitors for heart failure is a controversial topic. The results of several animal studies and short-term hemodynamic studies in patients have been contradictory. Some studies have indicated that ASA reduces the beneficial hemodynamic effects of ACE inhibitors in heart failure, whereas others have failed to demonstrate any interaction. Standard drug interaction textbooks refer to a "possible" hemodynamic interaction between ASA and ACE inhibitors in patients with heart failure.^{1,2}

The large amount of research devoted to this potential interaction reflects its clinical importance. Heart failure is a severe, progressive condition associated with an estimated 1-year mortality rate of 10% to 20% and a mean life expectancy of approximately 50% at 5 years.³ ACE inhibitors have repeatedly been demonstrated to improve survival or symptoms in patients with asymptomatic, moderate, and severe heart failure.^{4,6} As well, ACE inhibitors have been associated with lower mortality rates, as well as lower risk of severe heart failure in patients with left ventricular dysfunction after myocardial infarction.^{7,8} Ischemic heart disease is a major cause of heart failure,^{3,9} and low-dose ASA therapy leads to lower morbidity and mortality rates among patients with this condition.^{10,11} Therefore, both low-dose ASA and ACE inhibitors are likely to be prescribed for patients with ischemic heart disease and heart failure. As eloquently expressed in a recent review,¹² such patients could be "torn between two lovers" if these 2 therapies interact.

In this article the authors review and systematically critique the available evidence to demonstrate an approach to assessing conflicting data. The focus is on the potential hemodynamic interaction between low-dose ASA and ACE inhibitors in heart failure. This review does not include potential interactions involving higher, antiarthritic doses of ASA, other nonsteroidal anti-inflammatory drugs (NSAIDs), renal changes or interactions, changes in pulmonary function, or effects on blood pressure in the absence of heart failure. Data for patients who have already experienced myocardial infarction were included, because the prevention of heart failure is thought to be one of the main mechanisms by which ACE inhibitors exert their beneficial effects on mortality rate in this setting.¹³

METHODS

A thorough search of the published medical literature was performed, including searches of MEDLINE (January 1966 to January 2000), EMBASE (January 1982 to January 2000), and Reactions (January 1997 to December 1999). Key words used were heart failure (EMBASE only), ASA, and ACE inhibitors. The reference lists of the articles retrieved were examined for additional articles not identified in the initial searches. Searches were limited to the English-language literature. Searches of the databases of the Canadian Adverse Drug Reaction Monitoring Program (January 1965 to December 1999) and the World Health Organization Adverse Drug Reaction Monitoring Program (January 1988 to December 1998) were also performed. Studies and case reports were excluded if they did not involve heart failure (except for animal studies and studies of patients who had already experienced myocardial infarction) or if they involved higher, antiarthritic doses of ASA, other NSAIDs, renal hemodynamic changes or interactions, changes in pulmonary function, or effects on blood pressure in the absence of heart failure. The articles identified were assessed and critically evaluated.

RESULTS

The searches outlined above revealed 12 citations in MEDLINE and 7 in EMBASE; all articles retrieved by EMBASE were among those retrieved by MEDLINE. The other databases contributed no additional articles. Examination of the reference list of the articles retrieved identified 8 additional references, for a total of 20 studies.

The results are presented in order of increasing weight of evidence: theoretical basis, pharmacological studies in animals, pharmacological studies in humans, case reports, retrospective analyses of randomized trials, and randomized clinical trials.

Theoretical Basis

The opposing effects of ASA and ACE inhibitors on prostaglandin synthesis form the theoretical basis for this potential drug interaction.^{1,2} Thus, the interaction is thought to be pharmacodynamic, rather than pharmacokinetic.¹⁴ ACE inhibitors can increase the plasma concentrations of prostaglandins by inhibiting the degradation of kinins, ultimately producing vasodilation.¹⁵ ASA, through the inhibition of cyclooxygenase, reduces production of prostaglandins.

ASA might therefore inhibit the hemodynamic (particularly the vasodilating) effects of ACE inhibitors.

Critique: This theory is biologically plausible. However, its accuracy depends on the importance of prostaglandin-mediated vasodilation for the benefits of ACE inhibitors in heart failure. There is some evidence that prostaglandins might be important in this process: for example, increased levels of the vasodilatory prostaglandin E2 correlate with the beneficial hypotensive effects of ACE inhibitors,¹⁶ administration of the potent prostaglandin inhibitor indomethacin can be detrimental to hemodynamic function in patients with heart failure,¹⁷ and indomethacin can also reduce captopril-induced hemodynamic changes, as well as reducing synthesis of prostaglandin E2 and prostacyclin in forearm circulation.¹⁸ However, the hemodynamic benefits associated with ACE inhibitors could also be attributed to reductions in plasma concentrations of the vasoconstrictors angiotensin II and norepinephrine and increases in plasma concentrations of vasodilatory kinins.¹⁵ It is not clear whether prostaglandins are the only mechanism for the beneficial clinical effects of ACE inhibitors. For example, although angiotensin receptor blockers (e.g., losartan) theoretically have no effect on the kinin pathway, recent evidence suggests that these agents may in fact have effects similar to those of ACE inhibitors in heart failure.¹⁹⁻²¹

In addition, although some prostaglandins are vasodilators, others are vasoconstrictors.²² This interaction theory requires evidence that low-dose ASA selectively inhibits the formation of the vasodilating prostaglandins. In fact, there is evidence to the contrary: a daily 325-mg dose of ASA, as recommended for prevention of ischemic heart disease, produces only partial suppression of prostacyclin (a vasodilating prostaglandin) in vascular tissue and more profoundly inhibits the synthesis of the vasoconstricting prostaglandin thromboxane A2 in platelets.²³ Similarly, Baur and others²⁴ found that patients with class II to class III heart failure had an abnormally low ratio of the systemic synthesis of prostacyclin to that of thromboxane A2, which indicated a tendency toward vasoconstriction. Adding both an ACE inhibitor and a salicylate resulted in reversal of this ratio, with the balance tipping toward systemic prostacyclin synthesis; this effect would tend to enhance vasodilation and improve vascular function. ASA may thus actually produce vasodilating effects on prostaglandin balance in patients with heart failure.

Finally, Levi and others²⁵ have proposed that there may be an interaction between ASA and ACE inhibitors that involves norepinephrine. Both ACE inhibitors and

cyclooxygenase products can potentiate a bradykinin-induced release of norepinephrine from cardiac sympathetic nerves during myocardial ischemia. Such an effect would be deleterious, perhaps giving rise to reperfusion arrhythmias or worsening of heart failure. By inhibiting cyclooxygenase, ASA could theoretically reduce the release of norepinephrine. Evidence for such an interaction is limited, but this theory suggests that an interaction between ASA and ACE inhibitors could be positive rather than negative.

The bottom line: Although prostaglandin-mediated changes could account for some of the clinical benefits of ACE inhibitors in heart failure, it cannot be concluded that they are the only contributors. As well, the relative effects of ASA on vasodilating and vasoconstricting prostaglandins have not been fully elucidated.

Pharmacological Studies in Animals

The effects of ASA on vasodilation induced by ACE inhibitors have been studied in several animal models. Moroi and others²⁶ conducted an ex vivo study in which femoral arteries from healthy dogs were isolated and then constricted with either a prostaglandin (prostaglandin F2), norepinephrine, or potassium. A single dose (10^{-8} to 10^{-5} mol/L) of ACE inhibitor was then used to vasodilate the arteries. The addition of a single dose of ASA to the tissue bath (10^{-5} mol/L for 60 min) attenuated these vasodilatory effects.

Evans and others²⁷ used a canine model of severe heart failure to study the effect of low-dose ASA (325 mg/day for 4 days) on the hemodynamic effects of enalaprilat. Rapid ventricular pacing for 12 to 14 days produced severe heart failure in 11 dogs. Five of these dogs were chosen at random to receive ASA for the final 4 days of pacing. Mean arterial pressure, pulmonary capillary wedge pressure, and systemic vascular resistance, as well as renal and neurohormonal responses, were measured before and after administration of a single 0.625-mg dose of enalaprilat. The authors concluded that low-dose ASA alone had no adverse effect on hemodynamic or neurohormonal effects or on renal function in heart failure, and furthermore that the drug had no adverse effect on the acute response to enalaprilat.²⁷ Rose and others²⁸ demonstrated that the attenuation of myocardial stunning in dogs produced by a single dose of ACE inhibitor (ramiprilat 20 µg/kg IV) was not prevented by ASA at a dose of 1 or 10 mg/kg daily for 1 week.

Critique: These apparently contradictory findings may be explained by differences in study design and dosing. The one animal study that found an interaction



was an *ex vivo* study, performed on arteries taken from animals that did not have heart failure, with concentrations of ASA that may not be representative of those that occur clinically. However, it did show the potential for an interaction. The 2 other studies with low doses of ASA were consistent in their failure to detect a hemodynamic interaction.

The bottom line: A negative hemodynamic interaction was found in only one animal study, and that study had uncertain applicability to clinical practice.

Pharmacological Studies in Humans

The typical hemodynamic effects of ACE inhibitors in patients with heart failure are reductions in systemic vascular resistance, pulmonary vascular resistance, and left ventricular filling pressure, as well as increases in cardiac output, cardiac index, and stroke index.^{29,30} Table 1 summarizes the pharmacological studies³¹⁻³⁶ evaluating the interaction between ASA and ACE inhibitors.

Peripheral Circulation

Nakamura and others³¹ demonstrated antagonism of the peripheral vasodilation induced by ACE inhibitors in patients with New York Heart Association (NYHA) class II heart failure who received ASA. In that study, 20 patients were first evaluated for the effects of intra-arterial infusion of enalaprilat or placebo on forearm blood flow responses initiated by acetylcholine; enalaprilat enhanced the arterial vasodilation produced by acetylcholine. In the second part of the study, a 500-mg preinfusion dose of ASA attenuated the vasodilating effect of the enalaprilat. Thus, in the presence of ASA, enalaprilat did not significantly increase blood flow.³¹

Galatius and others³² also found evidence of an interaction. They conducted a nonrandomized, uncontrolled, retrospective analysis of a study designed to evaluate capillary fluid filtration and microvascular blood flow by venous occlusion plethysmography in 20 patients with New York Heart Association class II to class IV heart failure. To test the effect on heart failure alone and to eliminate the potential confounding effect of atherosclerosis, only patients with idiopathic dilated cardiomyopathy were included. All patients were taking an ACE inhibitor (drug and doses not specified). Patients who received ASA had lower blood flow in skeletal muscle than those not treated with ASA (mean \pm standard deviation 80 (20 mm Hg.min.mL⁻¹ with ASA and 56 (17 mm Hg.min.mL⁻¹ without ASA, $p < 0.01$). The

results suggested a decrease in peripheral blood flow and an increase in vascular resistance with daily doses of ASA as low as 75 to 150 mg.³²

In contrast, van Wijngaarden and others³³ failed to find an interaction. In a randomized crossover study, they evaluated peripheral vascular resistance by venous occlusion plethysmography. The study involved 13 patients with New York Heart Association class II to class IV heart failure whose condition had been stabilized with various ACE inhibitors at unspecified doses. A single 25-mg dose of captopril decreased mean arterial pressure and prolonged hyperemic blood flow, and a concomitant single 236-mg dose of ASA did not change these effects.³³

Katz and others³⁴ studied the immediate and long-term effects of ASA on the long-term (more than 3 months) vasodilating effects of enalapril in a randomized, double-blind, placebo-controlled trial. Sixty-two patients with New York Heart Association class II to class III heart failure who were taking at least 10 mg enalapril daily were given ASA 325 mg daily for 6 weeks. Forearm blood flow was measured by venous occlusion plethysmography before and 4 h after the first dose of ASA, and again after 6 weeks of concomitant therapy. Neither immediate nor long-term administration of ASA significantly affected the vasodilating effects of enalapril in the skeletal muscle circulation. This study had sufficient power to detect a clinically significant change of more than 30%.³⁴

Critique: The data regarding the ability of ASA to reverse peripheral vasodilation induced by ACE inhibitors are contradictory. Although Nakamura and others³¹ observed that ASA inhibited vasodilation, they measured vasodilation induced by acetylcholine, a highly specific situation. The 2 studies (out of 4 identified) that found an interaction were limited, in that they lacked randomization, blinding, and, most important, proper controls. The 2 studies with better designs showed no interaction in the peripheral circulation.

The bottom line: The studies with the best design merit readers' confidence. In this case, the best evidence suggests that there is no detrimental hemodynamic interaction in the peripheral circulation.

Central Circulation

Hall and others³⁵ studied the systemic arterial vasodilation associated with enalapril in 18 patients with chronic severe heart failure by assessing systemic vascular resistance, left ventricular filling pressure, and total pulmonary resistance by Swan-Ganz catheter in a randomized, double-blind, placebo-controlled crossover

Table 1. Pharmacological Studies Evaluating the Interaction between ASA and ACE Inhibitors in Humans

Reference	Study Design	ASA Dose	ACE Inhibitor Dose	Methodology	Results	Effect of ASA on Hemodynamic Effect of ACE Inhibitor
Peripheral vasodilation						
Nakamura and others ³¹	Randomized (<i>n</i> = 20); effect of enalaprilat was studied, then in a separate experiment subjects received ASA and then either enalaprilat or placebo	500 mg by intra-arterial infusion	Enalaprilat by intra-arterial infusion	Venous occlusion plethysmography to measure peripheral (forearm) blood flow	<i>Enalaprilat only</i> : enhanced Ach-induced vasodilation in forearm <i>Enalaprilat + ASA</i> : no enhancement of Ach-induced vasodilation	Reduction
Galatius and others ³²	Retrospective analysis of prospective study (<i>n</i> = 20)	75–150 mg PO (long term)	Unspecified ACE inhibitor (long term)	Venous occlusion plethysmography to measure peripheral (calf) blood flow	<i>ASA</i> : calf blood flow increased, vascular resistance decreased	Reduction
Van Wijngaarden and others ³³	Double-blind cross-over RCT (<i>n</i> = 13)	236 mg PO once	Maintenance ACE inhibitor (no wash-out), then captopril 25 mg once	Venous occlusion pleythmography to measure peripheral (calf) blood flow	<i>Captopril + placebo</i> : no change in calf blood flow <i>Captopril + ASA</i> : no change in calf blood flow	No reduction
Katz and others ³⁴	Double-blind RCT (<i>n</i> = 62)	325 mg PO daily for 6 weeks	Enalapril (10 mg PO daily before and during the study)	Venous occlusion plethysmography to measure peripheral (forearm) blood flow	<i>Enalapril + placebo</i> : no change in forearm blood flow <i>Enalapril + ASA</i> : no change in forearm blood flow	No reduction
Central circulation						
Hall and others ³⁵	Double-blind crossover RCT (<i>n</i> = 18)	350 mg PO once	Enalapril 10 mg PO once	Pulmonary artery catheter, blood pressure cuff	<i>Enalapril</i> : SVR, LVFP, and TPR decreased <i>Enalapril + ASA</i> : no change in SVR, LVFP, or TPR	Reduction
Spaulding and others ³⁶	Randomized double-blind (with ticlopidine control) (<i>n</i> = 20)	325 mg PO daily for 7days	Enalapril 10 mg PO once	Pulmonary artery catheter, blood pressure cuff	<i>Enalapril + ticlopidine</i> : SVR decreased <i>Enalapril + ASA</i> : no change in SVR	Reduction

ASA = acetylsalicylic acid, ACE = angiotensin-converting enzyme, Ach = acetylcholine, RCT = randomized controlled trial, SVR = systemic vascular resistance, LVFP = left ventricular filling pressure, TPR = total pulmonary resistance.

trial. They found that a single 10-mg dose of enalapril alone significantly decreased the above variables. However, when the enalapril was administered with a single 350-mg dose of ASA, the hemodynamic effects of enalapril were no longer statistically significant.³⁵

Spaulding and others³⁶ randomized 20 patients with New York Heart Association class III or class IV heart failure to receive enalapril 10 mg plus either ticlopidine (500 mg daily) or ASA (325 mg daily). Hemodynamic evaluation (including assessment of



systemic vascular resistance, total pulmonary resistance, cardiac output, and heart rate) was performed every hour for 4 h after 7 days of treatment. In patients who received enalapril and ticlopidine, the mean systemic vascular resistance (\pm standard deviation) decreased from 1741 ± 519 to 1364 ± 472 dyne.s.cm⁻⁵ ($p = 0.0013$), whereas in patients given enalapril and ASA, the systemic vascular resistance decreased from 1528 ± 294 at baseline to 1395 ± 207 dyne.s.cm⁻⁵ ($p = 0.4$). The authors concluded that enalapril reduced systemic vascular resistance and increased cardiac output only in the patients who received ticlopidine, not in those who received ASA. Pulmonary vascular resistance was significantly reduced only in the patients taking ASA.³⁶

Critique: Of more clinical relevance are these 2 studies documenting that ASA in a 325-mg dose given once or for 7 days altered systemic hemodynamic parameters such as systemic vascular resistance, left ventricular filling pressure, and total pulmonary resistance. Both studies were well designed, having randomization, blinding, and controls. One limitation of both studies was that the ACE inhibitor was given as a single dose. A randomized, placebo-controlled study in which long-term ASA therapy was added to existing long-term ACE inhibitor therapy and in which relevant variables such as systemic vascular resistance, left ventricular filling pressure, total pulmonary resistance, cardiac output, and stroke volume were measured would be desirable. However, such a study would be logistically and ethically difficult, as it would require insertion of a Swan-Ganz catheter for research purposes.

The bottom line: These studies indicate that an interaction might occur under carefully controlled experimental conditions. Investigation of clinical outcomes is required, since short-term changes in hemodynamic parameters (surrogate endpoints) do not necessarily correlate with long-term survival (a clinical endpoint).

Case Reports

If ASA does in fact reduce the benefit of ACE inhibitors in heart failure, clinicians might be expected to have identified the negative interaction in their own patients. For example, in a patient with heart failure whose condition has been stabilized by an ACE inhibitor, does the addition of ASA result in clinically noticeable changes, perhaps indicated by reduced exercise tolerance or a change in New York Heart Association classification? Our review of the medical literature did not reveal any published reports of worsening of heart failure attributed to this combination of drugs. A search of adverse drug reactions reported to the Canadian

Adverse Drug Reaction Monitoring Program³⁷ similarly did not reveal evidence of such an interaction. In the World Health Organization Adverse Drug Reaction Monitoring Program database³⁸ there were 9 reports of heart failure and 195 reports of edema associated with ASA in the period 1988 to 1998, but no evidence that these patients were receiving an ACE inhibitor or had previous heart failure.

Critique: The lack of case reports of aggravated heart failure in patients receiving concurrent therapy with ASA and ACE inhibitors can be interpreted in several ways: there may not be an interaction, the clinical effects of an interaction may be too subtle for identification in individual patients, or the interactive effects may have been seen but were not documented. Had case reports been identified, they would have lent weight to the theory that an interaction exists.

The bottom line: Although the existence of case reports can sometimes suggest the existence of drug interactions and other adverse drug reactions, in this case the information available neither confirms nor refutes the possibility of an interaction.

Retrospective Analyses of Randomized Trials

Several retrospective analyses of data have been conducted to address the possible negative long-term outcomes of concomitant use of ASA and ACE inhibitors^{7,8,39-51} (Table 2). Although the patients in these studies were initially randomized with regard to use of ACE inhibitors, the studies were not designed to investigate an interaction, so patients were not randomized with respect to ASA administration.

Treatment of Chronic Heart Failure

SOLVD: The Studies of Left Ventricular Dysfunction (SOLVD) were 2 large, long-term trials that evaluated the benefit of enalapril relative to placebo in patients with symptomatic heart failure (the treatment arm, $n = 2569$) or asymptomatic heart failure (the prevention arm, $n = 4228$).^{7,8} A subsequent cohort analysis of the data from these studies evaluated the effect of antiplatelet use (ASA in more than 95% of cases) on survival and morbidity.³⁹ Patients' use of antiplatelet drugs was identified at the beginning of the study, and outcomes were measured when the studies were completed, on average 37.4 to 41.4 months later. Data were sufficient for analysis for a total of 6512 patients from the combined studies; of this total population, 46.3% had used antiplatelet drugs. The exact numbers of patients in each group were not provided.



Table 2. Retrospective Analyses of Randomized Trials

Study	ASA	ACE Inhibitor	Duration	Results with ASA Alone	Results with ACE Inhibitor Alone	Results with ASA + ACE Inhibitor	Effect of ASA on Benefit of ACE Inhibitor
Treatment Studies in Chronic Heart Failure							
SOLVD treatment arm ³⁹ (n = 2569)	Baseline use, details unknown	Enalapril 2.5–20 mg daily	Approx. 3 years	Lower mortality rate	Lower mortality rate	No difference in mortality rate, but no interaction on heart failure outcome	Possible interaction but not a worsening of heart failure (ACE inhibitor may have reduced benefit of ASA)
2	Baseline use, mostly 250 mg daily	Mostly captopril (74%) or enalapril (26%); doses unknown	5 years	No data	Lower mortality rate (n = 579)	Lower mortality rate than with ACE inhibitor alone (n = 618)	No effect (ASA + ACE inhibitor more beneficial than ACE inhibitor alone)
Prevention Studies after Myocardial Infarction							
SAVE ⁷ (n = 2231)	Baseline use (dose undefined)	Captopril up to 150 mg daily	Average 42 months	Not analyzed	Lower mortality rate	Lower mortality rate	No effect
AIRE8 (n = 2006)	Baseline use (dose undefined)	Ramipril 2.5–10 mg daily	Average 15 months	Not analyzed	Lower mortality rate	Lower mortality rate	No effect
ISIS-441 (n = 58 050)	Concomitant; dose undefined	Captopril up to 100 mg daily	5 weeks	Not analyzed	Lower mortality rate	Lower mortality rate	No effect
SMILE ⁴² (n = 1556)	Concomitant (dose undefined)	Zofenopril 7.5–60 mg daily	6 weeks	Not analyzed	Lower mortality rate and rate of severe CHF	Lower mortality rate and rate of severe CHF	No effect
CONSENSUS II ^{43,44} (n = 6090)	Baseline use (dose undefined; also given ASA to treat MI)	Enalapril IV, then 2.5–20 mg daily	6 months	Lower mortality rate	No difference in mortality rate	Lower mortality rate	No effect (although ACE inhibitor may have reduced benefit of ASA)
GISSI-3 diabetic subgroup ⁴⁵⁻⁴⁷ (n = 2390)	For treatment of MI; dose undefined	Lisinopril 2.5–10 mg daily	6 weeks	Lower mortality rate	Lower mortality rate	Lower mortality rate	No effect
CATS ^{48,49} (n = 298)	Baseline “low-dose” use (also given 80–100 mg ASA to treat MI)	Captopril up to 25 mg 3 times daily	1 year	No difference in infarct size; less left ventricular dilatation	Smaller infarct size; no difference in left ventricular dilatation	Smaller infarct size; less left ventricular dilatation	No effect
GUSTO-1 subgroup without heart failure ^{50,51} (n = 31 328)	Use at discharge post-MI	Undefined 160–325 mg daily		Lower mortality rate	Not analyzed	No difference in mortality rate	Unknown (ACE inhibitor may have reduced benefit of ASA)

ASA = acetylsalicylic acid, ACE = angiotensin-converting enzyme, SOLVD = Studies of Left Ventricular Dysfunction, BIP = Bezafibrate Infarction Prevention study, SAVE = Survival and Ventricular Enlargement study, AIRE = Acute Infarction Ramipril Efficacy study, ISIS = International Study of Infarct Survival, SMILE = Survival of Myocardial Infarction Long-term Evaluation study, CHF = congestive heart failure, CONSENSUS = Cooperative New Scandinavian Enalapril Survival Study, MI = myocardial infarction, GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico, CATS = Captopril and Thrombolysis Study, GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries study.



In the antiplatelet analysis (combined trial data), the calculated adjusted hazard ratio for all-cause mortality in patients receiving antiplatelet drugs was 0.82 (95% confidence interval [CI] 0.73 to 0.92, $p = 0.0006$). However, Cox regression analysis indicated a significant interaction between enalapril and antiplatelet drugs in the total population. When patients randomized to receive enalapril were compared with those taking placebo, the adjusted hazard ratios for all-cause mortality were 1.00 (95% CI 0.85 to 1.17) for the group taking enalapril plus antiplatelet drugs and 0.68 (95% CI 0.58 to 0.80) for the group taking antiplatelet drugs alone ($p = 0.0005$). When patients were compared in relation to antiplatelet use, the adjusted hazard ratios for all-cause mortality were 1.10 (95% CI 0.93 to 1.30) for patients taking enalapril plus antiplatelet drugs and 0.77 (95% CI 0.67 to 0.87) for those taking enalapril without antiplatelet drugs ($p = 0.0005$). Therefore, the mortality rate was lower with enalapril alone and with antiplatelet drugs alone, but there was no difference in all-cause mortality when both agents were taken. Although the exact causes of death in these groups were not reported, the analysis indicated that the interaction did not result from an increase in problems related to heart failure, since there was no difference in rates of death or admission to hospital due to heart failure between the group that took enalapril alone and the one that took enalapril combined with antiplatelet drugs.

Results differed slightly between the treatment and prevention arms. In the treatment arm, enalapril was associated with a lower mortality rate, as well as lower rates of admission to hospital and death due to heart failure, and a significant interaction was detected between enalapril and antiplatelet drugs. In the prevention arm, enalapril was associated with a lower incidence of subsequent heart failure, but there was no difference in mortality rate. Antiplatelet use was associated with significantly lower rates of death and hospital admission for either heart failure or any cardiac event, as well as lower all-cause mortality rates. In the prevention arm, no interaction was seen between antiplatelet use and ACE inhibitor use.

These data suggest that combining an ACE inhibitor with an antiplatelet agent removes the benefit on total mortality of either agent in heart failure, but that this is not necessarily due to a worsening of heart failure. The data from the treatment arm also suggest that enalapril might reduce the potential benefits of ASA. This is the reverse of the originally proposed interaction. It has not been prospectively studied nor is the mechanism known, although it might be conjectured that

antagonism of prostaglandin effects works both ways.

BIP: A cohort study analyzed data from patients screened ($n = 11\,575$) for the Bezafibrate Infarction Prevention (BIP) study.⁴⁰ All patients had coronary artery disease, and all received ACE inhibitor therapy (primarily captopril; dose and indication not provided). Subjects were grouped as ASA users (most frequent dose 250 mg daily, $n = 618$) or non-ASA users ($n = 579$). Allocation depended on drug use at the beginning of the 5-year study period. Baseline characteristics differed between the 2 groups, but this difference was corrected for in the analysis. In contrast to the SOLVD study, the authors found that patients with coronary artery disease who were treated with ACE inhibitors had better survival with concurrent ASA use (mortality rate 19% and 27% respectively, $p = 0.002$). In a subgroup of patients with heart failure, the 5-year mortality rate was also lower in patients who received both ASA and ACE inhibitors ($n = 221$) than in patients who received ACE inhibitors alone ($n = 243$, adjusted relative risk for 5-year mortality 0.70 [95% CI 0.49 to 0.99]).

Critique: It might be expected that patients given 2 therapies that are apparently beneficial on their own would do as well or better when given both. Although this assumption proved true in the BIP study, it was not the case in the treatment arm of the SOLVD study. There are 2 possible explanations: either there is actually no negative interaction and the results in the SOLVD study are spurious, or there is a negative interaction and the BIP study failed to show it.

If there really is no negative interaction, it is then necessary to explain why the combination of the 2 drug therapies appeared to diminish any benefit on total mortality rate in the SOLVD treatment study. One explanation might be the lack of randomization to antiplatelet therapy. Patients who had more comorbid illnesses might have “self-selected” themselves to use ASA therapy and died despite the combination drug therapy. There was mention of adjustment for some confounders (e.g., ischemic heart disease), but it is not clear if adjustments were made for the higher incidence of smoking and the use of antiarrhythmic drugs or potassium supplements. However, the data suggest that lack of randomization did not produce an antiplatelet group more prone to morbidity, because this group showed lower all-cause mortality both within the group as a whole and among those who received only antiplatelet drugs.

The retrospective nature of the SOLVD analysis is a limitation. Determination of ASA use was based on interviews with patients at the beginning of the study

and was not verified throughout the more than 3 years of the study. However, the lack of verification of use of ASA and other antiplatelet drugs does not invalidate the findings, since data suggest that over time the trend would have been for nonusers of ASA to become users, as their symptoms worsened or as they became aware of potential benefits.⁴⁰ Such a change in ASA use would tend to reduce the ability to detect a difference between groups over time, but in fact both better survival and an interaction were detected in the patients who received antiplatelet drugs.

Finally, it could be argued that the group who received both antiplatelet drugs and ACE inhibitors might have been too small to yield sufficient power to detect a lower mortality rate in that group. Although the exact size of this group was not reported, the initial study population was large ($n = 2569$), and it was implied that approximately one-quarter of these subjects received both drugs.

The second hypothesis is that a negative interaction exists but was not detected in the BIP analysis. The finding of a positive interaction might be explained if, because of lack of randomization, the patients who received ASA were healthier than those who did not take ASA. However, the baseline patient characteristics indicate that the group taking ASA was less healthy, more of them having a history of stroke, hypertension, smoking, myocardial infarction, and peripheral vascular disease. Because of the retrospective nature of the study, information was lacking on both ACE inhibitor and ASA use; the authors indicated that over the study period of 5 years, patients who initially did not use ASA tended to start using it. Such a change in therapy would not explain the ability of the analysis to detect better survival with combination therapy.

The 2 studies differed in size, but this does not explain the different results. The SOLVD study was large and found a negative interaction, whereas the BIP study, although smaller, reported a positive interaction.

The bottom line: Neither study has greater validity than the other, and no conclusion can be drawn from the conflicting possibilities that combining ASA with ACE inhibitors reduces or improves the effect of the ACE inhibitor in the treatment of heart failure. Perhaps the opposing results were due to differences in patient populations, differences in ACE inhibitors, or differences in ASA doses. Epidemiological trials such as these can only suggest possible associations; they cannot prove an interaction. Furthermore, although the SOLVD study did suggest a negative interaction between ASA and ACE inhibitors in heart failure, it is not clear that the

interaction was hemodynamic in nature, since there was no change in morbidity rate related to heart failure. This analysis also suggests that ACE inhibitors might reduce the benefit of ASA in patients in heart failure.

Prevention of Heart Failure after Myocardial Infarction

SAVE: The benefits of captopril administered to patients with asymptomatic left ventricular dysfunction after myocardial infarction were demonstrated in the Survival and Ventricular Enlargement (SAVE) study.⁷ Analysis with a proportional hazards model indicated that captopril reduced all-cause mortality as well as cardiovascular death and morbidity, whether or not patients received ASA. There was a trend toward better outcome with both drugs.

AIRE: The Acute Infarction Ramipril Efficacy (AIRE) Study examined the benefits of the ACE inhibitor ramipril in patients who had experienced acute myocardial infarction and who had evidence of heart failure.⁸ Ramipril was associated with a lower mortality rate after an average follow-up period of 15 months. Subgroup analysis with a Cox proportional hazards regression model found no significant interaction between ramipril and ASA.

ISIS-4: The Fourth International Study of Infarct Survival (ISIS-4) assessed the use of captopril after suspected myocardial infarction and found a lower 5-week mortality rate.⁴¹ An analysis of concurrent treatment failed to find an interaction between captopril and ASA use; among patients who took both drugs, the total mortality rate was still lower.

SMILE: The benefit of the ACE inhibitor zofenopril given after anterior myocardial infarction was assessed in the randomized, placebo-controlled Survival of Myocardial Infarction Long-term Evaluation (SMILE) study.⁴² The ACE inhibitor reduced the incidence of death or severe heart failure after 6 weeks of therapy. Subsequent analysis of subgroups found no difference in outcome for patients who received concomitant ASA, although there was a nonsignificant trend toward better outcome with the combined therapy.

CONSENSUS II: The Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II study was a large ($n = 6090$), randomized, double-blind, placebo-controlled trial of enalapril after acute myocardial infarction.⁴³ Enalapril had no benefit in terms of mortality rate after 30 days or 6 months. In the initial analysis of the study, unadjusted Cox regression showed no interaction between ASA and enalapril. A



retrospective subgroup analysis of the data from this study, performed to further assess any differences in outcome related to ASA use, involved logistic regression and an additive interaction model.⁴⁴ Among patients receiving ASA at baseline ($n = 4697$), mortality rates were lower after 6 months than among those who had not been receiving ASA at baseline ($n = 1393$) (relative risk 0.47). However, there was a significant interactive effect of ASA and ACE inhibitor on mortality rate at 6 months (relative risk 0.57). The authors concluded that ASA diminished the “benefits” of enalapril on death after acute myocardial infarction. However, in this study enalapril alone was not beneficial in terms of mortality, so it is incongruous to conclude that ASA could have reduced this “lack of benefit”. Instead, the data presented suggest that the ACE inhibitor may have reduced the benefits of ASA after myocardial infarction.

GISSI-3: The Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico-3 (GISSI-3) study evaluated the effects of lisinopril after myocardial infarction.⁴⁵ Approximately 84% of the patients were treated with ASA. A subgroup analysis of diabetic patients found a trend toward better survival at 6 weeks in patients who were treated with both lisinopril ASA.⁴⁶ Another *post hoc* analysis reported (in abstract form) no difference in rates of hypotension when lisinopril and ASA were administered after myocardial infarction, a finding that argued against an acute adverse hemodynamic interaction.⁴⁷ The advantage of this analysis was that it evaluated the relationship between known ASA administration for treatment of myocardial infarction and an outcome within a short time period.

CATS: In the Captopril and Thrombolysis Study (CATS), patients who had experienced anterior-wall myocardial infarction were randomized to receive captopril or placebo, and left ventricular volume was assessed after 1 year.⁴⁸ A *post hoc* analysis of patients who took low-dose ASA at randomization and before admission to hospital⁴⁹ showed that these patients were more likely to have coronary artery disease and to use calcium-channel blockers, but these differences were adjusted for in the analysis. Some patients also received 80 to 100 mg ASA after myocardial infarction. ASA did not reduce the beneficial effect of captopril on infarct size, and the patients who took both captopril and ASA had less left ventricular dilatation and lower mortality rate after 1 year. Thus, no negative interaction was found in this study.

GUSTO: A *post hoc* analysis of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial⁵⁰ was

performed.⁵¹ In this uncontrolled analysis of patients who survived myocardial infarction and did not experience heart failure, the patients who used ASA alone had lower total mortality. However, among the myocardial infarction survivors without heart failure who used both ASA and ACE inhibitors, ASA did not reduce 1-year mortality. The authors concluded that ACE inhibitors might reduce the mortality benefit of ASA after myocardial infarction in patients without heart failure, although no mechanism was proposed.

Critique: None of these 8 analyses revealed a negative effect of ASA on the benefits of a variety of ACE inhibitors after acute myocardial infarction. The one study that suggested a negative interaction (CONSENSUS II) was not convincing on close examination.^{43,44} The consistency of these results suggests a lack of interaction, although caution is warranted, given that these were not prospective studies designed to determine the presence of an interaction. Several studies suggested that the inverse interaction might be possible — that ACE inhibitors might reduce the clear benefits of ASA after acute myocardial infarction. Patients were not randomized as to ASA therapy, and these reports lacked information regarding the duration and dosing of ASA. Lack of randomization might explain the failure to find an interaction, if the ASA group had more comorbid illnesses than the non-ASA group. In most of these studies information on comorbid illnesses was not provided. The lack of information on retrospective use of ASA might also explain the lack of an observed interaction, because over time, nonusers of ASA might tend to become users,⁴⁰ a phenomenon that would reduce any differences between groups. Without information on ASA use, this remains speculation.

The bottom line: No evidence was found that ASA reduces the benefits of ACE inhibitors when used after myocardial infarction.

Randomized Trials

A prospective randomized clinical trial would provide the greatest weight of evidence for or against a negative interaction. To date, no such trials have been conducted to answer the questions raised by the studies described above. The study closest to this ideal is the planned Warfarin-Antiplatelet Trial in Chronic Heart Failure (WATCH), which will compare the outcome of patients with heart failure who are prospectively randomized to receive ASA, clopidogrel, or warfarin.¹² Because most of these patients will also be receiving ACE inhibitors, this study may help to resolve the controversy about a potential interaction between ASA and ACE inhibitors.

However, it is not designed to test for an interaction, and the patients will not be randomly assigned to ACE inhibitor therapy.

DISCUSSION

Careful examination of the evidence concerning a potential negative hemodynamic interaction between ASA and ACE inhibitors in heart failure has failed to provide substantial clinical evidence for such an interaction. As summarized in Table 3, only the following conclusions can be drawn. First, hemodynamic studies in humans suggest the potential for an interaction. Second, in the *treatment* of chronic heart failure, the analyses of clinical outcomes are limited by their retrospective nature, and the results are inconclusive. Third, for *prevention* of heart failure after myocardial infarction there is no evidence for a negative interaction in patients treated with ASA and ACE inhibitors. Finally, the data suggest that ACE inhibitors may reduce the benefit of ASA after myocardial infarction.

Several reviewers have suggested that lower doses of ASA may be a safer alternative for patients receiving concomitant ACE inhibitor therapy.^{52,53} However, clinical doses must be based on the major trials that have shown a benefit in terms of mortality rate for ASA given to patients with ischemic heart disease. Those trials used medium doses (75 to 325 mg daily). As well, the doses

of ASA were not defined in many of the studies analyzed here (Tables 1 and 2), so no clear dose relationship emerged in this analysis.

Conflicting evidence can be difficult to assess. The approach presented here consists of the following steps.

1. Gather all relevant clinical and nonclinical data.
2. Organize the data according to potential importance, ranging from theoretical models to randomized clinical trials.
3. Consider each piece of evidence in terms of logic, strengths, and limitations.
4. Summarize the results, being careful to distinguish between the different types of evidence available.
5. Reach a conclusion by emphasizing the evidence derived from the studies with the best design as well as the greatest clinical relevance. Ideally, the data will consistently point to a clear conclusion. If not, it may be necessary to conclude that there is no conclusive answer.
6. Make clinically practical recommendations.

Recommendations

The studies reviewed here had design limitations and produced conflicting results. In addition, acceptable therapeutic alternatives are lacking for both agents. Therefore, patients with heart failure who may benefit from ACE inhibition and patients with ischemic heart disease who may benefit from low-dose ASA should not

Table 3. Summary of Analysis in Increasing Order of Weight of Evidence

Type of Evidence	Study Design	Clinical Relevance	Effect of ASA on Benefit of ACE Inhibitor
Biological theories	NA	Low	Inconclusive
Animal studies	Good (prospective, controlled)	Low	Conflicting results
Human pharmacology			
Peripheral circulation	Ranged from retrospective to prospective, randomized, controlled, double-blind design	Low	Conflicting results; no interaction found in studies with best designs
Central circulation	Good (randomized, double-blind, controlled)	Medium	Yes
Clinical case reports	Hypothesis-generating	High	Inconclusive
Retrospective analyses of clinical trials			
Treatment of chronic heart failure	Retrospective, nonrandomized, hypothesis-generating	High	Conflicting results (but possibly reduced benefit of ASA)
Prevention after myocardial infarction	Retrospective, nonrandomized, hypothesis-generating	High	No effect (but ACE inhibitor may have reduced benefit of ASA)
Randomized trials	Good	High	No randomized trials available

ASA = acetylsalicylic acid, ACE = angiotensin-converting enzyme, NA = not applicable.



be prevented from receiving a combination of these therapies.

In the absence of conclusive data, the best care that can be offered to patients is appropriate clinical monitoring. Patients should be assessed regularly for signs of worsening heart failure (decreased exercise tolerance, orthopnea, dyspnea, or peripheral edema) and observed for adverse reactions due to either agent. Any clinical signs of deterioration should be reported to the patient's physician. Any suspected adverse reactions should be reported to the Canadian Adverse Drug Reaction Monitoring Program. Forms and contact information are available in the *Compendium of Pharmaceutical Specialties*.⁵⁴

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