A Pill for Every Ill

To the Editor:

Dr Lip1 and The HOPE investigators2 again sing the praises of ACE inhibitors (“the pill for every ill”)—this time in the regression and prevention of ECG-LVH. The numerous “non–blood pressure” properties of ACE inhibition are elegantly described in Dr Lip’s editorial, as the benefits noted were not simply explained by blood pressure reduction. However, the blood pressure story may not be quite dead yet.

ACE inhibitors have a more favorable effect on central aortic pressure and pulsatile hemodynamics than other antihypertensive agents.3 End-organ damage is known to correlate with parameters of pulse wave morphology. The regression of carotid intima media thickness, for example, is closely correlated with regional reductions in pulse pressure.4 Pulse pressure, a marker of conduit vessel compliance, was a significant predictor of adverse cardiovascular events in both the SAVE (Survival And Ventricular Enlargement study) and SOLVD (Studies Of Left Ventricular Dysfunction) cohorts.5

ACE inhibitors decrease wave reflection and pulse wave velocity and to focus solely on the effects these agents have on systolic and diastolic blood pressures fails to appreciate these important components. Loss of arterial wall compliance per se is a stimulus to the development of atheroma—yet another manifestation of end-organ damage. It may well be that the “additional” benefits of ACE inhibitors are due to these beneficial changes in central aortic pulsatility. Examination of pulse pressure, or carotid pressure by tonometry, opens up yet another area of interest in these impressive drugs.

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Response

We agree with Dr Swan that ACE inhibitors have a favorable effect on arterial compliance and central pulse pressure. We also agree that this hemodynamic effect might be associated with clinical benefit. At the same time, we again emphasize our view that ACE inhibitors by virtue of their autocrine/paracrine effect might cause regression of left ventricular hypertrophy independent of their hemodynamic properties, based on the following points.

(1) Improvement of arterial compliance and reduction of pulse pressure by antihypertensive agents is not a unique property of ACE inhibitors. Properly controlled studies, for example, have shown that the ACE inhibitor enalapril and the β-blocker celiprolol have similar effects in this regard.1 as do nitrates.2 (2) Angiotensin II is a direct growth promoter to the myocardium at doses too low to affect blood pressure. (3) In addition to its circulating form, angiotensin II is also locally produced in the heart; all components of the renin-angiotensin system have been demonstrated in the heart muscle both at mRNA levels and at protein levels. (4) ACE inhibitors can block the hypertrophic effect of angiotensin II on the myocardium without affecting blood pressure. (5) In our study, the beneficial effect of ramipril on left ventricular hypertrophy was consistent in patients with or without hypertension by history, and in patients with various blood pressure levels; it was also independent of blood pressure reduction during the study. Therefore, in our study a direct antihypertrophic effect of the ACE inhibitor (over and above its effect through hemodynamic mechanisms) seems probable.

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Circulation. 2002;105:e82
doi: 10.1161/01.CIR.000012604.07640.10
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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