REVIEW ARTICLE

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Interaction between Aspirin and ACE Inhibitors in Patients with Heart Failure

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Contents

Abstract

Both aspirin (acetylsalicylic acid) and ACE inhibitors are often used concomitantly, especially in patients with both heart failure and ischaemic heart disease, which is the most common underlying cause of heart failure.

The safety of the association has been questioned because both drugs affect a related prostaglandin-mediated pathway. Thanks to their vasodilating properties, prostaglandins play an important role in heart failure where peripheral vasoconstriction occurs. Some of the beneficial effects of ACE inhibitors might be related to reduced degradation of bradykinin that enhances the synthesis of prostaglandins, while aspirin, through inhibiting the enzyme cyclo-oxygenase, inhibits the production of prostaglandins.

To date no prospective study has been conducted to investigate the effect of long term aspirin treatment in the postinfarction period allowing the possible

impact of the interaction between aspirin and ACE inhibitors upon survival to be confirmed or negated. However, the practitioner needs to know how to optimise the treatment of his or her patients.

In order to stimulate arguments for and against the use of aspirin in patients with heart failure receiving ACE inhibitors, we searched MEDLINE from 1960 to 2000 using the key words heart failure, aspirin, and ACE inhibitors for English language articles and conducted a review of the available data.

We report on the potential mechanisms of the interaction and the results of experimental studies on haemodynamic parameters. Results of retrospective clinical studies, subgroup analysis that were undertaken to evaluate the overall action upon haemodynamic parameters and survival of the association are summarised. Conflicting conclusions have been reported in the literature. Many explanations can be advanced to try to understand these conflicting conclusions: differences in study design (results of retrospective trials have to be interpreted with caution); differences in the choice of the evaluation parameter (problem of the clinical relevance of haemodynamic parameters); differences in the characteristics of the patient (different underlying cardiopathy, e.g. heart failure, hypertension or ischaemic cardiopathy); and differences in the type and the dosage of each treatment (especially ACE inhibitors and aspirin since an interaction might occur more often with dosage of aspirin greater than 250mg).

The prevalence of heart failure is increasing in industrialised countries, especially in the elderly population. It is the single most frequent cause for hospitalisation in individuals aged 65 years or older. It is mostly attributable to aging populations and to improved survival and management of coronary heart disease.[1,2] Ischaemic heart disease is the most common cause of heart failure with decreased systolic function.[3-5] Many authors have questioned the safety of the use of aspirin (acetylsalicylic acid) in patients with heart failure especially those patients who are being treated with ACE inhibitors.[6-12]

In order to stimulate arguments for and against the use of aspirin in patients with heart failure receiving ACE inhibitors, we searched MEDLINE from 1960 to 2000 using the key words heart failure, aspirin, and ACE inhibitors for English language articles and conducted a review of the available data.

1. Rationale for a Concomitant Use of Aspirin and ACE Inhibitors

Heart failure and ischaemic heart disease are frequently associated conditions. They often require treatment with both ACE inhibitors and aspirin,but these drugs have only been evaluated separately. Clinical trials have demonstrated that ACE inhibitors can reduce morbidity, mortality and improve quality of life and exercise performance in all stages of heart failure [e.g. moderate heart failure [Studies of Left Ventricular Dysfunction (SOLVD),[13] Vasodilator Heart Failure Trial (V Heft II)[14]] to severe heart failure [Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) I[15]] and after myocardial infarction[16] with decreased systolic function or clinical heart failure [Survival and Ventricular Enlargement Study (SAVE),[17] Acute Infarction Ramipril Efficacy Study (AIRE),[18] Trandolapril Cardiac Evaluation (TRACE)[19]]. A meta-analysis of trials with ACE inhibitors in heart failure demonstrated a 23% decrease in total mortality and a 35% decrease in the combined end-point of mortality or hospitalisation for congestive heart failure.[20] ACE inhibitors are recommended as first line treatment in systolic heart failure.[21] Furthermore, an overview of 7 trials demonstrated an improvement of overall survival with ACE inhibitor therapy started during acute myocardial infarction.[22] No significant difference of proportional

mortality reduction was noticed between patients with heart failure or Killip >1 at entry [11%; standard deviation (SD) 4%] and patients in Killip class 1 (5%; SD 3%). The absolute benefit of ACE inhibitor treatment was particularly large in patients with heart failure after myocardial infarction because they are at increased risk of death [14.1 (SD 5.4) *vs* 2.9 (SD 1.6) lives saved per 1000 in days 0 to 30].[22]

Aspirin is the reference treatment in acute ischaemic heart disease (unstable angina and myocardial infarction) and in the primary and secondary prevention of ischaemic events[23]. The Second International Study of Infarct Survival (ISIS-2) showed the mortality benefit of aspirin started early after myocardial infarction and followed for 6 weeks.[24,25] Whether aspirin needs to be given long term remains uncertain because of the lack of benefit demonstrated in long term studies with aspirin in patients with heart failure. The Antiplatelet Trialists reported from 11 trials with more than 20 000 patient years of follow-up on the effect of aspirin use in postinfarction patients. The first meta-analysis did not report a reduction in overall mortality in the long term postinfarction trials although a second analysis did.[26,27] It is possible that aspirin benefits only some subgroups of patients in the long term postinfarction trials and causes harm in others. Two postinfarction trials suggest that patients with heart failure do not benefit with aspirin.[28,29]

Aspirin and ACE inhibitors given alone both benefit patients in the weeks following a myocardial infarction but little is known about the concomitant use of these medications.[30] The safety of the combination was questioned because both drugs affect a related prostaglandin (PG)-mediated pathway (see section 2).[6] The effect of the association may theoretically be synergistic, neutral or negative but experimental data and retrospective studies suggested that there might be a negative interaction between aspirin and ACE inhibitors. To date no prospective clinical study has been conducted that investigates the overall impact of this combination of drugs upon survival.

2. Theoretical Background for Aspirin and ACE Inhibitor Interaction

A negative interaction between aspirin and ACE inhibitors is suspected because the both drugs affect a related PG-mediated pathway.[6]

ACE inhibitors have beneficial effects on the regulation of vascular tone, myocardial contractility and ventricular remodelling and modulation of neuroendocrine activation.[31,32] They act through 2 mechanisms. The first one is the inhibition of the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor which stimulates release of aldosterone and norepinephrine (noradrenaline) and causing water retention and further vasoconstriction.[33,34] The second one is the inhibition of the breakdown of kinins,[32] leading to increased concentration of bradykinin (a direct smooth muscle relaxant),[35] and the formation of vasodilator PGs (such as prostacyclin and PGE2).[36] Kinins may dilate vessels by endothelial stimulation of nitric oxide (NO) synthesis and release via specific bradykinin B2 receptors,[32,37] promoting the vasodilation and afterload reduction in patients with congestive heart disease and coronary artery disease.[7,38-40] ACE inhibitors potentiate the action of exogenous intravenously administered bradykinin by approximately 50-fold but can also potentiate the action of endogenous released kinins.[32,41] Moreover, a stimulation of PGE2 and prostacyclin synthesis by activating phospholipase and arachidonic acid release has been described with captopril.[42] But the contribution of PG to the haemodynamic effects of ACE inhibitors in heart failure remains uncertain. In a study involving 12 patients with heart failure randomised to double-blind cross-over treatment with enalapril 10mg twice daily followed by losartan potassium 25mg twice daily, or the reverse, each for 5 weeks, Davie et al.[43] observed that exogenous bradykinin did cause vasodilatation (forearm blood flow) and that this response was markedly enhanced by pretreatment with an ACE inhibitor compared with an angiotensin-1 antagonist. However, there was no evidence of an effect of endogenous bradykinin antagonism with a selective long acting bradykinin antagonist, irre-

spective of pretreatment with an ACE inhibitor or an angiotensin antagonist.[43]

Aspirin may antagonise these beneficial effects through the blockade of the enzyme cyclo-oxygenase (COX) and thus inhibiting the production of prostaglandins, resulting in vasoconstriction, reduction in cardiac output and aggravation of heart failure (fig. 1). Thus, Dzeka et al.[44] showed recently that a single dose of aspirin 325mg significantly increased venoconstriction to both exogenous and endogenous norepinephrine released following sympathetic activation during a cold pressor test.

The point is that the interaction between ACE inhibitors and aspirin may be particularly relevant and negative in congestive heart failure where PG synthesis is activated to limit vasoconstriction and maintain local blood flow.[38] This mechanism is hard to assess because of the difficulties in measuring plasma and urinary PG levels and because of its short half-life. Studies assessing a potential interaction between aspirin and ACE inhibitors have shown very variable results. Some demonstrated no significant changes in either PGE2 or prostacyclin metabolite levels[39,45,46] while others stated a decrease in PGE2 levels when aspirin was added to an ACE inhibitor.[47]

Results obtained with other antiplatelet agents that inhibit COX such as indomethacin are an indirect argument for a role of PG in the interaction. Inhibitors of PG synthesis are expected to be deleterious in patients with heart failure. Indomethacin intake induced a decrease in renal plasma flow and glomerular filtration rate[40] and lead to a deterioration in cardiac index, systemic vascular resistance and left ventricular filling pressure particularly in patients who were hyponatraemic.[38]

Clinical reports suggest that other pathways may be involved in the interaction between salicylates and ACE inhibitors. During the long term administration of spironolactone 25mg 4 times daily in 10 healthy men, the addition of 600mg of aspirin reduced the mean sodium content of overnight urine by 30%, which could affect the management of a patient receiving this therapy.[48]

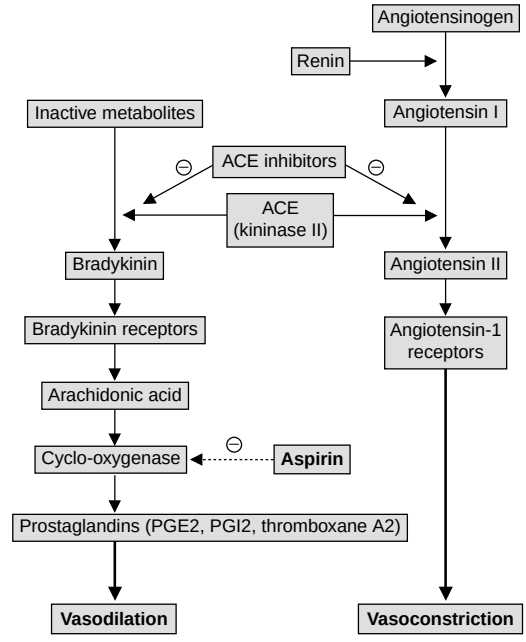

Fig. 1. Potential mechanism of the interaction between aspirin (acetylsalicylic acid) and ACE inhibitors. **ACE** = angiotensin converting enzyme; **PG** = prostaglandin; **PGI_2** = prostacyclin.

The mechanism of action of both aspirin and ACE inhibitors may lead to similar or opposite effects.[8] Salicylates not only block the constitutive COX enzyme but also inhibit phospholipase A2 (PLA2) activity and stimulate NO production. Aspirin and ACE inhibitors may be beneficial by both leading to inhibition of transcription factor NF-κB that modulates endothelial cell function and the expression of inflammatory mediators. But they may be antagonistic through the capacity of aspirin to exacerbate endothelin-1-induced vasoconstriction.[49] In a study investigating the role of local vascular production of NO or prostacyclin in the vasoconstriction induced by endothelin-1 *in vivo* in humans, Haynes and Webb[49] showed a potentiation of responses to endothelin-1 by aspirin, suggesting that endothelial production prostacyclin attenuates responses to endothelin-1 in human veins *in vivo*.

In contrast, Baur et al.[46] suggested that enalapril exerts an independent antithrombotic effect by reducing the formation of thromboxane A and that aspirin consequently does not induce any additive significant therapeutic effect in patients with heart failure treated with enalapril.[46] This view is founded in observing that angiotensin II–induced contraction of isolated blood vessels is attenuated by blockade of thromboxane receptors, suggesting the existence of a thromboxane-mediated mechanism of amplification. In fact, in the study including patients with coronary disease and heart failure receiving combined ACE inhibitors and salicylate, enalapril reduced angiotensin II–induced synthesis of systemic and renal prostacyclin and thromboxane A2, initially only during the day but later also at night. Then, it masked suppression of thromboxane A2 synthesis by salicylate. The overall effect of ACE inhibitors on platelet aggregability remains controversial but aspirin and ACE inhibitors may have similar effects on platelet activation.

Another possible mechanism for an adverse haemodynamic interaction between aspirin and ACE is a pharmacokinetic interaction. Captopril may limit the ability of indomethacin or other renally secreted nonsteroidal anti-inflammatory drugs (NSAIDs) to inhibit renal PG synthesis through competition for access to the renal medulla.[50]

Overall, the exact mechanism of the interaction between ACE inhibitors and aspirin is not known and may be synergistic or antagonistic. It is important that this interaction is characterised because understanding it may induce changes in to the way in which patients with heart failure and coronary disease are treated. Should patients with ischaemic heart failure treated with ACE inhibitors be given aspirin? Are ACE inhibitors effective in patients with heart failure treated with aspirin? If effects are nonadditive, each drug will be unnecessary in the presence of the other.

3. Data on the Potential Interaction between ACE Inhibitors and Aspirin

The interaction between ACE inhibitors and aspirin has been investigated in both experimental and clinical studies. None of them leads to a clear conclusion but they provide some elements for discussion.

3.1 Animal Studies

Some animal pharmacological experiments suggest a negative interaction between ACE inhibitors and NSAIDs but the results of such studies are not unanimous.[10] Some of them are detailed here.

Aspirin has been found to partially block the endothelium-dependent relaxation induced by captopril in isolated canine femoral artery segments,[51] but no significant effect on the haemodynamic and the renal response to acute administration of enalapril was measured after 4 days treatment with aspirin 325 mg/day in a canine pacing model of heart failure.[52]

The availability of a specific bradykinin receptor antagonist (icatibant) allowed investigators to determine the contribution of bradykinin to the effects of ACE inhibitors in animals and a potential way of interaction between ACE inhibitors and aspirin. Concomitant treatment with icatibant abolished the beneficial effects of ACE inhibitor treatment (moexipril) on ventricular remodelling in rats with heart failure caused by coronary artery ligation (i.e. infarct size, the ratio of total heart weight to bodyweight and end-diastolic pressure), while losartan potassium did not affect any of these cardiac parameters.[53] The authors concluded that the cardioprotective effects of the ACE inhibitor administered before myocardial infarction were the result of the reduced breakdown of kinins rather than of the reduced synthesis of angiotensin II.[53] In another study with dogs, aspirin in dosages sufficient to inhibit platelet aggregation did not alter the attenuation of myocardial stunning induced by ramipril (assessed by measuring systemic haemodynamics, posterior myocardial blood flow and wall thickening).[54]

3.2 Human Studies

3.2.1 Clinical Trials

ACE inhibitors exert their beneficial effects by improving haemodynamic parameters, renal func-

tion, pulmonary dynamics and reducing ventricular remodelling.[31] Previous studies gave evidence to support concerns that aspirin may impair the effects of ACE inhibitors on haemodynamic parameters and exercise capacity although findings were not all unanimous. Therefore, reports about the influence of NSAIDs on forearm blood flow in response to sodium nitroprusside (reflecting vascular reactivity) in patients treated with ACE inhibitors are conflicting.

Haemodynamic Studies

Nishimura et al.[55] observed that a single dose of indomethacin 50mg inhibited forearm blood flow vasodilation induced by a single dose of captopril 25mg in patients with heart failure as measured using plethysmography. Nakamura et al.[56] found that pretreatment with high dose aspirin but not an inhibitor of nitric oxide synthesis decreased the endothelium dependent vasodilation induced by intra-arterial enalapril in 10 patients in New York Heart Association (NYHA) II heart failure. But these findings were not observed by other authors. Katz et al.[57] demonstrated that the vasodilating effects of long term enalapril 20mg in the skeletal muscle circulation of patients with heart failure (62 patients with mild to moderate heart failure) are not altered by aspirin. Nonsignificant difference was observed between patients receiving aspirin 325mg, ifetroban 250mg (a specific inhibitor of thromboxane A2) or placebo.[57] In 15 patients with NYHA III heart failure, Jeserich et al.[58] observed that 3 months of treatment with aspirin 100mg was as effective as perindopril 4mg in increasing vascular reactivity. But combined therapy did not further increase vascular reactivity. The authors concluded that the mechanism of action of ACE inhibitors involves COX factors and that the action of aspirin and ACE inhibitors is not additive.[58] In a double-blind, randomised crossover study with patients with severe congestive heart failure, Hall et al.[59] observed that a prior or concomitant single dose of aspirin 325mg totally reversed the systemic haemodynamic effect of enalapril 10mg (decrease in left ventricular filling pressures, systemic end vascular resistances and increase in cardiac output). Similar results were reported with indomethacin. Townend et al.[60] showed that a single dose of indomethacin attenuates the increase in cardiac output and renal blood flow in response to captopril (but not the increase in forearm or calf blood flow). Some systemic haemodynamic studies of the coadministration of NSAIDs and ACE inhibitors are in accordance with these findings. They demonstrated a significant interaction, suggesting a similar pathway. Spaulding et al.[61] investigated the haemodynamic effect of a single dose of oral enalapril 10mg in patients randomly assigned to ticlopidine 500mg or aspirin 350mg for 7 days. Aspirin did not induce any pulmonary effect but abolished the ACE inhibitor induced vasodilation while ticlopidine did not.[61]

In contrast, no significant effect on haemodynamics was identified by Van Wijngaarden et al.[47] in 13 patients with severe heart failure (mean ejection fraction of 21%) receiving a single dose of captopril 25mg with or without short term concomitant aspirin 236mg.[47] Baur et al.[46] reached similar conclusions in 20 patients with NYHA II to III heart failure and ejection fractions below 40%. Short term treatment with aspirin 250mg did not significantly change the blood pressure reduction induced by ACE inhibitor (enalapril 10 to 15mg) administration or alter measures of angiotensin or norepinephrine or renal function. Böger et al.[39] observed that aspirin 100mg did not interfere with the haemodynamic effect of captopril. These studies are summarised in table I.

Renal Function Studies

There is also a potential interaction between ACE inhibitors and aspirin on renal function in patients with heart failure.

ACE inhibitors have been shown to improve the renal function of patients with heart failure. Concomitant treatment of ACE inhibitors with aspirin induced a reduction in renal PGE2 and a commensurate decrease in renal sodium excretion.[62] The retrospective analysis of Dietz et al.[63] concluded that aspirin decreased the ACE inhibitor–induced improvement in glomerular filtration and renal plasma flow.[63] By contrast, Van Wijngaarden et al.[47] did

Table I. Haemodynamic studies assessing the interaction between ACE inhibitors and antiplatelet agents (APA)

Reference	Study population	ACE inhibitor	APA	Duration	Findings	Interaction
Nishimura et al.[55]	14 CHF (NYHA class III & IV)	Captopril 25mg	Indomethacin 50mg	Single dose of each	Inhibits ACE inhibitor induced forearm bloodflow vasodilation	I+
Katz et al.[57]	62 mild or severe CHF (EF < 40%)	Enalapril 20mg	Aspirin (acetylsalicylic acid) 325mg	Long term (4 wk ACE, 6 wk aspirin)	Forearm blood flow not altered by aspirin in patients receiving ACE inhibitors	0
Jeserich et al.[58]	15 CHF (NYHA class III)	Perindopril 4mg	Aspirin 100mg	3 mo	Improved vascular reactivity with aspirin, perindopril or both	0
Hall et al.[59]	8 CHF (EF < 40%)	Enalapril 10mg	Aspirin 350mg	Single dose	Systemic haemodynamic effect: inhibits enalapril induced reduction in systemic vascular resistance, left ventricular filling pressure, total pulmonary resistance and increase in cardiac output	I+
Townend et al.[60]	12 CHF (NYHA class III & IV)	Captopril 25mg	Indomethacin 50mg	Single dose	Inhibits captopril-induced increase in cardiac output and renal flow	I+
Spaulding et al.[61]	20 CHF (NYHA class II & III)	Enalapril 10mg	Ticlopidine 500mg, aspirin 325mg	Single dose of enalapril; 7 days AAP	Inhibits the ACE inhibitor–induced vasodilation	I+
Van Wijngaarden et al. [47]	13 CHF (NYHA class II-IV)	Captopril 25mg	Aspirin 236mg	Single dose >3 wks of either enalapril or captopril	No change in liver or calf blood flow or calf vascular resistance	0
Baur et al.[46]	20 CHF (NYHA II & III; EF < 40%)	Enalapril 5 to 10 mg/day	Aspirin 250mg on second day of ACE Inhibitor	2 days	Unloading abolished in 3 of the 20 patients	0
	12 CHF (NYHA II & III; EF < 40%	Enalapril 5 to 10mg	Aspirin 250 mg/day during last 4 wks of ACE inhibitor	8 wk	Unloading abolished in 1 of the 12 patients	0
Böger et al.[39]	13 healthy women	Captopril 25mg twice daily	Aspirin 100mg	7 days	No effect on blood pressure reduction induced by captopril	0

CHF = cardiac heart failure; **EF** = ejection fraction; **I+** = inhibition of ACE inhibitor–induced effects; **NYHA** = New York Heart Association.

not find any deleterious effect on renal function following the co-administration of aspirin 230mg and captopril. Schwartz et al.[64] observed in 10 elderly patients with heart failure that only 1 patient had a marked fall in creatinine clearance on receiving the combination therapy.

Pulmonary Studies

A very important effect of ACE inhibitor treatment is the improvement in pulmonary function and exercise tolerance that they produce. These are impaired in patients with chronic heart failure and are a major cause of exercise disability. This beneficial action seems to be mediated through prostaglandin activation which might be attenuated by treatment with aspirin.[65]

In a randomised, double-blind, study involving 16 patients with heart failure and 16 age and gender matched control individuals, Guazzi et al.[66] reported that aspirin 325 mg/day counteracted the improvement in pulmonary dynamics and function (improvement in pulmonary carbon monoxide diffusion, peak oxygen consumption, ratio of dead space to tidal volume, carbon dioxide production) induced by the ACE inhibitor enalapril given at a dosage of 10mg twice daily. However, aspirin did not cause any effect on patients who were not taking ACE inhibitors.[66]

Moreover, while aspirin inhibited the beneficial effects of enalapril on pulmonary function and dynamics, it did not interfere with the effects of losartan potassium (increase in peak oxygen consumption, decrease in ratio of dead space to tidal volume and improvement in exercise tolerance).[67]

In another study, aspirin was given to 26 patients with primary dilated cardiomyopathy whose treatment included an ACE inhibitor (n = 18) or not (8) for 8 weeks.[65] In the study, aspirin was found to affect the pulmonary diffusion for carbon monoxide ($M\dot{V}O_2$), and the ventilatory response to exercise in patients receiving ACE inhibitors while it does not modify ventilation efficiency and peak $M\dot{V}O_2$ in patients not taking ACE inhibitors.[65] More recently, the same group pointed out the mechanism responsible for the beneficial action of ACE inhibitors on pulmonary function.[68] They found that the improvement in the diffusing capacity is caused by gradually evolving increases in the alveolar capillary membrane conductance, independent of changes in capillary volume.[68]

In a placebo-controlled study of enalapril, Dickstein et al.[69] corroborate these findings. They did not observe any decrease in cardiopulmonary exercise performance in men with mild heart failure and previous myocardial infarction most of whom were receiving aspirin.[69]

3.2.2 Survival Trials

The above studies provide information about the action of both ACE inhibitor and aspirin on the pathway characteristics of heart failure but the most crucial question involves the effect of these agents on mortality rate.

There are disparities between clinical trials evaluating a potential interaction between ACE inhibitors and aspirin. The main explanation is that it has never been the primary end-point of a prospective, randomised, clinical study. However, some information is provided by *post hoc* subgroup analysis of the results of large clinical trials. Yusuf et al.[70] already pointed out in 1992 that patients with a low ejection fraction taking aspirin did not receive full advantage of the ACE inhibition. Cleland[71] reported from postinfarction clinical trials the benefit provided by ACE inhibitors in patients with heart failure taking or not aspirin. He observed a negative interaction between both drugs. The mortality reduction with ACE inhibitors was less important in the aspirin group, except in the SAVE trial.[17] In this trial, patients on aspirin at baseline had a better prognosis. In a recent overview of 5 long term randomised trials assessing ACE inhibitors in patients with left ventricular dysfunction or heart failure, the proportional benefits of ACE inhibitors were similar whether or not the patients were taking aspirin at baseline.[72] Another overview of the effect of early ACE inhibitor treatment for acute myocardial infarction in the presence or absence of aspirin in 96 712 randomised patients had similar findings.[73] Both aspirin and ACE inhibitors were found to be beneficial in acute myocardial infarction and the reduction in 30-day mortality associ-

Table 2

ated with ACE inhibitors was not significantly different among patients taking aspirin and those who were not.[73]

Some other trials involving patients with heart failure were examined to evaluate the effect on long term mortality of enalapril-aspirin interaction (table II).

Retrospective analysis of data from CONSENSUS II showed that the effect of enalapril in patients with heart failure after myocardial infarction using aspirin at randomisation was less favourable than among patients not taking aspirin at baseline, indicating a negative interaction between aspirin and enalapril (relative risk of mortality of 1.23 versus 0.86 respectively, $p = 0.047$).[74] Coats[77] criticised the methodology of the study and noticed the limitations of the retrospective study.

Taking into account the use of an antiplatelet agent at randomisation, the results of the combined (treatment and prevention) SOLVD trial[13] lead to the same conclusion: enalapril did not improve the prognosis of patients with heart failure taking aspirin whereas it did in 46.3% of patients not receiving concomitant aspirin. In addition, enalapril therapy did not improve the prognosis of patients receiving antiplatelet therapy at randomisation.[78]

It does not mean that aspirin is deleterious in patients with heart failure, because the use of aspirin at baseline was associated in both these studies with a reduction in all-cause mortality risk, even after adjusting for differences in baseline characteristics between the 2 groups.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 3 (GISSI-3) trial, which included patients with diabetes mellitus who had experienced a myocardial infarction, reported a reduced benefit of lisinopril on 6-week mortality postmyocardial infarction in patients receiving aspirin (7.7 *vs* 10.1% mortality in the lisinopril and the placebo group, respectively) compared with patients who were not (13.5 *vs* 24.7% mortality in the lisinopril and the placebo group, respectively).[75]

In contrast, no significant interaction was observed in other trials. The Captopril and Thrombol-

Table II. Clinical trials assessing the interaction between ACE inhibitors and aspirin (acetylsalicylic acid)

Trial	Study population [no. of patients]	Follow-up period	ACE inhibitor	Aspirin	Mortality ACE inhibitor		Mortality placebo	
					aspirin	placebo	aspirin	placebo
CONSENSUS II[74]	Acute MI (<24h) [6090] NYHA (253)	1d to 20mo	IV enalapril 1mg for 2 to 3h	Aspirin (dose unknown)	RR = 0.86	RR = 0.64	RR = 1.23[a]	RR = 0.81
SOLVD[13]	Heart failure (EF < 35%) [6512]	6mo	Enalapril 20 mg/day	Aspirin (dose unknown)	34.8%	35.2%	30.7%	40.3%
GISSI-3[75]	MI (<24h) [2790][b]	6 wks	Lisinopril 2.5, 5 and 10 mg/day	Aspirin (dose unknown)	7.7%	13.5%	10.1%	24.7%
BIP[76]	Stable coronary patients [1247]; 464 patients with CHF	5y	Enalapril or lisinopril (dose unknown)	Aspirin (dose unknown)	24%	35%		
SAVE[17]	MI (3 to 16 days); EF < 40% [2231]	24 to 60mo (mean = 42)	Captopril 50mg 3 times per day	Aspirin (dose unknown)	16.6%	26%	21.4%	29.2%
TRACE[19]	MI & decreased left ventricular function [1749]	24 to 50mo	Trandolapril 4mg	Aspirin (dose unknown)	33.7%	45.2%	27.7%	60%

a p = 0.047.

b Subgroup of patients with diabetes mellitus.

BIP = Bezafibrate Infarction Prevention; **CHF** = cardiac heart failure; **CONSENSUS II** = Cooperative North Scandinavian Enalapril Survival Study II; **EF** = ejection fraction; **GISSI-3** = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; **IV** = intravenous; **MI** = myocardial infarction; **NHYA** = New York Heart Association class; **RR** = relative risk; **SAVE** = Survival and Ventricular Enlargement Study; **SOLVD** = Studies of Left Ventricular Dysfunction; **TRACE** = Trandolapril Cardiac Evaluation.

ysis Study (CATS), evaluating the effect of captopril 75mg, showed that the use of aspirin 80 to 100mg before hospitalisation at the time of randomisation decreased significantly the left ventricular dilation at 1 year in 298 patients with acute anterior infarction receiving streptokinase, irrespective of captopril treatment (2.2 ± 3.0 ml/m^2 *vs* 1.9 ± 2.9 ml/m^2 in patients taking aspirin and 9.6 ± 3.0 ml/m^2 *vs* 7.3 ± 2.4 ml/m^2 in patients who were not). Aspirin did not attenuate the favourable effect of captopril on ventricular dilation (left ventricular volume at 1 year).[79] These results were questioned by Davie[80] because of the evaluation criteria and the doubt about the use of aspirin during the 1 year study. In a retrospective study about 755 stable patients with heart failure (mean ejection fraction: $31.5 \pm 11.5\%$) receiving different ACE inhibitors, aspirin intake did not change the prognosis, whatever the dose of ACE inhibitor and aspirin (mean of 180mg).[81]

Retrospective analysis of the Bezafibrate Infarction Prevention (BIP) trial registry evaluating the effect of bezafibrate in 11 575 stable patients with ischaemic cardiopathy (with or without heart failure)[76] does not confirm the hypothesis that aspirin attenuates the benefit of ACE inhibitors. In the subgroup of patients receiving ACE inhibitors (11%), the use of aspirin was associated with improved 5 years-survival (19 *vs* 27%, $p < 0.0001$), especially among patients with heart failure (464 patients, 24 *vs* 37%, $p = 0.007$).[7]

4. Analysis of the Discrepancies in Trials Investigating the Interaction between Aspirin and ACE Inhibitors

Studies assessed in the review and discussed in section 3 arrived at diverging conclusions. Many factors may be responsible for the differing results seen.

4.1 Methodology of the Studies

The short term experimental studies used only a single dose[46,47,55,59-61] of either agent and involved only small sample sizes.[39,46,47,55-61,64,65,68,82] The chronic effects of long term aspirin ACE inhibitor use can not be determined from such studies.

Analysis of clinical survival studies was retrospective and this limits the applicability of the findings of such studies.[70-76,78,79,81]

Many explanations might be given for the better prognosis seen in patients taking aspirin regardless of whether or not they were receiving ACE inhibitors and the reduced benefit of ACE inhibitors in the presence of aspirin. However, it is impossible to determine from these studies[70-76,78,79,81] whether aspirin was merely a marker of a better prognosis or induced it.

The mechanism of action of both drugs has been suggested to explain the reduced benefit seen with concomitant aspirin and ACE inhibitors. ACE inhibitors favour prostaglandin synthesis by inhibiting the degradation of bradykinin while aspirin inhibits this process. An alternative explanation is that the characteristics of patients at inclusion were not comparable between the studies (severity of heart failure, aetiology of heart failure, ongoing treatment); it is possible that patients treated with aspirin had a lower baseline risk than those not treated with aspirin, independently of concomitant treatment with ACE inhibitors. In addition, crossover between groups might have occurred during a study and underestimated the effect of the drugs. For example, in the survival studies, it was reported what therapy patients were receiving at the time of inclusion into the study and this might not accurately reflect what the patients were actually receiving during the majority of the follow-up period.

The reported studies were short and long term. The effect of the treatment might be different in both cases, whereas the benefit appears only after a long time.

4.2 Interindividual Variability

It is possible that some patients are be more susceptible to the coadministration of aspirin and ACE inhibitor than others. Guazzi et al.[82] showed that in 26 patients with mild or severe hypertension receiving enalapril 20mg twice daily for 5 days, the addition of aspirin 300 mg/day for 5 days can re-

duce both the decrease in BP produced by enalapril (attenuation of more than 20% of the mean BP decrease) and the renin increase induced by enalapril in approximately 50% of patients.[82] This suggests that the action of an ACE inhibitor may vary from one individual to another when either prostaglandin activation (in responders) or angiotensin II blockade (in nonresponders) is predominant.[82]

4.3 Variability in Pathology

The interaction between aspirin and ACE inhibitors has been investigated in various patients: healthy volunteers,[39] patients experiencing hypertension,[82-84] patients with myocardial infarction (CONSENSUS II[74], GISSI-3[75]), chronic ischaemic heart disease (BIP[76]) and pure heart failure (SOLVD[13]). The physiological substrate is very different and may explain the contradictory findings. For example, the heart failure model induces activation of prostaglandin to limit vasoconstriction. In healthy volunteers, Böger et al.[39] found no interaction of low dose aspirin (100mg) with the hypotensive and humoral effect of captopril (25mg x 2), while it did inhibit thromboxane A2 formation. In patients with essential hypertension, low dose aspirin (100 mg/day for 2 weeks) was not found to interfere significantly with the antihypertensive effects of ACE inhibitors (enalapril 20 to 40 mg/day for 4 to 8 weeks).[83] Nawarskas et al.[84] drew similar conclusions in a study involving patients with hypertension receiving 2 daily doses of aspirin (81 or 325 mg) in addition to enalapril or losartan potassium. Mean, systolic and diastolic blood pressures were unchanged.[84] Among patients with myocardial infarction without heart failure treated with concomitant aspirin and ACE inhibitor, 1-year mortality was unchanged (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries I),[85] according to the hypothesis of Baur et al.[46] that aspirin and ACE inhibitor both reduce the formation of thromboxane and therefore do not have additive effects. In a high risk population without heart failure or low ejection fraction, ramipril (10 mg/day) significantly reduced the rates of death, myocardial infarction and stroke (14 *vs* 17.8%, $p < 0.001$), irrespective of the intake of aspirin.[86] Conversely, patients with heart failure seem to be more susceptible to an interaction. Hall et al.[59] demonstrated that 350mg of aspirin deteriorates the beneficial effect of 10mg of enalapril.

The aetiology of heart failure also seems important. In the SOLVD trial,[13] aspirin did not influence the benefit of enalapril in patients with nonischaemic cardiopathy but in patients with ischaemic cardiopathy, the association between aspirin and enalapril did not induce any benefit.

4.4 Treatment Variability

The studies discussed in section 3 were conducted using different types of ACE inhibitors and different dosages of aspirin. The findings might be different with structurally different ACE inhibitors and NSAIDs.

Experimental studies have demonstrated that different ACE inhibitors have different properties (e.g. ability to inhibit tissue ACE) and therefore quite different vasodilating effects. The effect of enalapril upon PGE2 is patient-dependent,[46] and captopril might have a more important effect upon PGE2 than enalapril. Hornig et al.[87] reported that the peripherally-induced vasodilation by quinapril is more important than the one induced by enalapril in patients receiving aspirin.

Differences between NSAIDs may also account for some conflicting data. In fact, 2 distinct COX isoenzymes have been identified (COX-1 and COX-2). Both are able to generate PGs but COX-1 is thought to produce PGs important for regulating physiological processes and COX-2 PGs are produced mainly at sites of inflammation. All NSAIDs inhibit COX-1 and COX-2 but to a variable degree: drugs that preferentially inhibit COX-1 may therefore interact with ACE inhibitors to a greater extent than those that preferentially inhibit COX-2. This might help explain why indomethacin, which inhibits COX-1 more than 20-fold more than COX-2, seems to interact with ACE inhibitors to a greater extent than aspirin, which inhibits COX-1 and COX-2 to an equal extent.[9]

In addition, in some studies, patients received single doses of aspirin and an ACE inhibitor while in others studies patients were receiving a stable regimen of aspirin with an ACE inhibitor. Results of acute administration should not be extrapolated to long term treatment.

The mechanism of action of ACE inhibitors and therefore the influence of coadministration of an antithrombotic dose of aspirin may be different in short or long term treatment with ACE inhibitors. Short term ACE inhibition results in inhibition of bradykinin breakdown and stimulation of prostaglandin synthesis. During long term inhibition, bradykinin levels normalise and inhibition of angiotensin II appears to be the predominant method of action in long term ACE inhibitors treatment.[47]

The interaction between aspirin and ACE inhibitor might be dose-dependent. This is an important consideration because small doses of aspirin being increasingly used in cardiology, although there is no long term data from postinfarction trials showing a benefit with aspirin at doses less than 300 mg/day. Even aspirin 75 mg/day appears to be enough to severely impair the synthesis of vasodilator PG that is not significantly affected by congestive heart failure. An infusion of arachidonic acid, a metabolic precursor of prostacyclin, into the forearm of healthy controls and patients with heart failure treated with ACE inhibitor resulted in vasodilation. Administration of aspirin 75 mg/day for 14 days inhibited mean vasodilation by 55%.[88]

Guazzi et al.[82] observed that a dose of aspirin 300mg induced a BP increase of 60 to 90% when it was added to an ACE inhibitor while a 100mg dose did not induce any significant BP change.[82]

The different dosages of aspirin used in the previously cited studies discussed in section 3 and the fact that dosages are often not specified (e.g. in the BIP[76] study the aspirin dose was quoted as low and as 200mg in the discussion) might account for the discordances in the results. Aspirin has in fact very different actions at an antithrombotic dosage. The study by Van Wijngaarden et al.[47] illustrates the point that aspirin acts selectively through prostaglandin synthesis at antithrombotic doses (40 to 350mg). A 325mg dose of aspirin decreases both prostacyclin and thromboxane production (vasoconstricting) while lower doses (<100 mg) reduce thromboxane production but does not affect prostacyclin synthesis, and a dosage over 160 mg/day reduces renal and extrarenal PG synthesis.[74]

This mechanism is in accordance with findings of Hall et al.[59] (a dose of aspirin 350mg given the day before enalapril 10mg was administered was found to inhibit enalapril-induced vasodilation), of Van Wijngaarden et al.[47] (a single dose of aspirin 236mg combined with captopril was found to produce to similar haemodynamic alterations to those observed with captopril alone) and of Böger et al.[39] (aspirin 100mg did not change the haemodynamic effects of captopril), Guazzi et al.[65] (aspirin 100 mg/day had no effect on blood pressure).

However, high dosages of aspirin may reduce the benefits of ACE inhibitors in patients with hypertension or congestive heart failure, whereas low dosages appear to interact less.[9]

The evidence suggests that lower dosages of aspirin should be used in patients with heart failure treated with ACE inhibitors because such dosages are less likely to have a negative effect on haemodynamic parameters.

5. Discussion

5.1 A Probable Interaction?

Overviewing the reports about the potential interaction between ACE inhibitors and aspirin, it can be presumed that there may be in fact be an interaction. However, this interaction might be overlooked when treatment is monitored with routine measurements of blood pressure[59] or the attenuation is small and observed only at relatively high dosages of aspirin.[8]

5.2 Clinical Impact

The interaction between ACE inhibitors and aspirin may be clinically relevant if it influences the survival of patients receiving both drugs. For this reason, retrospective studies can not be used to as-

sess the clinical relevance of this potential interaction.

Further studies will clarify some aspects of this interaction but will not answer all the questions that require answers. The Warfarin/Aspirin Study of Heart Failure (WASH) randomised trial, a pilot study to Warfarin Antiplatelet Trial in Congestive Heart Failure (WATCH) was aimed at comparing the effect of no antithrombotic treatment, aspirin (300 mg/day) or warfarin [target International Normalised Ratio (INR) = 2.5] on outcome (a composite of myocardial infarction, stroke, death) in patients with heart failure (ejection fraction < 0.35) receiving diuretics.[89] 279 patients aged 63 years were included and followed 27 months; 60% had coronary artery disease, 90% were receiving ACE inhibitors, 90% were in sinus rhythm. The outcome was not significantly different in the control group (21, 7, 2% for myocardial infarction, stroke and death, respectively), in the aspirin group (30, 9, 2%, respectively) and the warfarin group (25, 3, 0%, respectively). This small open study could not assess the interaction between aspirin and ACE inhibitors because of the size of the study, the absence of double-blind and the high percentage of patients who left the study prematurely (approximately 30% per group).

The double-blind randomised WATCH study comparing the effect of warfarin (target INR = 2.5 to 3), aspirin (162.5 mg/day) and clopidogrel (75 mg/day) in 4500 patients with heart failure will look especially at interactions between aspirin and ACE inhibitors with a mean follow-up of 3 years. Results are expected in 2004.

The double-blind randomised Heart Failure Long Term Antithrombotic Study (HELAS) will compare for 2 years the effect of warfarin (target INR = 2 to 3) with aspirin (325 mg/day) in patients with postinfarction heart failure, and the effect of warfarin (target INR = 2 to 3) with placebo in patients with heart failure and idiopathic or hypertensive dilated cardiomyopathy.[90]

5.3 Practical Issues

After considering the available data, the coadministration of aspirin and ACE inhibitors cannot be rejected. The findings of studies conducted to date are conflicting: some authors recommend stopping aspirin when starting an ACE inhibitor in patients with heart failure while others are in favour of the co-prescription of both drugs in some cases[9]. Recently, Pfeffer[91] indicated that the available data should not deny any patient with acute myocardial infarction from treatment with aspirin and ACE inhibitors when the patient presents with pulmonary congestion or left ventricular dysfunction.[91] The dosage of aspirin might account for the clinical significance of the association with ACE inhibitors but most of postinfarction trials administered dosages of at least 300 mg/day, leaving the efficacy of lower dosages unproved for this use.[9]

In summary, further prospective studies are necessary. At first, experimental studies using a range of aspirin dosages in patients with heart failure treated with ACE inhibitors should be conducted. These should be followed by long term survival studies that focus on the effects of different doses of aspirin given concomitantly with ACE inhibitors in patients with heart failure.[11] The WATCH and HELAS studies will clarify the effect of coadministration of aspirin and ACE inhibitors in patients with heart failure and ischaemic heart disease and precise the place of clopidogrel in ischaemic cardiac disease and heart failure.

While waiting for the results of such studies, it would seem reasonable to give low dose aspirin to patients who have heart failure and concomitant ischaemic heart disease and who are receiving ACE inhibitors with appropriate blood pressure and haemodynamic monitoring. For patients with heart failure of another aetiology, there is no strong enough argument to recommend prescribing simultaneous administration of ACE inhibitors and aspirin.

References

1. Goldberg RJ. Assessing the population burden from heart failure. Arch Intern Med 1999; 159: 15-7

2. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. Eur Heart J 1997; 18: 208-25
3. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: rationale for preventive strategies and comprehensive disease management. Am Heart J 1997; 133: 703-12
4. Teerlink JR, Goldhaber SZ, Pfeffer MA. An overview of contemporary etiologies of congestive heart failure. Am Heart J 1991; 121: 1852-3
5. Ho KKL, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol 1993; 22 Suppl. A: 6A-13A
6. Cleland JGF, Bulpitt CJ, Falk RH, et al. Is aspirin safe for patients with heart failure? Br Heart J 1995; 74: 215-9
7. Leor J, Reicher-Reiss H, Goldbourt U, et al. Aspirin and mortality in patients treated with angiotensin-converting enzyme inhibitors. A cohort of 11575 patients with coronary heart disease. J Am Coll Cardiol 1999; 33: 1920-5
8. Garcia-Dorado D, Velasco Rami J, Virgos Lamela A, et al. Interaction between antiplatelets agents and ACE inhibitors in patients with acute myocardial infarction. Eur Heart J 1999; 1 Suppl. F: 24F-28F
9. Nawarskas JJ, Spinler SA. Does aspirin interfere with the therapeutic efficacy of angiotensin-converting enzyme inhibitors in hypertension or congestive heart failure? Pharmacotherapy 1998; 18: 1041-52
10. Teerlink JR, Massie BM. The interaction of ACE inhibitors and aspirin in heart failure: torn between two lovers. Am Heart J 1999; 138: 193-7
11. Song KH, Fedyk R, Hoover R. Interaction of ACE inhibitors and aspirin in patients with congestive heart failure. Ann Pharmacother 1999; 33: 375-7
12. Stys T, Lawson WE, Smaldone GC, et al. Does aspirin attenuate the beneficial effects of angiotensin-converting enzyme inhibition in heart failure? Arch Med Intern 2000; 160: 1409-13
13. The SOLVD Investigators. Effects of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 1991; 325: 293-302
14. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991; 325: 303-10
15. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316: 1429-35
16. Latini R, Maggioni AP, Flather M, et al. ACE inhibitors use in patients with myocardial infarction: summary of evidence from clinical trials. Circulation 1995; 92: 3132-7
17. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327: 669-77
18. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821-8
19. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995; 333: 1670-6
20. Garg R, Yusus S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995; 273: 1450-6
21. The Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. Eur Heart J 1997; 18: 736-53
22. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction. Circulation 1998; 97: 2202-12
23. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease. A statement for healthcare professionals from the American Heart Association. Circulation 1997; 96: 2751-3
24. ISIS-2 (Second International Study of Infarct Survival) collaborative group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988; II: 349-60
25. Baigent C, Collins R, Appleby P, et al. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) collaborative group. BMJ 1998; 316: 1337-43
26. Antiplatelet Trialists Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. BMJ 1988; 296: 320-31
27. Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81-106
28. Aspirin Myocardial Infarction Study Research Group. A randomised, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA 1980; 243: 661-8
29. The Persantine-Aspirin Reinfarction Study (PARIS) Research Group. Persantine and aspirin in coronary disease. Circulation 1980; 62: 449-62
30. Hennekens CH, Albert CM, Godfried SL, et al. Adjunctive drug therapy of acute myocardial infarction: evidence from clinical trials. N Engl J Med 1996; 335: 1660-7
31. Patten RD, Udelson JE, Konstam MA. Ventricular remodeling and its prevention in the treatment of heart failure. Curr Opin Cardiol 1998; 13: 162-7
32. Bönner G. The role of kinins in the antihypertensive and cardioprotective effects of ACE inhibitors. Drugs 1997; 54 Suppl. 5: 23-30
33. Williams GH, Dluhy RG. Control of aldosterone secretion. In: Genest J, Kuchel O, Hamet P, et al., editors. Hypertension: physiopathology and treatment, 2nd ed. New York (NY): McGraw-Hill, 1983: 320-38
34. Schwieler JH, Kahan T, Nussberger J, et al. Converting enzyme inhibition modulates sympathetic neurotransmission in vivo via multiple mechanisms. Am J Physiol 1993; 264: E631-7
35. Mason DT, Melmon KL. Effects of bradykinin on forearm venous tone and vascular resistance in man. Circ Res 1965; 17: 106-13
36. Schrör K. Role of prostaglandins in the cardiovascular effects of bradykinin and angiotensin-converting inhibitors. J Cardiovasc Pharmacol 1992; 20 Suppl. S: 68S-73S
37. Cockroft JR, Chowienczyk PJ, Chrosch R, et al. Inhibition of bradykinin-induced vasodilation in the human forearm vasculature by iactibant, a B2-receptor antagonist. Br J Clin Pharmacol 1994; 38: 317-22
38. Dzau VJ, Packer M, Lilly LS, et al. Prostaglandins in severe congestive heart failure. Relation to activation of the renin-

angiotensin system and hyponatremia. N Engl J Med 1984; 310: 347-52
39. Böger RH, Bode-Böger SM, Kramme P, et al. Effect of captopril on prostacyclin and nitric oxide formation in healthy human subjects: interaction with low dose acetylsalicylic acid. Br J Pharmacol 1996; 42: 721-7
40. Gottlieb SS, Robinson S, Krichten CM, et al. Renal response to indomethacin in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1992; 70: 890-3
41. Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. Circulation 1997; 95: 1115-8
42. Luque M, Martin P, Martell N, et al. Effects of captopril related to increased levels of prostacyclin and angiotensin (1-7) in essential hypertension. J Hypertens 1996; 14: 799-805
43. Davie AP, Dargie HJ, McMurray JJV. Role of bradykinin in the vasodilator effects of losartan and enalapril in patients with heart failure. Circulation 1999; 100: 268-73
44. Dzeka TN, Kuzminski P, Arnold JMO. Venous responsiveness to norepinephrine in healthy subjects: effects of single doses of 325mg aspirin. Clin Pharmacol Ther 2000; 67: 299-304
45. Smith SR, Coffman TM, Svetkey LP. Effect of low-dose aspirin on thromboxane production and the antihypertensive effect of captopril. J Am Soc Nephrol 1993; 4: 1133-9
46. Baur LH, Schipperheyn JJ, van der Laarse A, et al. Combining salicylate and enalapril in patients with coronary artery disease and heart failure. Br Heart J 1995; 73: 227-36
47. Van Wijngaarden J, Smit AJ, de Graeff PA, et al. Effects of acetylsalicylic acid on peripheral hemodynamics in patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. J Cardiovasc Pharmacol 1994; 23: 240-5
48. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. N Engl J Med 1973; 289: 198-200
49. Haynes G, Webb DJ. Endothelium-dependent modulation of responses to endothelin-1 in human veins. Clin Sci 1993; 84: 427-33
50. Quilley J, Duchin KL, Hudes EM, et al. The antihypertensive effect of captopril in hypertension: relationship to prostaglandins and the kallikrein-kinin system. J Hypertens 1987; 5: 121-8
51. Moroi M, Akatsuka N, Fukazawa M, et al. Endothelium-dependent relaxation by angiotensin-converting enzyme inhibitors in canine femoral arteries. Am J Physiol 1994; 266: 583-9
52. Evans MA, Burnett Jr CJ, Redfield MM. Effect of low dose aspirin on cardiorenal function and acute hemodynamic response to enalaprilat in a canine model of severe heart failure. J Am Coll Cardiol 1995; 25: 1445-50
53. Stauss HM, Zhu YC, Redlich T, et al. Angiotensin-converting enzyme inhibition in infarct-induced heart failure in rats: bradykinin versus angiotensin II. J Cardiovasc Risk 1994; 1: 255-62
54. Rose J, Ehring T, Sakka SG, et al. Aspirin does not prevent the attenuation of myocardial stunning by the ACE inhibitor ramiprilat. J Mol Cell Cardiol 1996; 28: 608-13
55. Nishimura H, Kubo S, Ueyama M, et al. Peripheral hemodynamic effects of captopril in patients with congestive heart failure. Am Heart J 1989; 117: 100-5
56. Nakamura M, Funakoshi T, Arakawa N, et al. Effect of angiotensin-converting enzyme inhibitors on endothelium-dependent peripheral vasodilation in patients with chronic heart failure. J Am Coll Cardiol 1994; 24: 1321-7
57. Katz SD, Radin M, Graves T, et al. Effect of aspirin and ifetroban on skeletal muscle blood flow in patients with congestive heart failure treated with enalapril. J Am Coll Cardiol 1999; 34: 170-6
58. Jeserich M, Pape L, Just H, et al. Effect of long-term angiotensin-converting enzyme inhibition on vascular function in patients with chronic congestive heart failure. Am J Cardiol 1995; 76: 1079-82
59. Hall D, Zeitler H, Rudolf W. Counteraction of the vasodilator effects of enalapril by aspirin in severe heart failure. J Am Coll Cardiol 1992; 20: 1549-55
60. Townend JN, Doran J, Lote CJ, et al. Peripheral haemodynamic effects on inhibition of prostaglandin synthesis in congestive heart failure and interactions with captopril. Br Heart J 1995; 73: 434-41
61. Spaulding C, Charbonnier B, Cohen-Solal A, et al. Acute hemodynamic interaction of aspirin and ticlopidine with enalapril: results of a double blind randomized comparative trial. Circulation 1998; 98: 757-65
62. Riegger GA, Kahles HW, Elsner D, et al. Effects of acetylsalicylic acid on renal function in patients with chronic heart failure. Am J Med 1991; 90: 571-5
63. Dietz R, Nagel F, Osterziel K. Angiotensin-converting enzyme inhibitors and renal function in heart failure. Am J Cardiol 1992; 70 Suppl. C: 119C-25C
64. Schwartz D, Kornowski R, Lehman H, et al. Combined effect of captopril and aspirin on renal haemodynamics in elderly patients with congestive heart failure. Cardiology 1992; 81: 334-9
65. Guazzi M, Pontone G, Agostini P, et al. Aspirin worsens exercise performance and pulmonary gas exchange in patients with heart failure who are taking angiotensin-converting enzyme inhibitors. Am Heart J 1999; 138: 254-60
66. Guazzi M, Marenzi G, Alimento M, et al. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. Circulation 1997; 95: 1930-6
67. Guazzi M, Melzi G, Agostini P. Comparison of changes in respiratory function and exercise oxygen uptake with losartan versus enalapril in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1997; 80: 1572-6
68. Guazzi M, Agostini P. Decrease by ACE-inhibition of the excessive alveolar-capillary membrane resistance to gas transfer in chronic heart failure. Cardiologia 1998; 43: 625-30
69. Dickstein K, Barvik S, Aarsland T. Effect of long-term enalapril therapy on cardiopulmonary exercise performance in men with mild heart failure and previous myocardial infarction. J Am Coll Cardiol 1991; 18: 596-602
70. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet 1992; 340: 1173-8
71. Cleland JGF. Anticoagulation and antiplatelet therapy in heart failure. Curr Opinion Cardiol 1997; 12: 276-87
72. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000; 355: 1575-81
73. Latini R, Tognoni G, Maggioni AP, et al. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96712 randomised patients. J Am Coll Cardiol 2000; 35 (7): 1801-7

74. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). Am J Cardiol 1997; 79: 115-9
75. Zuanetti G, Latini R, Maggioni AP, et al. Effect of the ACE inhibitor lisinopril on mortality in diabetic patients with acute myocardial infarction. Data from the GISSI-3. Circulation 1997; 96: 4239-45
76. Goldbourt U, Behar S, Reicher-Reiss H, et al. Rationale and design of a secondary prevention trial of increasing serum high-density lipoprotein cholesterol and reducing triglycerides in patients with clinically manifest atherosclerotic heart disease (the Bezafibrate Infarction Prevention Trial). Am J Cardiol 1993; 71: 909-15
77. Coats AJS. Enalapril, aspirin interaction. Am J Cardiol 1997; 80 (8): 1122
78. Al-Khadra AS, Salem DN, Rand WM, et al. Antiplatelets agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Trial. J Am Coll Cardiol 1998; 31: 419-25
79. Oosterga M, Anthonio RL, de Kam PJ, et al. Effects of aspirin on angiotensin-converting enzyme inhibition and left ventricular dilatation one year after acute myocardial infarction. Am J Cardiol 1998; 81: 1178-81
80. Davie AP. Effects of aspirin on angiotensin-converting enzyme inhibition and left ventricular dilation one year after acute myocardial infarction. Am J Cardiol 1999; 83: 641
81. Aumégeat V, de Groote P, Meurice T, et al. Aspirin and angiotensin-converting enzyme inhibitors in 445 patients with moderate congestive heart failure [abstract]. J Am Coll Cardiol 1999; 33: 214A
82. Guazzi M, Campodonico J, Celeste F. Antihypertensive efficacy of angiotensin converting enzyme inhibition and aspirin counteraction. Clin Pharmacother 1998; 63: 79-86
83. Polonia J, Boaventura I, Gama G, et al. Influence of non-steroidal anti-inflammatory drugs on renal function and 24h ambulatory blood pressure-reducing effects of enalapril and nifedipine gastrointestinal therapeutic system in hypertensive patients. J Hypertens 1995; 13: 925-31
84. Nawarskas JJ, Townsend RR, Cirigliano MD, et al. Effect of aspirin on blood pressure in hypertensive patients taking enalapril or losartan. Am J Hypertens 1999; 12: 784-9
85. Peterson JG, Laur MS, Young JB, et al. Evidence for an adverse interaction between ACE inhibitors and aspirin following myocardial infarction: the GUSTO-I Trial [abstract]. J Am Coll Cardiol 1998; 31 Suppl. A: 96A
86. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145-53
87. Hornig B, Arakawa N, Drexler H. Differential effects of quinaprilat and enalaprilat on endothelial function of conduit arteries in patients with heart failure. Circulation 1998; 98: 2842-8
88. Davie AP, Love MP, McMurray JJ. Even low-dose aspirin inhibits arachidonic acid-induced vasodilation in heart failure. Clin Pharmacol Ther 2000; 67: 530-7
89. The WASH Study Steering Committee and Investigators. The WASH Study/Warfarin/Aspirin Study in Heart Failure: rationale design and end points. Eur J Heart Failure 1999; 1: 95-9
90. Cokkinos DV, Toutouzas PK. Antithrombotic therapy in heart failure: a randomised comparison of warfarin vs aspirin (HELAS). Eur J Heart Failure 1999; 1: 419-23
91. Pfeffer MA. ACE Inhibitor in acute myocardial infarction. Patient selection and timing. Circulation 1998; 97: 2192-4

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