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Telmisartan to Prevent Recurrent Stroke: The PRoFESS Study

Was the Baby Thrown Out With the Bathwater?

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In retrospect, the choice of PRoFESS as the acronym for this trial may be considered unwise. The dictionary definition of the verb "to profess" is "to declare or to claim, often insincerely or falsely." What does PRoFESS declare and can we believe the claim?

Blood pressure reduction initiated several months after stroke reduces cardiovascular complications, including recurrent stroke.[1] Would earlier intervention be beneficial? To address this question, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial evaluated the effects of therapy with the angiotensin receptor blocker, telmisartan. Blockade of the renin–angiotensin system is said to reduce the risk of stroke independent of blood pressure.[2,3] Indeed, a small study of unusual design[4] suggested that an angiotensin receptor blocker started soon after stroke reduced rates of death and cardiovascular events despite no blood pressure reduction.

Telmisartan at 80 mg daily was compared with placebo in 20 392 patients with prior ischemic stroke. Because PRoFESS used a factorial design allowing comparison of 2 antiplatelet regimens, patients with hemorrhagic stroke were excluded. All patients received treatment for blood pressure control at the discretion of the investigators. The primary outcome was recurrent stroke. Secondary outcomes were major cardiovascular events and the incidence of new-onset diabetes.

The median interval to randomization was 15 days post-stroke and median follow-up was 2.5 years. Although 74% of participants had a history of hypertension, mean blood pressure at randomization was 144.1/83.8 mm Hg. During follow-up, blood pressure fell in both groups but more so in the telmisartan arm (mean blood pressure difference 3.8/2.0 mm Hg).

The results strongly support the null hypothesis. Hazard ratios were 0.95 (95% CI, 0.86 to 1.04; $P=0.23$) for recurrent stroke, 0.94 (0.87 to 1.01; $P=0.11$) for major cardiovascular events, and 0.82 (0.65 to 1.04; $P=0.10$) for new-onset diabetes. The findings were consistent across various subgroups of stroke and in prespecified subgroups of patients. There were no interactions with the antiplatelet regimens.

Thus, therapy with telmisartan initiated soon after ischemic stroke and continued for 2.5 years did not significantly lower the rate of recurrent stroke, major cardiovascular events, or new diabetes.

Critique

The landmark PROGRESS trial[1] demonstrated reduced risk of recurrent stroke and other cardiovascular events with blood pressure-lowering started at least 2 weeks after stroke, although the median time to randomization was 8 months. In contrast, PRoFESS failed to provide evidence of benefit when treatment was started after a median period of 15 days. Time to randomization was 10 days or less in 40% of participants and this subgroup showed similar results as those in the entire group. However, approximately 50% of the PRoFESS population was randomized beyond 2 weeks, as in PROGRESS,[1] but experienced no benefit from blood pressure reduction.

What Is the Explanation for the Outcome Differences Between PRoFESS and PROGRESS?

In PRoFESS, but not in PROGRESS, patients with hemorrhagic strokes were excluded and baseline blood pressure was lower (144/84 mm Hg versus 147/86 mm Hg). Although patients with intracerebral hemorrhages and highish blood pressure might be expected to show proportionally greater benefits from blood pressure reduction, the PROGRESS findings[1] suggest that neither of these characteristics influenced outcome, at least in the long-term. The PRoFESS authors suggest that lesser blood pressure-lowering is a possible explanation. They note that most of the benefit in PROGRESS[1] was seen in the group receiving perindopril plus indapamide in which blood pressure reduction was

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12.3/5.0 mm Hg, whereas those receiving perindopril alone experienced a blood pressure reduction of only 4.9/2.8 mm Hg and no significant benefit.

Can We Disentangle Blood Pressure Reduction From Mode of Action?

This explanation is unconvincing if there is indeed a blood pressure-independent beneficial effect of blocking the renin–angiotensin system as speculated by the PRoFESS authors. In favor of this hypothesis is superficial interpretation of the results of the HOPE[2] and LIFE[5] trials, whereas the findings of PRoFESS and the monotherapy arm of PROGRESS[1] are more difficult to reconcile. Of course, it may be that stroke prevention in HOPE[2] was in fact due to the blood pressure-lowering effect of the angiotensin converting enzyme inhibitor; blood pressure changes may well have been underestimated in that study.[6] In LIFE,[5] the advantage of losartan over atenolol in stroke prevention may have been due to the shortcoming of the β-blocker[7] rather than any speculated advantage of the angiotensin receptor blocker.

In PRoFESS, blood pressure was lower in the telmisartan group throughout. Differences were maximal in the first month and declined over time. This pattern is typical of trials in which one group is randomized initially to placebo.[8] Compared with the telmisartan group, more patients randomized to placebo received additional antihypertensive therapy, minimizing by an estimated 33% the difference in blood pressure between the groups. However, the disadvantaged placebo group did not catch up. Because events are usually evenly spaced over a trial, the variability in differential blood pressure control over time means that reliance on average blood pressure difference underestimates the influence of early blood pressure changes. Furthermore, at the end of PRoFESS, only approximately 70% of patients randomized to telmisartan remained on an angiotensin receptor blocker, whereas 2.5% of those randomized to placebo were receiving an angiotensin receptor blocker, diluting the influence of angiotensin receptor blockade. Thus, the study design was not optimal for teasing out the potentially competing influences of blood pressure reduction and mode of action.

Was PRoFESS Powered Adequately?

There is concern that the study was underpowered. The protocol specified a sample size of 15 500 patients, which would yield 2170 with recurrent stroke during 4 years' follow-up. Despite an increase in sample size to over 20 000, only 1814 participants had recurrent strokes in 2.5 years of follow-up. It is a frequent finding that event rate in outcome trials is less than that predicted. Perhaps, the PRoFESS investigators now regret the decision to modify the power calculation during the study.

What About Intermediate Outcomes?

Not only did telmisartan-based therapy fail to reduce the risk of recurrent stroke and cardiovascular events, but the incidence of new-onset diabetes was not influenced significantly. Furthermore, atrial fibrillation was significantly more common after telmisartan. These observations are in sharp contrast with findings from other trials with angiotensin converting enzyme inhibitors and angiotensin receptor blockers in which protection against new diabetes and atrial fibrillation has been suggested.[9,10] Thus, PRoFESS calls into question these intermediate end points as markers for benefits beyond blood pressure-lowering of drugs that block the renin–angiotensin system.

What Can Be Salvaged From the Wreckage of PRoFESS?

Post hoc explanatory analyses suggest the possibility of time-dependent benefit with telmisartan. No significant benefit was seen up to 6 months after randomization, although a small but significant advantage for stroke and cardiovascular events was seen thereafter. The differences between the 2 periods was significant and adjustment for postrandomization blood pressure did not markedly affect the estimates. Although these analyses must be seen as hypothesis-generating, there is some support from other trials. In PROGRESS,[1] HOPE,[2] and LIFE,[5] little benefit was apparent in the first 6 months with graded and continuing lessening of rates of stroke and major cardiovascular events thereafter. These findings are also consistent with those from TRANSCEND[11] (telmisartan versus placebo in high-risk patients intolerant of angiotensin converting enzyme inhibitors) and other trials of antihypertensive agents[12] and lipid-lowering therapy.[13,14] Considerable time may be necessary to modify the atherosclerotic process. The mean duration of therapy in PRoFESS may have been too short at 2.5 years; assuming constant hazard, average time to event was only 1.25 years. In PROGRESS,[1] mean duration of therapy was 4 years and in HOPE[2] 4.5 years.

In trials of new interventions to prevent further cardiovascular events when added to existing therapies, only moderate (10% to 15%) benefits can be realistically expected. To ensure that full benefit is apparent, treatment periods have to be prolonged. This is perhaps the most important message from PRoFESS. The pressure to design and conduct major trials to generate results as quickly as possible must be resisted. Otherwise, the huge investment, both financial and in patients, may be wasted. After more than 50 000 patient-years devoted to PRoFESS, we simply cannot declare whether early reduction of blood pressure after stroke has long-term benefits and we certainly can make no reliable claim to support any advantage or disadvantage of renin–angiotensin system blockade. Expediency may have resulted in the baby being thrown out with the bathwater.

Disclosures

None.

References

1. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen study among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;3581:1033–1041.
2. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.
3. Schrader J, Lüders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener HC: MOSES Study Group. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for sec-

ondary prevention. Principal results of a prospective randomised controlled study (MOSES). *Stroke*. 2005;36:1218–1226.
4. Schrader J, Lüders S, Kulschewski A, Berger J, Zidek W, Treib J, Einhäupl K, Diener HC, Dominiak P; Acute Candesartan Cilexetil Therapy in Stroke Survivors Study Group. The ACCESS study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke*. 2003;34:1699–1703.
5. Dahlöf B, Devereux RB, Kjeldson SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
6. Svensson P, de Faire U, Sleight P, Yusuf S, Östergren J. Comparative effects of ramipril on ambulatory and office blood pressure: a HOPE substudy. *Hypertension*. 2001;38:E28–E32.
7. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet*. 2004;364:1684–1689.
8. Brenner BM, Cooper ME, De Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Ribeiro AB, Schluchter MD, Snavely D, Zhang Z, Simpson R, Ramjit D, Shahinfar S; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–69.
9. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–207.
10. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. A meta-analysis. *J Am Coll Cardiol*. 2005;45:1832–1839.
11. TRANSCEND Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet*. 2008;372:1174–1183.
12. Blood Pressure Lowering Treatment Trialist Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–1535.
13. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis to date from 90 056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
14. Ford I, Murray H, Packard CJ, Shepherd J, MacFarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med*. 2007;357:1477–1486.

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