symptoms progress at a measurable rate, providing biomarkers that could be used as putative surrogate clinical endpoints for disease-modification studies. Detection of clinical abnormalities and increased rate of striatal and whole-brain atrophy, additionally, might remove ethical reservations and methodological obstacles to treat presymptomatic people. Clinical trials in presymptomatic people have been delayed because the alleged criterion that they were not patients but merely mutation carriers and because it was difficult to focus on useful clinical endpoints. Preliminary analysis of the hypothetical number of patients needed to show disease-modifying effects with the data shown by Tabrizi and colleagues reveals that, assuming neuroprotective effects consistent with slowing of the progressive deterioration of some of these biomarkers by 25–50%, with a power of 80–90%, and with a drop out of 10–20%, the number of participants needed for a successful clinical trial, in terms of patient years, would be tens to about a 100, for each experimental arm of the study, numbers that are realistic in the actual context of international collaborative research in HD. Therefore, we expect to see some of these neuroprotection trials done in asymptomatic mutation carriers of HD in the following years.

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I declare that I have no conflicts of interest.

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Methodological issues in the assessment of cognitive decline in ONTARGET and TRANSCEND

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The ONTARGET and TRANSCEND trials compared the effects of blood-pressure-lowering drugs on cardiovascular outcomes. Cognitive impairment was a predefined secondary outcome, assessed as an investigator-reported diagnosis of dementia or significant cognitive dysfunction, or a score of 23 or less on the Mini-Mental State Examination (MMSE). In this issue of *The Lancet Neurology*, Anderson and colleagues¹ report the results of a pooled analysis of these data. They found that different approaches to blocking of the renin-angiotensin system given on top of usual (background) antihypertensive treatment had no apparent beneficial effects on cognitive outcomes, even though systolic blood pressure was lowered in patients treated with a combination of telmisartan and ramipril therapy (–2.4 mm Hg) and telmisartan alone (–0.9 mm

Hg) compared with those treated with ramipril alone in ONTARGET, and in patients treated with telmisartan (–4.0 mm Hg) compared with those on placebo in TRANSCEND.

Long-term prospective studies have clearly shown that hypertension at middle age is a risk factor for dementia later in life.² Currently, 24.3 million people have dementia, with an annual worldwide incidence of 4.6 million new cases.³ Because populations are ageing at a fast rate, the number of patients with dementia will increase two-fold every 20 years to 81.1 million by 2040, with more than 60% living in developing countries.³ The question of whether the risk of dementia associated with hypertension is reversible is therefore clinically very relevant. The ONTARGET and TRANSCEND investigators have to be congratulated

for having put cognitive impairment on their research agenda. However, one wonders whether the design of these large simple trials really created the opportunity to address this question in a reliable manner. As conceded by the authors, the MMSE is insensitive to early or mild stages of cognitive impairment.^{1,3} In the Syst-Eur⁴ and HYVET⁵ trials, brain imaging studies were systematically used to confirm the diagnosis of dementia and to differentiate vascular dementia from Alzheimer's disease or mixed types of cognitive impairment. In these two trials, experts masked to results adjudicated the cases of dementia, whereas in ONTARGET and TRANSCEND, a clinical diagnosis of dementia could be made by any investigator. Syst-Eur and HYVET were placebo-controlled primary prevention trials and active treatment was standardised and not given on top of varying background treatments. In these meticulous trials,^{4,5} systolic blood pressure was lowered by more than 10 mm Hg and short follow-up (2 years) did not preclude detection of a positive outcome.

We have reviewed placebo-controlled trials of antihypertensive therapy in primary prevention of dementia² and primary⁶ and secondary⁷ prevention of stroke. For trials involving a diuretic agent or a calcium-channel blocker as part of the active treatment, the reduction in events was statistically significant, whereas this was not the case in trials of renin-angiotensin system inhibitors. As suggested by the results of Anderson and colleagues' metaregression,¹ the magnitude of blood-pressure reduction might account for these differences between drug classes. Experimental studies, reviewed elsewhere,^{2,6} support the hypothesis that inhibition of the inward current of calcium ions in neurons protects against necrosis and apoptosis, and clinical studies have shown that diuretic agents⁷⁻⁹ and calcium-channel blockers^{9,10} probably have a small (5–10%) benefit beyond blood-pressure lowering in protecting the brain. By contrast, Fournier's hypothesis¹¹ that angiotensin type-1 receptor blockers might have advantages over angiotensin-converting enzyme inhibitors in the protection of the brain still awaits proof in randomised clinical trials.

Probably in view of the disappointing absence of a beneficial effect on cognition in the individual randomised trials, Anderson and colleagues¹ combined the ONTARGET and TRANSCEND data into a single observational cohort. In multivariable-adjusted analyses (table 4),¹ each 10 mm Hg increase in the achieved systolic

blood pressure was associated with a 3% increased risk of cognitive impairment (odds ratio 1.03, 95% CI 1.00–1.07). From a methodological viewpoint, this association was cross-sectional, because both outcome and achieved blood pressure were measured throughout the trial. This approach might lead to an underestimation of the true relation, because blood pressure falls around the time that dementia develops or progresses, as blood-pressure regulating nuclei deteriorate.¹² Cross-sectional analyses cannot reliably assess the relation between cognitive impairment and dementia, as illustrated by two Framingham reports.^{13,14} In stroke-free Framingham participants, there was no relation between the scores of eight cognitive tests, administered in 1976–78, and the concurrently measured blood pressure.¹³ However, high blood-pressure levels over five earlier biennial examinations (1956–64), when few hypertensive patients were taking antihypertensive drugs, significantly predicted low scores of attention, memory, and global cognition in 1976–78.¹⁴ Anderson and colleagues might have avoided bias in the cohort analysis by predicting cognitive decline from data on systolic blood pressure within the first months after randomisation, when the blood-pressure gradients persisting throughout ONTARGET and TRANSCEND had already been achieved.

In conclusion, ONTARGET and TRANSCEND attempted to answer a clinically relevant question but, because of the caveats inherent to large simple trials, they did not contribute much to an answer. A precise and sufficiently powered trial comparing a long-acting dihydropyridine calcium-channel blocker or a diuretic with a renin-angiotensin system inhibitor in the primary prevention of dementia is needed, but such an orphan trial will not find a sponsor easily.

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Infantile parkinsonism-dystonia due to dopamine transporter gene mutations: another genetic twist

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Several genes have been identified for inherited dystonias and parkinsonian disorders, but an important early-onset group in which both features are prominent is often overlooked. Distinct genes for these early-onset parkinsonism-dystonias continue to be identified, and, though characterised mainly by a combination of both dystonia and parkinsonism, these disorders often manifest with other features such as cognitive

impairment and spasticity.¹ Differential diagnosis can be a challenge, especially because clinical signs overlap with a range of other early-onset disorders. Some children can be mistakenly diagnosed with cerebral palsy, and thus clinical vigilance is important.

Infantile parkinsonism-dystonia has long been recognised as a presentation of inborn errors of metabolism affecting the dopamine biosynthetic pathway.² The dopamine metabolite homovanillic acid is usually decreased in the cerebrospinal fluid (CSF) of these patients, indicating decreased dopamine production. Kurian and colleagues³ identified three cases of a particularly interesting form of infantile parkinsonism-dystonia, which was characterised by increased CSF concentrations of homovanillic acid due to autosomal recessive, loss-of-function mutations in the *SLC6A3* gene encoding the dopamine transporter.^{3,4} Because these presynaptic transporters retrieve secreted dopamine from the synaptic cleft, their dysfunction results in increased extracellular dopamine concentrations, with a concomitant increase in metabolites, such as homovanillic acid, in CSF. The subsequent dysregulation of dopaminergic neurotransmission probably has an important role in disease pathogenesis.⁴

CSF analysis could enable diagnosis of dopamine transporter deficiency syndrome