EDITORIAL COMMENT

The Aspirin–Angiotensin-Converting Enzyme Inhibitor Tradeoff: To Halve and Halve Not*

Donald Hall, MD, FACC
Munich, Germany

Aspirin is an effective drug that, through inhibition of platelet aggregation, has been shown to lower morbidity and mortality in almost every aspect of coronary artery disease, including primary prevention, secondary prevention after acute myocardial infarction, unstable angina pectoris and after coronary artery bypass graft surgery (1). It is inexpensive and easy to use. Angiotensin-converting enzyme (ACE) inhibitors are also effective drugs. In heart failure, through a number of actions, including improved hemodynamics centered on systemic arterial vasodilation, enhanced renal perfusion and function, rectification of electrolyte disturbances, arrhythmia suppression, as well as a favorable influence on hypertrophy and cell proliferation, ACE inhibitors have been shown to ameliorate symptoms and lower morbidity and mortality (2–6). Because coronary artery disease is the most common cause of heart failure, obviously, there is considerable potential for combined treatment with aspirin and an ACE inhibitor, with the intention of providing the benefits of both drugs. Can we double the benefit? There is abundant data from short-term experimental and clinical investigations questioning the expedience of this practice, and on the basis of results of major, controlled, long-term, morbid-event studies of ACE inhibitors, the yield of the combination appears to be a consistent lessening of the risk reduction of cardiovascular events by about one-half.

The interaction is primarily between aspirin and the compensatory hemodynamic mechanisms of heart failure and not necessarily between aspirin and a given ACE inhibitor. However, because ACE inhibitors share and enhance the effects of these desirable compensatory mechanisms, they are particularly susceptible to the interaction and subsequently incur a loss of benefits (7). The more severe the heart failure, the more appreciable the interaction, and this thread goes back as far as 1980, before the era of ACE inhibitors, at which time both the Aspirin in Myocardial Infarction Study (AMIS) and Persantine Aspirin ReInfarction Study (PARIS) studies showed that aspirin may be helpful in patients with well-preserved ventricular function, but harmful in those with considerable ventricular damage (8,9).

The pharmacodynamic actions of aspirin and ACE inhibitors are mutually counteractive. Consequently, it is not surprising that we cannot obtain meaningful potentiation by stimulating with one drug the same system we inhibit with another. Angiotensin-converting enzyme inhibition promotes prostaglandin synthesis. In addition to a reduction in vasoconstrictive factors incurred through blockade of angiotensin II generation, ACE inhibitors also antagonize the action of structurally identical kininase II, thereby impeding the degradation of bradykinin, a potent vasodilator in its own right, which also enlists further vasodilatory support by enhancing production of prostaglandins. Aspirin, in contrast, inhibits prostaglandin synthesis, and its intended action in coronary artery disease is achieved through blockade of the enzyme cyclooxygenase, which catalyzes the first step in the biosynthesis of platelet thromboxane A2 and all other prostaglandins from arachidonic acid.

Is the prostaglandin system really so important? In normotensive, euvolemic, sodium-replete subjects, it may be difficult to objectify any hemodynamic effects of prostaglandin synthesis inhibition. In hypertensive patients, however, interactions with aspirin or other nonsteroidal anti-inflammatory drugs have been known for many years; they are easily detected and have been reported to attenuate the blood pressure–lowering effects of nearly every antihypertensive drug ever used clinically, such as beta-adrenergic blocking agents, diuretics, direct-acting and alpha-blocking vasodilators, as well as ACE inhibitors (10,11).

Analogously, in patients with left ventricular dysfunction and no or only a mild degree of heart failure, the hemodynamic effect of aspirin may be discrete and elude detection on an individual basis. In patients with severe heart failure, this is not the case. As the severity of the disease increases, there is escalation of neurohumoral activity with increases in vasoconstrictive angiotensin II, norepinephrine and vasopressin, with a concomitant increase in vasodilator prostaglandin synthesis to a degree sufficient to restrain the pressor action and maintain a balance of forces, albeit deranged (12). Treatment with ACE inhibitors fortifies the restraint of the prostaglandin system, the activity of which is also stimulated by the use of diuretics. Under these circumstances, the relevance and magnitude of the restraining forces can be best appreciated by turning them off. Instead of the significant increase in cardiac output and significant decreases in systemic vascular resistance and left ventricular filling pressure when enalapril was given without aspirin, when given with or on the day after a 350-mg dose of

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From the German Heart Center, Technical University of Munich, Munich, Germany.
In heart failure, aspirin can not only offset the direct hemodynamic benefits of ACE inhibition, but also encumber optimal treatment through adverse effects on renal function, which can surreptitiously worsen the condition and necessitate initiation of or increased use of diuretics. The fact that aspirin and other nonsteroidal anti-inflammatory drugs can cause depression of the glomerular filtration rate not only in patients with compromised renal perfusion due to heart failure or other causes, but also in normal subjects, was documented decades ago (14,15). Here, too, the more the prostaglandin system is activated to preserve renal function, the more likely is a clinically manifest interaction. The natriuretic effects of the diuretics used as a cornerstone of most heart failure regimens are also attenuated by interactions with aspirin and similar drugs (16,17). In addition, the prostaglandins stimulated in response to elevated levels of norepinephrine, angiotensin II and vasopressin (i.e., heart failure) also function as a negative feedback loop to restrain the action of vasopressin on hydroosmotic water flow in the distal tubule and collecting ducts, and experimental studies have repeatedly demonstrated enhanced vasopressin action after prostaglandin synthesis inhibition (18,19). In patients with severe heart failure, despite diuretic treatment and ACE inhibition, which may lower prevailing vasopressin levels, loss of the inhibitory action of prostaglandins after a single dose of aspirin imposed a further burden on circulatory homeostasis by increasing total body water, with significant decreases in the serum sodium concentration and plasma osmolality (20). Not only does this dictate the need for higher diuretic dosages, but also, in some patients, the changes in fluid volume and composition were of sufficient magnitude to result in hyponatremia, and this alone may be associated with a less favorable prognosis (21).

Even though the prostaglandin-dependent hemodynamic and renal effects of ACE inhibitors may be counteracted by aspirin, ACE inhibition, per se, is still achieved when aspirin is given concomitantly. Plasma active renin concentrations are increased, and there is a reduction in plasma norepinephrine associated with slowing of the heart rate and tendencical decreases in mean right atrial and pulmonary artery pressures, indicating maintenance of prostaglandin-independent effects (7). Effects on myocardial hypertrophy and cell proliferation may be unaltered, but the clinical relevance remains to be established. Arrhythmia suppression, which is more likely related to norepinephrine concentrations, may persist, and this could account for the findings in the second Veterans Administration Vasodilator Heart Failure Trial (V-HeFT II) comparing enalapril with the combination of hydralazine and isosorbide dinitrate (2). About one-half of the patients had coronary artery disease, and it is reasonable to assume that the majority was taking aspirin, although the number was not specified. In patients without coronary artery disease, there was a trend toward a preferential beneficial effect on mortality, and those taking enalapril fared better than those taking hydralazine plus isosorbide dinitrate. Overall, there was no difference in mortality from pump failure between the two drug regimens, and the significantly better outcome in the enalapril group was exclusively due to a reduction in sudden death. Here, the question arises whether it could be possible that, in patients with coronary artery disease, vasodilation with either an ACE inhibitor or hydralazine plus isosorbide dinitrate was equally affected by aspirin, leading to no change in heart failure deaths. Other major studies have also demonstrated some benefits of treatment with an ACE inhibitor when aspirin was given concomitantly, however, the benefits were conspicuously and consistently less in patients reported to be taking aspirin, and in those studies in which the number of patients taking aspirin was not reported, in those with coronary artery disease who were more likely to be taking aspirin (Table 1). Even in patients with no overt manifestations of heart failure in the Studies Of Left Ventricular Dysfunction (SOLVD) Prevention trial, possibly by virtue of the large number of patients, there was a significantly lesser reduction in mortality by enalapril in patients taking aspirin (22), and, similarly, significantly less favorable outcome of treatment with enalapril was reported in patients also taking aspirin from the combined analysis of the SOLVD Prevention and Treatment trials. In two other studies—the Survival And Ventricular Enlargement (SAVE) study using captopril (5) and the Acute Infarction Ramipril Efficacy (AIRE) study (6)—both of which enrolled only about one-half of the number of patients as in the SOLVD Prevention trial, the trend toward a more favorable outcome without aspirin was unmistakable, and this was explicitly pointed out by the authors of the latter study.

The second COoperative North Scandinavian ENalapril SUsvival Study (CONSENSUS II) (23), one of the largest of the studies, showed a trend toward less favorable outcome in patients receiving enalapril as compared with placebo. In an analysis performed subsequently, specifically to address the question of an interaction between aspirin and ACE inhibitors, a significant excess in mortality was observed when enalapril was randomized to patients using aspirin (24). In all of these studies, it was apparent that ACE inhibitors work better when given without aspirin. Depending on the degree of heart failure and neurohumoral activation, the magnitude of the interaction may range from subtle to overt. Moreover, it appears that the clinical problem cannot be circumvented with an aspirin-based compromise using low doses. Our hospital records docu-
Table 1. Risk Reduction in Major Heart Failure Studies of Angiotensin-Converting Enzyme Inhibitors

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>Drug (Dose)</th>
<th>CAD (%)</th>
<th>Aspirin* (%)</th>
<th>ΔRisk† (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIRE (6) n = 2,006</td>
<td>Ramipril (10 mg in 77%) vs. placebo</td>
<td>All</td>
<td>Ramipril (77%) vs. placebo (78%)</td>
<td>Aspirin (−15%) vs. no aspirin (−27%)</td>
<td>Authors: &quot;even greater benefit in those not receiving aspirin.&quot;</td>
</tr>
<tr>
<td>CONSENSUS II (23) n = 6,090</td>
<td>Enalapril (20 mg in 82%) vs. placebo</td>
<td>All</td>
<td>Enalapril (77%) vs. placebo (78%)</td>
<td>Enalapril (8%) vs. placebo (3%)</td>
<td>Significant excess in mortality in patients with enalapril and aspirin.</td>
</tr>
<tr>
<td>SAVE (5) n = 2,231</td>
<td>Captopril (150 mg in 79%) vs. placebo</td>
<td>All</td>
<td>Captopril (59%) vs. placebo (59%)</td>
<td>Aspirin (−20%) vs. no aspirin (−29%)</td>
<td></td>
</tr>
<tr>
<td>SOLVD (4) Prevention n = 4,228</td>
<td>Enalapril (17 mg) vs. placebo</td>
<td>Enalapril (83%) vs. placebo (83%)</td>
<td>Enalapril (56%) vs. placebo (53%)</td>
<td>Not reported</td>
<td>Significantly lesser effect on mortality in patients taking aspirin.</td>
</tr>
<tr>
<td>SOLVD (3) Treatment n = 2,569</td>
<td>Enalapril (16 mg) vs. placebo</td>
<td>Enalapril (70%) vs. placebo (72%)</td>
<td>Enalapril (33%) vs. placebo (34%)</td>
<td>CAD (−12%) vs. no CAD (−27%)</td>
<td>Significantly less favorable outcome in patients with aspirin (combined analysis with SOLVD Prevention).</td>
</tr>
<tr>
<td>V-HeFT II (2) n = 804</td>
<td>Enalapril (15 mg) vs. hydralazine (199 mg) + ISDN (100 mg)</td>
<td>Enalapril (54%) vs. hydralazine + ISDN (51%)</td>
<td>Not reported</td>
<td>CAD (−13%) vs. no CAD (−26%)</td>
<td>Mortality reduction only with enalapril and only due to a reduction in sudden deaths but not heart failure deaths.</td>
</tr>
<tr>
<td>Latini et al. (25) n = 96,712</td>
<td>Various ACE inhibitors vs. control</td>
<td>All</td>
<td>ACE inhibitors (91%) vs. control (90%)</td>
<td>Heart failure Aspirin (−3%) vs. no aspirin (−9%)</td>
<td>7-Day mortality Aspirin (−7%) vs. no aspirin (−15%)</td>
</tr>
</tbody>
</table>

*This includes patients reported to be taking aspirin, or, if the number of those taking aspirin was not reported, patients with coronary artery disease who were more likely to be taking aspirin. In patients taking aspirin, the risk reduction is consistently about one-half of that of patients not taking aspirin. †Reported change (Δ) in percent risk of a cardiovascular event.

Data in parentheses for coronary artery disease (CAD), aspirin and Δ risk are presented as percentage of patients.

AC = admission criteria; ACE = angiotensin-converting enzyme; AIRE = Acute Infarction Ramipril Efficacy; AMI = acute myocardial infarction; CCS-1 = Chinese Cardiac Study; CONSENSUS II = second COoperative North Scandinavian ENalapril Survival Study; EF = ejection fraction; GISSI-3 = Gruppo Italiano per lo studio della nell’Infarto myocardico; ISDN = isosorbide dinitrate; ISIS-4 = International Study of Infarct Survival; NYHA = New York Heart Association; SAVE = Survival And Ventricular Enlargement; SOLVD = Studies Of Left Ventricular Dysfunction; V-HeFT II = Veterans Administration Vasodilator Heart Failure Trial.
ment that, on repeated occasions, in some patients with otherwise terminal, catecholamine-dependent heart failure, marked hemodynamic improvement, stabilization and abatement of hyponatremia with reduced diuretic dosages resulted from discontinuation of a daily, 100-mg dose of aspirin with no additional therapeutic manipulations.

In this issue of the Journal, Latini et al. (25) report the meta-analyzed data from a vast number of patients in four of the largest multicenter studies ever undertaken (Chinese Cardiac Study [CCS-1], CONSENSUS II, Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico 3 [GISSI-3] and International Study of Infarct Survival 4 [ISIS-4]) (24). There were no significant differences in the risk reductions after acute myocardial infarction with an ACE inhibitor in the two groups of patients: those concomitantly treated with aspirin and those who did not receive aspirin. Consequently, the investigators surmise that guidelines suggesting a possible negative interaction between aspirin and ACE inhibitors should be reconsidered. So let’s reconsider.

The most obvious limitation of the interpretation of their results is that the two groups of patients are substantially disparate; the 30-day mortality rate in those receiving aspirin was 7%, and those who did not receive aspirin had a 30-day mortality rate of 14%. The difference was significant, but the reasons for giving or withholding aspirin were not reported. The latter group of patients was older and sicker. In addition, at about one-tenth the size, the no-aspirin group is decisively at a statistical disadvantage. What we can derive from their analysis is that the combination of an ACE inhibitor and aspirin does, in fact, reduce mortality (albeit, from 6.7% to 6.3%—not very impressive). However, nearly identical figures have been reported in the other studies, and even ISIS-4, which supplied ~60% of the patients, characterized this reduction as “only moderate.” None of the four studies, in which almost 90% of the patients were taking aspirin, was able to show a significant reduction in heart failure with the various ACE inhibitors, and in three of the four studies, the incidence of cardiogenic shock was increased, in one significantly. The combined analysis showed that the trend toward a proportional reduction in heart failure in patients receiving aspirin (3.3%), again, was less than one-half of that in those not receiving aspirin (8.8%). This leaves open a distinct possibility that the difference could be significant if there had been 90,000 patients in the non-aspirin group. Differences in the reduction of seven-day mortality (15% vs. 7%) and 30-day mortality (10% vs. 6%) in control subjects in the no-aspirin and aspirin groups, respectively, are discarded as nonsignificant. On the basis of the available data, however, the study by Latini et al. had only 13% power to detect whether any of these differences are significant. Interestingly, in the studies included in their analysis, there were also no significant reductions in postinfarction angina, the need for interventions, reinfarction or ventricular fibrillation. If you are still wondering exactly what the ACE inhibitor did, the question is justified. Apparently, the only significant result was an excess of stroke in the aspirin group as compared with the no-aspirin group.

Latini et al. (25) have not made their case for zero interaction. Although there may be some short-term benefit of giving enalapril and aspirin to patients with acute myocardial infarction, for those who have done investigations to determine whether this benefit is really the best we can do for our patients, the argument is not very persuasive and, in any case, cannot be extrapolated to long-term treatment. Directly or indirectly, studies such as AIRE and ISIS-4 have already addressed the issue, and not one, except perhaps for CONSENSUS II, has shown that ACE inhibitors are of no benefit when given together with aspirin. Nevertheless, numerous studies have reported that without aspirin, the benefits of ACE inhibitors are more favorable than with aspirin. Basically, Latini et al. have done more to corroborate than refute this. Table 1 shows that the extent of attrition of the risk reduction—invariably about one-half—is the same as that seen in other major studies, either as a trend or a significant difference. Without a comparable control group (an approximate number of “healthy” patients with infarction with a 30-day mortality rate of ~7% who did not receive aspirin, or a similar number of “sick” patients with infarction with a 30-day mortality rate of 14% who did receive aspirin), a valid comparison cannot be made; again, if an appropriate control group had been available, it is possible that in this study, too, without aspirin, the risk reduction for heart failure and mortality may have been statistically greater.

In conclusion, if guidelines exist, there is no convincing reason to abandon them. To whatever extent the improvement in symptoms and survival rendered by treatment with ACE inhibitors is attributable to their effects on the circulation and kidneys, this benefit can be rescinded by concomitant administration of aspirin. Although some useful prostaglandin-independent actions may persist, shutting down the entire prostaglandin system at the level of cyclooxygenase and trading off about one-half of the potential risk reduction, with forfeit of salutary hemodynamic and renal effects, is a high price to pay just to stop production of thromboxane A₂.

Accordingly, for patients requiring long-term treatment for heart failure, the physician is still well advised, if possible, to avoid aspirin and to respect the integrity of prostaglandin metabolism—the more severe the heart failure, the more compelling. There are other ways to inhibit platelet aggregation, and some are equally effective or even better than aspirin. Orally active platelet glycoprotein IIb/IIIa receptor antagonists, which promise to be substantially more efficient than aspirin, have been developed and are now in clinical testing. Ticlopidine and clopidogrel, although more expensive than aspirin, can be used as an alternative. As another option, because patients with more severe heart failure are likely to be those with very low ejection fractions, they are good candidates for oral antico-
agulation, even though this treatment requires additional monitoring.

Reprint requests and correspondence: Dr. Donald Hall, German Heart Center, Technical University of Munich, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: hall@dhm.mhn.de.

REFERENCES