Pulse Pressure and Antihypertensive Agents

To the Editor:

In their subanalysis of the LIFE study,1 the authors conclude that they “show superior protection against stroke in patients treated with losartan when compared with atenolol ... This difference may be related to specific effects of angiotensin type 1 receptor antagonism ... beyond blood BP reduction.” The authors do not consider the alternative hypothesis: that the changes in pulse pressure (PP) might differ markedly under losartan and atenolol and also according to the site of PP arterial measurements.2

As a consequence of differences in arterial stiffness and timing of wave reflections along the arterial tree, PP is lower in central than in peripheral arteries, whereas mean arterial pressure (MAP) is nearly the same. This phenomenon is attenuated in aged people and in the presence of bradycardia.2 Thus, mechanical forces at the site of target organ damage are not accurately measured by the brachial BP cuff. Furthermore, antihypertensive agents may cause the same MAP reduction at the brachial and central arteries sites but with different values of central PP.2,3 For instance, in double-blind studies comparing converting enzyme inhibitors and β-blockers, atenolol does not modify carotid or aortic PP, whereas converting enzyme inhibitors markedly reduce carotid PP for the same MAP reduction.4,5

In the present study, brachial PP is a predictor of stroke when measured in baseline conditions, mostly in the higher PP tertile of the population, in which mean age is 69 years. Under drug treatment by atenolol, it is expected that central PP remains unchanged, whereas under losartan, central PP is expected to be reduced. Thus, the role of local mechanical forces such as PP should have to be raised in the mechanism of stroke prevention. Therapeutic trials have shown that the brain is the location where the role of mechanical factors is of major importance for the reduction of CV events.

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Response

The important comment of Safar and O’Rourke1 on our subanalysis of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study concerning baseline pulse pressure (PP) and cardiovascular outcomes2 is timely and welcome. Indeed, we concluded that we “show superior protection against stroke in patients treated with losartan when compared with atenolol” and we still do so. We also wrote that “this difference may be related to specific effects of angiotensin type 1 receptor antagonism ... beyond blood pressure reduction.” In view of the extensive evidence of vasculoprotective effects of angiotensin receptor blockers, this statement may still be valid. Safar and O’Rourke offer the “alternative hypothesis, that the changes in pulse pressure (PP) might differ markedly under losartan and atenolol, and also according to the site of PP arterial measurements.”

We did not include this hypothetical explanation in our discussion because no measurements of aortic or central blood pressures were made in the LIFE study. We agree that although reduction of brachial blood pressures and PP were similar in both treatment groups, losartan may have lowered central systolic pressure and PP more than atenolol. This difference may explain part of the superiority of losartan-based treatment over atenolol-based treatment in LIFE. Assuming that the difference between losartan- and atenolol-treated patients in reduction of central systolic pressure and PP was largest in the highest quartile of baseline brachial PP, this could explain in part the particularly marked protection by losartan compared with atenolol against stroke in these patients.2 However, LIFE patients in the highest quartile of PP, were also older and had more diabetes as well as the highest prevalence of known atherosclerotic cardiovascular disease (35% versus 26% to 31%; P<0.001),2 all conditions that blunt augmentation of systolic pressure from central to peripheral arteries. This makes it likely that there was less differential effect of losartan compared with atenolol in LIFE patients than has been documented in younger individuals with less prevalent cardiovascular disease.

In this context, a fact to be considered is that a majority of LIFE patients also received the diuretic hydrochlorothiazide equally in the losartan and atenolol treatment groups. Diuretics lower central systolic pressure and PP more than β-blockers,3 but no reports on the effect of diuretic/β-blocker or diuretic/angiotensin receptor blocker combinations on central pressures are available. Combined treatment with indapamide and perindopril compared with atenolol showed “more pronounced effects using central than brachial measurements, and a longer delay in central return of wave reflections under perindopril/indapamide.”4 In this regard, combined losartan and diuretic may act similarly. However, no measurements of central blood pressure were performed in the LIFE study. When planning future drug trials in hypertension, the importance of central blood pressure5 should be assessed. We agree in principle with the comments of Safar and O’Rourke but cannot be certain about the importance of central to peripheral arterial PP amplification and the effects of treatment thereon in the LIFE study population.

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