Stroke Prevention: Indapamide, a Forgotten Option?

To the Editor:
We have read with interest the article by MacWalter et al., the comment made by Fournier et al., and the authors’ reply. We would like to comment.

We disagree with some of the comments made by MacWalter et al. The recommendation of the use of angiotensin-converting enzyme inhibitors (ACEIs) cannot be made on the basis of the findings of PROGRESS. The risk reduction observed with perindopril was a nonsignificant 5%. As has been described elsewhere, the lack of a factorial design, which must have included a group on indapamide alone, makes it impossible to know how much, if any, of the reduction observed with the combination therapy is attributable to perindopril.

We agree that the use of ACEI might be beneficial, but, although members of a drug class share main actions, they may have clinically important differences in terms of efficacy and safety, which might explain the differences encountered with the efficacy of ramipril and perindopril alone. Comparative clinical effectiveness can be determined only by large randomized outcome trials comparing these 2 drugs head-to-head, and without that information we cannot recommend the use of perindopril. In the view of the beneficial effects of ramipril and indapamide, it will be very interesting to know if the combination therapy with ramipril and indapamide is more effective than with each drug separately.

Finally, we would like to remark that it is now clear, in opposition to MacWalter et al., that indapamide is renoprotective. Since Gambardella et al published in 1991 the renoprotective effect of long-term indapamide treatment, defined as a reduction in urinary protein loss in patients with type 2 diabetes and persistent microalbuminuria, many other authors have reported the renoprotective effect of indapamide, this drug being as effective as ACEIs.

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Response
We read the comments of Dr Parra Ruiz et al with interest. There have been few trials comparing the effects of thiazide diuretics with ACE inhibitors in terms of renoprotection. These have been in patients with type 2 diabetes mellitus and proteinuria. In one study, the researchers noted that hydrochlorothiazide was as effective as enalapril in preserving glomerular filtration rate as well as in reducing albuminuria for 3.5 years. In another study, captopril and indapamide appeared to have similar effects. These apparent renoprotective effects of thiazide diuretics may be specific to diabetic patients.

There are some data to suggest that, at least in patients with acute renal failure, diuretic use is associated with increased mortality, nonrecovery of renal function, and prolonged time to initiation of dialysis. These effects applied equally to those patients taking loop and loop plus thiazide diuretics. This study has received criticism, but the area is worthy of further exploration. It may be that patients with dehydration do not do particularly well on diuretic therapy.

We do agree with most of the comments made by Parra Ruiz et al, but the fact remains that it is only for ACE inhibitors that there is such an enormous database from both the HOPE and the PROGRESS studies in terms of long-term cardiovascular outcome, which is the most important end point here. The small studies quoted by Parra Ruiz et al to show that diuretics are renoprotective suggest a hypothesis that a diuretic given to a normotensive stroke patient may be as cardioprotective as ACE inhibitors. However, this is merely a hypothesis and there is no large trial which addresses that question precisely. Indapamide on its own was never tested in the PROGRESS trial—due to the unusual design of the trial, its use may have been limited to those with higher blood pressures initially or in those with blood pressure that is more difficult to control; albeit this has never been explained by the trialists. The PATS study using indapamide alone after stroke was conducted in China and has never been published in full, while HOPE and PROGRESS were large multinational trials.

We do agree with Parra Ruiz et al that further work in the area is required and certainly a randomized controlled trial of a thiazide diuretic with an ACE inhibitor or angiotensin receptor blocker would be immensely interesting and may help answer many of the questions raised. However, it is unlikely that such a trial will ever be done, so we have simply to live with the evidence that we already have and the largest body of evidence belongs to the ACE-inhibitor based antihypertensive regimen trials.

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