Acute Hemodynamic Interaction of Aspirin and Ticlopidine With Enalapril
Results of a Double-Blind, Randomized Comparative Trial

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Background—Coprescription of aspirin and ACE inhibitors is frequent in heart failure caused by coronary artery disease. Negative interaction between aspirin and enalapril has been reported, presumably through inhibition by aspirin of ACE inhibitor–induced prostaglandin synthesis. Ticlopidine is a potent antiplatelet agent without interaction with prostaglandin synthesis.

Methods and Results—The objective of this study was to compare the influence of a coadministration of ticlopidine or aspirin on the hemodynamic effects of an ACE inhibitor (enalapril) in patients with chronic heart failure. Twenty patients with severe heart failure were enrolled in a double-blind comparative trial and allocated to ticlopidine (500 mg daily, 12 patients) or aspirin (325 mg daily, 8 patients). Hemodynamic evaluation was performed after 7 days of treatment, every hour for 4 hours after an oral administration of 10 mg of enalapril. Significant reductions in systemic vascular resistance were observed in the ticlopidine group, in contrast to no significant decrease in the aspirin group. A significant \( P=0.03 \) time-by-treatment interaction indicated significant aspirin-enalapril drug interaction. Total pulmonary resistance decreased significantly in both groups, with no difference between patients assigned to aspirin or ticlopidine.

Conclusions—Enalapril reduced systemic vascular resistance more effectively when given in combination with ticlopidine than with aspirin. In contrast, the reduction in total pulmonary resistance is similar when enalapril is administered in combination with aspirin or ticlopidine. Negative aspirin-enalapril interaction on prostaglandin synthesis presumably alters vasodilatation in systemic vessels, whereas prostaglandin-independent actions of ACE inhibition such as pulmonary arterial vasodilatation are maintained. (Circulation. 1998;98:757-765.)

Key Words: aspirin ■ angiotensin ■ coronary disease ■ heart failure ■ prostaglandins

Angiotensin-converting enzyme inhibitors are effective drugs that have been shown to lower morbidity and mortality rates in heart failure. Coronary artery disease is the most common cause of heart failure. Aspirin, through inhibition of platelet aggregation, can improve both short-term and long-term prognosis for patients with coronary artery disease. Coprescription of aspirin and ACE inhibitors is therefore common practice, with the intention of providing the benefits of both drugs. However, in a double-blind, randomized crossover study with patients with severe congestive heart failure, aspirin was found to attenuate the acute vasodilator effect of enalapril. Furthermore, a retrospective analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) on the effect of enalapril therapy started within 24 hours of the onset of acute myocardial infarction demonstrated a less favorable effect of enalapril among patients taking aspirin. The mechanism for aspirin–ACE inhibitor interaction possibly involves prostaglandin synthesis (Figure 1): ACE inhibitors impede the degradation of bradykinin, which stimulates the synthesis of prostaglandins. In contrast, aspirin inhibits cyclooxygenase, thereby reducing the production of vasodilating prostaglandins. Ticlopidine is a potent platelet inhibitor with clinically proven efficacy that is commonly prescribed after coronary artery stent placement and for peripheral obliterator and cerebrovascular diseases. It does not interact on prostaglandin synthesis and therefore is presumably devoid of negative effects on ACE inhibitor–mediated vasodilatation.

The prescription of both ACE inhibitors and potent platelet inhibitors such as aspirin or ticlopidine is increasing. Consequently, a comparison of the coprescription of ACE inhibitors with aspirin or ticlopidine is clinically relevant. We therefore

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designed a double-blind, randomized trial in 2 parallel groups of patients with heart failure to compare the effects of aspirin and ticlopidine on the hemodynamic actions elicited by an ACE inhibitor (enalapril).

**Methods**

**Patient Selection**

Patients were considered for inclusion if they had (1) chronic and stable heart failure, stage III or IV of the New York Heart Association classification, (2) left ventricular ejection fraction of <35% measured within the last 3 months, (3) heart failure caused by ischemic heart disease, idiopathic dilated cardiomyopathy, or hypertensive cardiopathy, and (4) sinus rhythm. Exclusion criteria included (1) infarction or stroke within 3 months, (2) treatment with the following drugs <2 weeks before randomization: vasodilators including ACE inhibitors, heparin, oral anticoagulants, platelet aggregation inhibitors, β-blockers, α-blockers, or calcium channel blockers, nonsteroidal anti-inflammatory agents, and corticosteroids, (3) past history of allergy to ticlopidine, aspirin, or ACE inhibitors, and (4) age <18 years or >80 years. The protocol was accepted by the ethics committee of our institution, and all patients included gave written informed consent. The procedures followed were in accordance with institutional guidelines.

**Study Protocol**

Patients were randomized to receive for 7 days in a double-blind fashion 500 mg per day (250 mg BID) ticlopidine or 325 mg per day (162.5 mg BID) aspirin. They were given a metabolically standardized diet and fixed regimens of digitalis and diuretics that were kept constant during the study. Nitrates were discontinued 48 hours before inclusion. Vasodilators or drugs listed in the exclusion criteria were forbidden.

On the evening of day 6, a balloon-tipped catheter was inserted in the pulmonary artery. Hemodynamic measurements were performed on day 7 after a standard breakfast and administration of the study treatment. The following baseline data were collected: right atrial pressure (RAP), pulmonary artery pressure (PAP), cardiac output (CO) with the thermodilution technique. CO measurements were obtained in triplicate. Patients were excluded if baseline PCWP was <15 mm Hg. An ECG was performed to record heart rate, and systemic arterial pressure was measured by cuff and mercury column sphygmomanometer. Mean RAP and mean PAP were obtained by electronic integration. Mean systolic arterial pressure (MAP) was calculated as diastolic pressure plus one third of the pulse pressure. Systemic vascular resistance (SVR) and total pulmonary resistance (TPR) were expressed as dyne·s·cm⁻² and calculated as SVR=80×(MAP−RAP)/CO and TPR=80×PAP/CO, respectively. After the baseline measurements, 10 mg of enalapril was administrated orally, and the same measurements were repeated 1, 2, 3, and 4 hours after administration of enalapril.

**Statistical Analysis**

The primary end point was SVR, and all other hemodynamic measurements were secondary end points. The number of patients to be studied was based on the results observed in a previous study on the hemodynamic interaction between aspirin and enalapril. Using a 2-sided test with α=0.05 and β=0.10, 14 patients in each group were considered necessary to detect a significant difference in SVR between groups. Hemodynamic measurements were summarized with mean and standard deviations. Summary plots of mean changes from baseline over time, with 95% for confidence intervals for the end points, were generated. Homogeneity of variance-covariance matrixes was tested between the 2 treatment groups, and repeated-measures ANCOVA, with baseline values as the covariate, was performed. In the case of significant results on test for sphericity, the adjusted probability value with the use of the Grenhouse-Geisser method was used. All statistical analyses were performed with the SAS statistical package version 6 at the 0.05 significance level with a 2-tailed test.

**Results**

**Study Population**

Twenty-eight patients were enrolled in the study. Three patients were withdrawn before hemodynamic evaluation because of poor compliance or refusal to pursue the study and 5 patients because PCWP was <15 mm Hg at baseline evaluation. Twenty patients (12 in the ticlopidine and 8 in the aspirin group) completed the study: Baseline characteristics were similar in both groups (Table 1).

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Ticlopidine</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Age, y</td>
<td>60 (42–67)</td>
<td>59 (39–71)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (83.3)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
| Left ventricular ejection fraction (%) | 28 (11–35) | 27 (15–30)

*Age and left ventricular ejection fraction are expressed as median (10th–90th percentile). All differences are nonsignificant.*
TABLE 2. Hemodynamic Parameters at Baseline and 4 Hours After Administration of Enalapril in Ticlopidine and Aspirin Groups

<table>
<thead>
<tr>
<th>Hemodynamic Parameters</th>
<th>Baseline</th>
<th>4 h</th>
<th>P</th>
<th>Baseline</th>
<th>4 h</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR</td>
<td>1741±519</td>
<td>1364±472</td>
<td>0.0013</td>
<td>1528±294</td>
<td>1395±207</td>
<td>0.4</td>
</tr>
<tr>
<td>MAP</td>
<td>102±17</td>
<td>87±15</td>
<td>0.0008</td>
<td>94±13</td>
<td>90±19</td>
<td>0.3</td>
</tr>
<tr>
<td>Systolic AP</td>
<td>132±27</td>
<td>113±21</td>
<td>0.003</td>
<td>129±16</td>
<td>121±23</td>
<td>0.9</td>
</tr>
<tr>
<td>Diastolic AP</td>
<td>87±14</td>
<td>77±13</td>
<td>0.0015</td>
<td>79±11</td>
<td>75±16</td>
<td>0.23</td>
</tr>
<tr>
<td>TPR</td>
<td>572±198</td>
<td>393±178</td>
<td>0.0006</td>
<td>502±232</td>
<td>337±141</td>
<td>0.02</td>
</tr>
<tr>
<td>PVR</td>
<td>173±66</td>
<td>134±50</td>
<td>0.06</td>
<td>138±47</td>
<td>115±64</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>31±7</td>
<td>23±7</td>
<td>0.0001</td>
<td>27±6</td>
<td>20±6</td>
<td>0.002</td>
</tr>
<tr>
<td>Systolic PAP</td>
<td>44±8</td>
<td>33±8</td>
<td>0.0001</td>
<td>38±8</td>
<td>30±9</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic PAP</td>
<td>24±8</td>
<td>18±8</td>
<td>0.0004</td>
<td>21±6</td>
<td>15±5</td>
<td>0.003</td>
</tr>
<tr>
<td>PCWP</td>
<td>21±5</td>
<td>14±5</td>
<td>0.0001</td>
<td>19±5</td>
<td>13±3</td>
<td>0.0004</td>
</tr>
<tr>
<td>RAP</td>
<td>6±4</td>
<td>5±4</td>
<td>0.19</td>
<td>7±2</td>
<td>5±1</td>
<td>0.009</td>
</tr>
<tr>
<td>CO</td>
<td>4.7±1</td>
<td>5.2±1.4</td>
<td>0.042</td>
<td>5±1.5</td>
<td>5±1</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart rate</td>
<td>92±15</td>
<td>87±16</td>
<td>0.11</td>
<td>83±17</td>
<td>80±13</td>
<td>0.24</td>
</tr>
</tbody>
</table>

AP indicates arterial pressure; PVR, pulmonary vascular resistance.

MAP, systolic AP, diastolic AP, mean PAP, systolic PAP, diastolic PAP, PCWP, and RAP are expressed in mm Hg; SVR, TPR, and PVR in dyne·s·cm⁻²; heart rate in bpm; and CO in L/m.

**Hemodynamics**

Results are displayed in Table 2 and Figures 2 and 3. No significant difference was noted in baseline values. The primary end point was SVR: A consistent decrease after enalapril intake in patients who had received ticlopidine was noted. This resulted in significant reductions within and after 3 hours of enalapril intake (1741±519 to 1364±472 dyne·s·cm⁻²). Nonsignificant decreases in SVR were noted in the aspirin group (1528±294 to 1395±207 dyne·s·cm⁻²), with a significant time-by-treatment interaction (P=0.03) indicating significant aspirin-enalapril drug interaction. A consistent significant decrease in mean systemic arterial pressure in the ticlopidine group was noted (102±17 to 87±15 mm Hg), with no significant reductions in the aspirin group (94±13 to 90±19 mm Hg), resulting in significant difference between the 2 groups (P=0.02).

TPR, PCWP, and systolic, diastolic, and mean pulmonary resistance decreased significantly in both groups, with no significant differences between the treatment groups. No significant change in heart rate was found in or between groups (Figure 3).

**Adverse Events**

No patient had a drug-related adverse event or complication as the result of right heart catheterization.

**Discussion**

The main findings of our study are (1) a significant decrease in SVR after enalapril intake in the ticlopidine group with no decrease in the aspirin group, resulting in a significant difference between both groups, and (2) significant decreases in TPR in both groups, with no difference between patients assigned to ticlopidine or aspirin.

**Aspirin-Enalapril Interaction**

ACE inhibitors, in addition to a reduction in vasoconstrictive and sodium- and water-retaining factors incurred through blockade of angiotensin II production, also antagonize the action of structurally identical kininase II (Figure 1). Degradation of bradykinin is therefore impeded. Bradykinin is a potent vasodilator and further enlists systemic vasodilatory support by enhancing production of vasodilating prostaglandins. Aspirin, in contrast, inhibits prostaglandin synthesis through blockade of the enzyme cyclooxygenase, which catalyzes the first step in prostaglandin synthesis from arachidonic acid.10 Conflicting data exist on the clinical effect of the antagonism of ACE inhibitors by aspirin or other prostaglandin inhibitors. In a canine model, Evans et al15 found no adverse effect of aspirin on the acute response to enalaprilat. Nishimura et al16 used plethysmography to study the effects of indomethacin on captopril-induced changes in peripheral hemodynamics in patients with heart failure. Indomethacin attenuated the effects of captopril. Townend et al17 showed that single doses of indomethacin attenuated the increase in cardiac output and renal blood flow in response to captopril but not the increase in forearm or calf blood flow. Hall et al,7 in a study in 18 patients with severe heart failure, demonstrated an inhibition of the vasodilator effects of enalapril by 350 mg of aspirin: In a double-blind, randomized crossover protocol, enalapril given before aspirin led to significant decreases in SVR, left ventricular filling, and TPR, together with a significant increase in CO. When given with or on the day after aspirin, enalapril failed to elicit significant changes in any of these variables.7 van Wijngaarden et al18 studied 13 patients with congestive heart failure who were already receiving maintenance treatment with an ACE inhibitor. Patients received in a randomized crossover fashion a single dose of 25 mg of captopril combined with 236 mg of aspirin or placebo. Both regimens produced a similar increase of hyperemic calf blood flow studied noninvasively by venous occlusion plethysmography. Baur et al19 performed a double-blind crossover study in 20 patients for 3 days followed by an extended study over 2 months of once-daily enalapril plus
Figure 2. Summary plots of mean changes in SVR and MAP. Values plotted are mean change from baseline with 95% nonadjusted CI. Resistance is expressed in dyne·s·cm\(^{-5}\), pressure in mm Hg, and time in hours after administration of enalapril. Consistent decrease in SVR was noted in patients receiving ticlopidine, with significant reductions 3 and 4 hours after enalapril intake. In contrast, nonsignificant decreases in SVR were noted in the aspirin group, with a significant time-by-treatment interaction \(P=0.03\) indicating significant aspirin-enalapril drug interaction. Consistent significant decrease in mean systemic arterial pressure was noted in the ticlopidine group, with no significant reductions in the aspirin group, resulting in significant difference between the 2 groups \(P=0.02\).
300 mg of carbaspirin (which corresponds to 250 mg of aspirin) and enalapril plus placebo. Salicylate addition to enalapril had an average no significant effect on the lowering of blood pressure induced by enalapril, which was abolished in only 3 of the 20 patients in the short-term study and in 1 of the 12 in the extended study. At night, when other effects of enalapril on blood pressure had waned and the bradykinin-induced effect persisted, salicylate significantly reduced the remaining small hypotensive effect. Smith et al26 found no adverse effect of low-dose aspirin (75 mg/d) on the blood pressure response to captopril.

Several multicenter randomized studies have demonstrated the benefits of ACE inhibitors on morbidity and mortality rates in patients with heart failure. However, the benefits appear to be diminished in patients taking aspirin: In the Acute Infarction Ramipril Efficacy (AIRE) study, a clear benefit was seen with enalapril in aspirin-treated patients, but there was a trend toward an even greater benefit in those not receiving aspirin.21 The second Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS II) compared enalapril and placebo in patients with an acute myocardial infarction.8 A retrospective subgroup analysis found evidence of a negative enalapril-aspirin interaction with an even less favorable outcome among patients taking aspirin.9

In contrast to indomethacin, aspirin has selective effects on prostaglandin synthesis when given in low doses. Wexler et al22 studied the ability of various doses of aspirin to inhibit prostacyclin synthesis by human arterial and venous tissue and to inhibit thromboxane A2 synthesis by platelets. A 325 mg dose of aspirin markedly reduced both prostacyclin and thromboxane production. In contrast, doses of 40 or 80 mg inhibited thromboxane synthesis but had much less effect on prostacyclin production in arterial and venous endothelium. Therefore because inhibition of the hemodynamic effects of ACE inhibitors by aspirin is presumably related to the interaction of aspirin with ACE inhibitor induced synthesis of vasodilating prostaglandins, this effect may only be obtained with aspirin doses of 325 mg or more. In the long-term studies on the effect of ACE inhibitors in patients with heart failure, the dosage of aspirin was not standardized. However, doses of $\geq$325 mg are commonly used in clinical practice and may have favored a negative interaction between aspirin and ACE inhibitors. In our study, patients received 325 mg of aspirin and 10 mg of enalapril. No significant decrease in SVR was noted, with a significant time-by-treatment negative interaction between aspirin and enalapril. Our results are similar to those of Hall et al,7 who administered 350 mg of aspirin daily. In contrast, the lack of interaction noted in the previously mentioned studies15–20 may be related to the use of low (<325 mg) doses of aspirin.

**Ticlopidine and Enalapril**

In contrast to aspirin, a significant reduction in SVR by enalapril was obtained in the ticlopidine group. Ticlopidine is devoid of effects on prostaglandin synthesis. Platelet aggregation inhibition is obtained by another mechanism: ADP-induced platelet activation is blocked by selective and irreversible inhibition of the binding of this agonist to its receptor on platelets, thereby affecting ADP-dependent activation of the Gp IIb-IIIa complex, the major receptor for fibrinogen present on the platelet surface.24 Decreases of similar magnitude in systemic vascular resistance were noted in previous studies with enalapril alone23 or with enalapril and placebo.7 These results therefore support the absence of interaction between ticlopidine and enalapril on systemic vascular resistance.

**Similar Effects of Ticlopidine and Aspirin on Total Pulmonary Resistance**

A significant decrease in TPR was obtained with both ticlopidine and aspirin, with no significant difference between both treatment groups. Hall et al7 also noted an appreciable reduction, although nonsignificant, in pulmonary MAP when enalapril was given with or after aspirin, which was attributed to a lack of interaction between aspirin and enalapril in the pulmonary vessels. Conflicting data exist regarding the role of bradykinin and prostaglandins in pulmonary artery tone; several mechanisms can therefore be postulated to explain these findings. First, ACE inhibitors can reduce PAP by bradykinin-independent mechanisms such as a decrease in norepinephrine. Increased sympathetic nerve activity has been suggested as an important contributor to the abnormal vasoconstriction observed in heart failure.24,25 and ACE inhibitors reduce plasma norepinephrine levels.26,27 Moreover, norepinephrine has been reported as an important regulator of pulmonary artery tone.28 TPR reduction after enalapril intake could therefore be mediated by a similar ACE inhibitor–induced reduction in norepinephrine in both treatment groups. Second, ACE inhibitors increase bradykinin levels in systemic and pulmonary circulation by impeding its degradation. Bradykinin further enlists vasodilatory support in the systemic circulation, mostly by enhancing production of vasodilating prostaglandins. In contrast, a bradykinin-induced increase in endothelin-derived nitric oxide has been proposed as the main pathway in the pulmonary circulation.29 Moreover, nitric oxide production by pulmonary artery endotheli-um is further increased in chronic heart failure.30 A decrease in pulmonary artery resistance would therefore be obtained by a prostaglandin-independent mechanism that involves bradykinin. Third, there is evidence that differences in ACE exist between tissues. In a preliminary report, Lechat et al31 noted differential effects of ACE inhibition on tissue-levels of bradykinin in rats. Quinapril increased bradykinin tissue levels in the aorta and kidney but not in the heart and lungs. Bradykinin-induced prostaglandin production and vasodilatation during ACE inhibitor therapy could therefore be limited to the systemic circulation.

**Ticlopidine-Related Secondary Effects**

No adverse effect caused by ticlopidine was noted in our study. However, ticlopidine was only administrated for 7 days. Severe neutropenia has been noted in 0.8% of patients receiving long-term ticlopidine therapy; in all cases it occurred in the second and third months of therapy and was fully reversible after the discontinuation of ticlopidine.32

**Study Limitations**

The number of patients included in our study is small. However, because hemodynamic measurements with contin-
uous right heart catheterization during 4 hours were required, a large-scale study seemed difficult to conceive. Second, no placebo group was planned because the purpose of our study was not to duplicate established findings on the interaction between ACE inhibitors and aspirin but to compare aspirin and ticlopidine when given with ACE inhibitors. An interaction between ticlopidine and enalapril cannot therefore be completely excluded. However, there is no pharmacological background for such interaction, and the magnitude of changes observed in the ticlopidine group are similar to those obtained in previous studies with enalapril alone or with enalapril and placebo. Third, we

**Figure 3.** Summary plots of mean changes in TPR; pulmonary vascular resistance; systolic, diastolic, and mean pulmonary artery pressures; PCWP; mean CO; heart rate; and RAP. Values plotted are mean change from baseline with 95% nonadjusted CI. Resistance is expressed in dyne⋅s⋅cm⁻², pressure in mm Hg, and time in hours after administration of enalapril. TPR, mean pulmonary resistance, systolic and diastolic pulmonary pressures, and PCWP decreased significantly in both groups, with no significant difference between treatment groups. No significant change in heart rate was noted in or between groups. A nonsignificant increase in CO was noted in patients receiving ticlopidine, and RAP decreased significantly in the aspirin group. In both cases, no significant difference was noted between the treatment groups.
only studied the acute effects of a single dose of 10 mg of enalapril. We therefore cannot conclude on long-term interaction or on the effect of aspirin on a lower dosage of enalapril.

**Clinical Implications**

In patients with severe heart failure, concomitant use of 325 mg of aspirin could therefore compromise part of the beneficial hemodynamic effects of ACE inhibitors. Despite the
small number of patients included, our study supports the absence of interaction between ticlopidine and ACE inhibitors. Ticlopidine could therefore be an alternative to aspirin in patients with heart failure caused by coronary artery disease. However, its potentially beneficial effects on coronary artery disease have not been tested in large clinical trials. Furthermore, severe side effects such as neutropenia are rare but may occur in the second or third month of therapy. Clopidogrel is chemically related to ticlopidine. Its inhibition of ADP-mediated platelet adhesion is greater than that of ticlopidine in animal models of thrombosis. A large-scale clinical trial in patients with atherosclerotic vascular disease has recently shown clopidogrel to be slightly but significantly more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death. Moreover, its overall safety profile was as least as good as that of medium-dose aspirin. This new platelet inhibitor will therefore probably be prescribed in patients with coronary artery disease. Because clopidogrel is also devoid of action on prostaglandin synthesis, absence of interaction between clopidogrel and ACE inhibitors is likely but must be validated by randomized studies. Finally, no interaction was found between ACE inhibitors and low (<325 mg) doses of aspirin in previous studies. Another alternative would therefore be to combine low doses of aspirin with ACE inhibitors. However, most of the long-term studies on the benefit of aspirin in coronary artery disease used doses >325 mg daily. Comparative trials in patients at risk of stroke have not shown any major difference in benefit or harm with doses ranging from 75 to 1200 mg daily. In these trials, lower doses in aspirin did not show a clear reduction in coronary events when compared with placebo. The long-term benefit of low doses of aspirin therefore remains unknown.

In summary, our study shows that a single dose of 10 mg of enalapril reduced SVR more effectively when given with 500 mg of ticlopidine than with 325 mg of aspirin. No difference was noted on enalapril-mediated TPR decrease. Negative aspirin-enalapril interaction on prostaglandin synthesis presumably alters vasodilatation in systemic vessels, whereas prostaglandin-independent actions of ACE inhibition such as pulmonary arterial vasodilatation are maintained. Our findings are clearly relevant to clinical practice because coprescription of aspirin and ACE inhibitors is common. In patients with well-established indications of ACE inhibitors and platelet inhibition, alternate associations may be required. Our study demonstrates that ticlopidine clearly has no interaction with enalapril. Low-dose aspirin may be an acceptable alternative, and clopidogrel should be evaluated in a prospective trial.

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References


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