Good for the heart and good for the brain?

With no effective treatment available, Alzheimer's disease and other dementias present a major global public-health challenge.[1] Prevention has been highlighted as pivotal in managing the huge burden of these diseases.[2] Alzheimer's disease and other dementias are complex, multifactorial conditions, and several modifiable risk factors have been identified throughout the life-course, including midlife hypertension.[3,4] Hypertension is the leading preventable cause of death worldwide, as population growth and aging are driving its increasing burden.[5]

Several randomised controlled trials assessing antihypertensive treatments for the prevention of cognitive decline or dementia have produced inconsistent results. These trials have also had several methodological weaknesses (eg, short intervention and follow-up periods and suboptimal assessment of cognition).[3,4]

The results from the Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition in Decreased Hypertension (MIND) study have now been published.[6] This large (n=9361) randomised controlled trial was conducted at 102 sites in the USA and Puerto Rico, and enrolled adults aged 50 years and older (mean age 68 years) with hypertension and increased risk of cardiovascular disease, but without diabetes or history of stroke. Participants were randomly assigned to standard blood pressure control (goal <140 mm Hg) or intensive blood pressure control (goal <120 mm Hg). The trial was stopped early because of benefits on its primary outcome—a composite of cardiovascular events and all-cause mortality.[7] The median intervention period was 3·3 years and the cognitive assessment and dementia adjudication continued after the SPRINT trial ended for a median total follow-up of 5·1 years. Incidence of probable dementia was lower, although the difference was not significant, in the intensive treatment group than in the standard treatment group (7·2 *vs* 8·6 cases per 1000 person-years; hazard ratio [HR] 0·83, 95% CI 0·67–1·04), which was the primary cognitive outcome. Furthermore, there was a significant reduction in the risk of developing mild cognitive impairment (MCI; 14·6 *vs* 18·3 cases per 1000 person years; HR 0·81, 95% CI 0·69–0·95) and the risk of any cognitive impairment (MCI or dementia; 20·2 *vs* 24·1 cases per 1000 person-years; HR 0·85, 95% CI 0·74–0·97), which were secondary outcomes.

Several key questions affect interpretation of these findings and their clinical implementation. Early termination of the trial and fewer cases of dementia than expected could have resulted in the study being underpowered for the primary cognitive outcome. Insufficient power has been an issue in several recent prevention trials as a result of a lower rate of cognitive decline and fewer dementia cases than expected. The between-group difference in systolic blood pressure was reduced during the follow-up (from 13·3 mm Hg at the time of termination of the intervention, through 10·5 mm Hg during the closeout period, to 6·4 mm Hg during the extended follow-up). Thus, the real effect of intensive blood pressure treatment could be even larger than reported.

Another clinically important question is whether the same recommendations regarding blood pressure lowering can be applied for all age groups. Optimal therapeutic targets among the oldest age groups (eg, >75 years) remains a central question. In the SPRINT-MIND trial, 28% of the participants were 75 years or

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older and the between-group difference in probable dementia was similar in this group to overall. However, no results were presented for the oldest-old (>85 years), possibly because this group was too small to conduct any meaningful analyses, thus it is unclear if results can be applied to this age group. Dementia and mixed pathology (vascular and neurodegenerative) are very common among the oldest age groups, and treatment effects might differ. Previous trials of blood pressure lowering for prevention of cognitive decline have not shown an increase in adverse events, possibly because of the inclusion of few people older than 85 years, but some observational studies have indicated an association between low blood pressure and high risk of cognitive impairment in the oldest old age groups, although this association could be due to reverse causality. In the initial report of the SPRINT trial,[7] the intensive systolic blood pressure lowering group had a greater frequency of some side effects in all age groups, including orthostatic hypotension and syncope. These events were no longer monitored after the intervention phase ended. This information will be essential to weigh benefits of treatment with adverse outcomes, especially among the oldest-old, who might be more prone to adverse effects.

Different classes of antihypertensive medication have been purported to have different protective effects,[4] including those beyond the effects of direct blood pressure lowering. SPRINT used a pragmatic approach, with use of certain antihypertensives encouraged but not mandated for first-line use or for specific patient groups. Individual practitioners were provided with the same protocol with recommended drugs, but could approach systolic blood pressure control differently; most participants were taking a combination of drugs. Therefore, further studies are needed to clarify whether certain antihypertensive agents are more beneficial for cognitive outcomes.

Beyond hypertension, given the multifactorial aetiology of late-onset dementia, simultaneous targeting of several risk factors (multidomain interventions) might be the most effective way to prevent dementia.[3] Combination therapies with non-pharmacological and pharmacological interventions tailored for various risk groups have been introduced in some dementia prevention trials.[3]

Despite existing guidelines and availability of blood pressure lowering medications, hypertension is still inadequately controlled.[5] The SPRINT trial has already affected clinical practice in some countries, such as the USA, and it will be interesting to see how the SPRINT-MIND results will further shape research and clinical practice, and awareness of the possibilities for the prevention of cognitive impairment. This is the first trial that has demonstrated an effective and feasible pharmacological strategy to reduce the risk of cognitive impairment. This trial supports the notion that what is good for the heart is good for the brain, and is a major step forward.

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