

Very low SBP targets and the boom-and-bust cycle of benefit and adverse kidney events

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We present a personal critical review of the long-term mortality and kidney failure outcomes of participants in the Systolic Blood Pressure Intervention Trial (SPRINT) trial and their implication for the treatment of hypertension, the management of chronic kidney disease (CKD) and the research agenda [1–3].

The US SPRINT trial randomized 9361 persons aged at least 50 years (mean $\pm$ standard deviation 67.9 ± 9.4 years) with hypertension, a systolic blood pressure (SBP) of 130 mmHg or higher and an increased cardiovascular risk to an SBP target of <120 mmHg (intensive treatment) or <140 mmHg (standard treatment) between November 2010 and March 2013 [4]. Patients with diabetes mellitus, autosomal dominant polycystic kidney disease, proteinuria >1 g/day [urinary albumin:creatinine ratio (UACR) >600 mg/g], glomerulonephritis treated with immune suppressants or estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m² were excluded, so the following discussion does not apply to them. Despite these exclusion criteria, around 28% had CKD G3–G4 from other causes. The intervention was stopped early after a median follow-up of 3.26 years. At 1 year, the mean SBP was 121.4 mmHg in the intensive-treatment group and 136.2 mmHg in the standard-treatment group, down from 139.7 ± 15.8 and 139.7 ± 15.4 mmHg, respectively, for a drop of 18.3 and 3.5 mmHg. Furthermore, more than 50% of participants in the intensive-treatment group had a SBP >120 mmHg. The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes. Intensive treatment decreased the incidence rate of the primary composite outcome (1.65% versus 2.19% per year) with a hazard ratio (HR) of 0.75 [95% confidence interval (CI) 0.64–

0.89]. It also decreased all-cause mortality (HR 0.73; 95% CI 0.60–0.90). However, this was achieved at the expense of higher rates of serious adverse events or emergency visits for hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure in the intensive-treatment group than in the standard-treatment group (range of HR 1.38–1.71, incidence in the standard-treatment group 3.4%–4.4%). Additionally, among participants without CKD at baseline, incident CKD G3–G5 was 3.5-fold more common in the intensive-treatment group ($P < .001$).

From SPRINT we also learnt that achieving and maintaining an SBP target of <120 mmHg long term is not easy. It was not achieved in many participants in the intensive-treatment arm (mean SBP 121.4 mmHg at 1 year during the trial) [4]. Moreover, in a subset of participants randomized to the intensive arm in which long-term post-trial follow-up was available, mean SBP was 133 mmHg at 5 years postrandomization and 140 mmHg at 10 years postrandomization [1]. Several post-hoc analyses of SPRINT have recently addressed the long-term impact of roughly 3 years of intensive blood pressure control [1–3]. The higher SBP levels in the long-term were associated with the loss of survival benefits and of kidney adverse events. Thus, by a median follow-up of 8.6 years (interquartile range 8.0–9.1 years), having participated in the intensive-treatment arm of SPRINT was neutral from the point of view of cardiovascular mortality (HR 1.02; 95% CI 0.84–1.24) or all-cause mortality (HR 1.08; 95% CI 0.94–1.23) when compared with the standard treatment arm [1] (Fig. 1A). Additionally, there was no evidence of kidney protection by intensive blood pressure control, in either the short (duration of the trial) or long term (8.6 years) [2, 3] (Fig. 1A). A worrying trend toward a higher and

Received: January 25, 2025; Editorial decision: February 24, 2025

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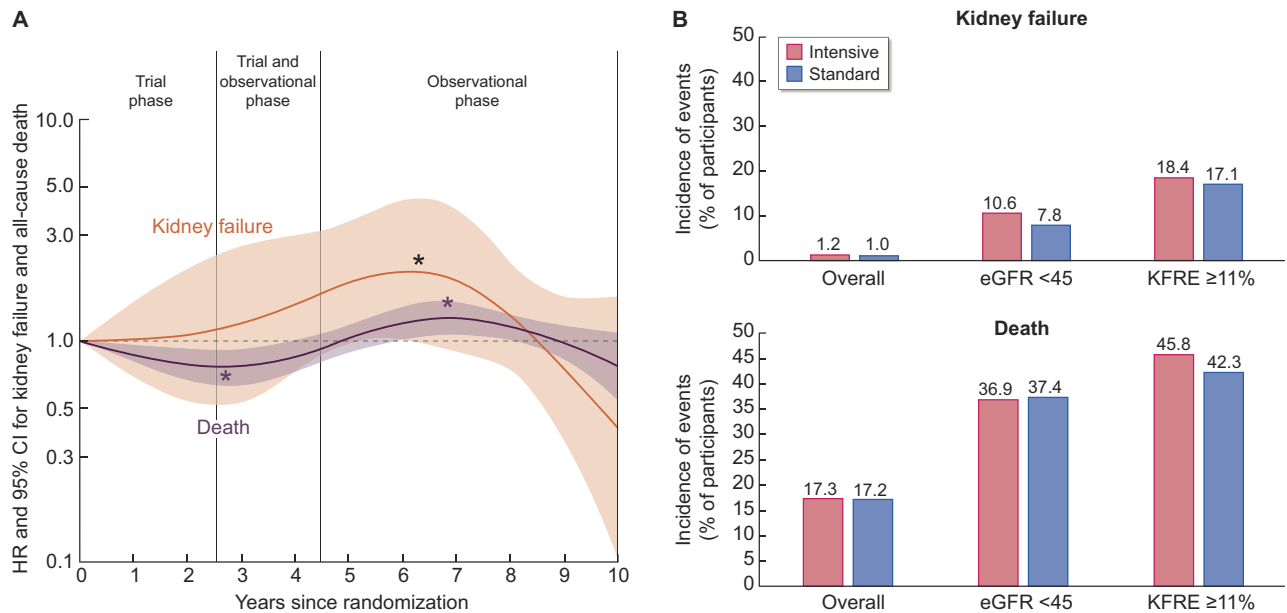


Figure 1: Long-term kidney and survival outcomes of participants in the SPRINT trial. SPRINT randomized US participants with hypertension (SBP >130 mmHg, baseline SBP 140 ± 15 mmHg) and high cardiovascular risk to intensive (target SBP <120 mmHg) versus standard blood pressure control (target SBP <140 mmHg). The intervention was stopped early after a median follow-up of 3.26 years. Occurrence of kidney failure (initiation of dialysis therapy or transplantation) and all-cause mortality in participants were checked in national databases through 2020, after a median follow-up of 8.6 years (interquartile range 8.0–9.1 years). People with diabetes, autosomal dominant polycystic kidney disease and proteinuria >1 g/day were excluded. **(A)** HR and 95% CI for kidney failure and all-cause death. Opposing trends were observed for mortality (decreasing) and kidney failure (increasing) for the duration of the trial. Both trends were reversed during the observation period where SBP values progressively returned to pre-trial levels. Color-coded asterisks mark the approximate point of potential changes of slope for the HR for kidney failure (black asterisks) and death (purple) asterisks. **(B)** Cumulative incidence of kidney failure and all-cause death. There were no statistically significant differences between groups. Outcomes are shown for all participants (overall) and for participants with eGFR <45 mL/min/1.73 m² (eGFR <45 mL/min/1.73 m²) using the race-free 2021 CKD Epidemiology Collaboration creatinine equation, and for participants with a higher risk of developing kidney failure (KFRE, risk $\geq 11\%$). None of the numerical differences was statistically significant. No long-term benefit was observed for either kidney failure or survival. Adapted with permission from Pajewski et al. The legacy effect of intensive versus standard BP control on the incidence of needing dialysis or kidney transplantation. *J Am Soc Nephrol* 2024;35:1737–45.

increasing incidence of kidney failure (dialysis or transplantation) over time was observed during the trial and in the early post-trial follow-up (up to 6–7 years). However, this was followed by a shift in the slope of the HR for kidney failure, which decreased over time towards 1.0, coinciding with the progressive increase of SBP values. Overall, mortality was more frequent than kidney failure (Fig. 1B). Numerically, deaths and kidney failure were more common in the long-term follow-up of the intensive-treatment arm, especially in people with lower baseline GFR (kidney failure) or higher risk of kidney failure (kidney failure, deaths) (Fig. 1B). The 5-year risk of kidney failure was assessed by the Kidney Failure Risk Equation (KFRE, <https://kidneyfailurerisk.com/>) which incorporates age, sex, eGFR and UACR. Using the KFRE equation, kidney failure risk was categorized using a 11% cut-off point which roughly corresponded to the 95th percentile in the SPRINT population.

The recent updates of the long-term follow-up of SPRINT [1–3] pose some key questions.

First, to what extent is the long-term maintenance of SBP <120 mmHg feasible outside a clinical trial context? The increase in SBP during post-trial follow-up may have been influenced by older SBP targets. However, SBP progressively increased, and eventually roughly 50% of participants reached a state of uncontrolled hypertension, despite the fact they and their physicians were expected to understand the survival benefits of stricter SBP control because of participation in the trial. This timeline and endpoint

suggest that sustaining an SBP <120 mmHg may not be feasible for most people outside clinical trials.

Second, what would be the impact of achieving and sustaining an SBP target of <120 mmHg over 9 years on the risks of death and kidney failure? The current 2024 KDIGO guideline on CKD suggests that adults with high blood pressure and CKD be treated with a target SBP of <120 mmHg, when tolerated, using standardized office BP measurement (2B) [5]. A Practice Point indicates to consider less intensive blood pressure-lowering therapy in people with frailty, high risk of falls and fractures, minimal life expectancy or symptomatic postural hypotension. By contrast, the European Society of Hypertension-European Renal Association 2023 guidelines suggested that (i) the blood pressure target for proteinuric nondiabetic CKD applies to patients with proteinuric diabetic kidney disease as well, and (ii) for both patient categories, a target SBP of <130 mmHg and diastolic blood pressure <80 mmHg, if well tolerated, can be associated with protection against CKD progression in individuals with an albuminuria >30 mg/g. A similar target may be associated with a reduction in mortality in most patients with CKD [6]. Thus, the discordance between guidelines regarding SBP targets, which is very confusing for clinicians, continues 4 years later. Still, the long-term impact of a very low target may be insignificant because it is unfeasible [7, 8].

Third, would a not-so-strict SBP target be more feasible to achieve in routine clinical care and better tolerated, and

therefore result in long-term survival and kidney benefit rather than neutrality? In this regard, the Chinese Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial tested a more achievable SBP target (110 to <130 mmHg) in 8511 people with hypertension. It observed a similar benefit on a composite combined primary outcome (stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation or death from cardiovascular causes) over 3.34 years (HR 0.74; 95% CI 0.60–0.92) without observing differences in the serious adverse event syncope or in new onset CKD nor CKD G4–G5 [9]. There was no information on other severe adverse events reported in SPRINT. However, there was no impact on all-cause death (HR 1.11; 95% CI 0.78–1.56), which was 2.8-fold less common in the standard treatment group than in SPRINT. The low mortality is consistent with the lack of a high cardiovascular risk inclusion criterion. STEP enrolled patients with SBP ≥ 140 mmHg. Baseline SBP was 146 ± 17 mmHg, achieved SBP 127.5 mmHg in the intensive-treatment group and 135.3 mmHg in the standard-treatment group for a mean decrease in SBP of 19.4 mmHg and 10.1 mmHg, respectively. Thus, the magnitude of the decrease in SBP was even larger than for SPRINT. It also enrolled patients aged 60–80 years with a mean age of 66.2 ± 4.8 years, similar to SPRINT, but 19% had diabetes mellitus and patients with eGFR <30 mL/min/1.73 m² were excluded, resulting in a prevalence of CKD G3 of 2.3%, over 10-fold lower than in SPRINT.

Fourth, could tighter blood pressure targets be achieved without adverse kidney events? Effects of Intensive Systolic Blood Pressure Lowering Treatment in Reducing Risk of Vascular events (ESPRIT) [10] was the largest trial (11 255 participants) on intensive versus standard antihypertensive treatment. It aimed at similar SBP targets as the SPRINT trial and also enrolled participants with high cardiovascular risk (although 38.7% had diabetes mellitus). The mean age and baseline blood pressure of the participants and the length of the trial and achieved SBP (119.1 ± 11.1 and 134.8 ± 10.5 mmHg at 1 year) were not dissimilar to SPRINT but only 6% had CKD G3a. Like SPRINT, the intensive treatment arm had fewer occurrences of the primary composite outcome of major adverse cardiovascular events (HR 0.88; 95% CI 0.78–0.99) but an increased risk of kidney adverse events. A sustained decline in eGFR of $\geq 40\%$ from baseline was observed in 3% of the participants in the intensive versus 1.8% in the standard treatment arm (HR 1.70; 95% CI 1.33–2.17).

Overall, a blood pressure target range of 110 to <130 mmHg may be more feasible and potentially safer from the kidney point of view while maintaining the cardiovascular and survival benefits. However, differences in healthcare systems, culture and ethnicity, and other differences between the study populations preclude direct comparisons between these trials. Given the differences across countries in healthcare systems, life expectancy and the epidemiology of cardiovascular–kidney–metabolic diseases, a pan-European pragmatic clinical trial may best address the question of the optimal target SBP in the European context.

Finally, the short- and long-term results of SPRINT suggest some divergence in the ‘dose-response’ relationship of SBP targets and the consequent CVD or renal outcomes. Whereas a lower SBP target was associated with lower risk of stroke or CVD death, the opposite appeared to be true for renal outcomes such as worsening kidney function or incident kidney failure.

In conclusion, recent megatrials support the efficacy of lower SBP targets, although very low SBP targets may be less safe for the kidneys in at least some populations. However, the long-term follow up of SPRINT participants argues against a very low SBP target in the studied population (non-diabetic, low proteinuria, older

than 50 years) as it may not be feasible to maintain over time in large segments of the hypertensive population outside a clinical trial environment. The inability to maintain a very low SBP target appeared to be associated with an improved kidney safety as compared with the very low SBP target. However, it was also associated with loss of the survival advantage. As a research proposal, pragmatic research should focus on the long-term feasibility, efficacy and safety of strict (SBP <120 mmHg) versus not-so-strict (SBP 110–<130 mmHg) SBP targets and on understanding the barriers to the long-term maintenance of SBP targets in our European environment. In the meantime, long-term follow-up of STEP and ESPRIT trial participants may provide further insight into optimal strategies for selecting and maintaining SBP targets to improve long-term outcomes.

ACKNOWLEDGEMENTS

The EuReCa-M Working Group is an official body of the European Renal Association.

FUNDING

Comunidad de Madrid en Biomedicina P2022/BMD-7223, CIFRA_COR-CM. Instituto de Salud Carlos III (ISCIII) (PI22/00469, PI22/00050, PI21/00251, PI21/01099, PI23/00627, ERA-PerMed-JTC2022 (SPAREKID AC22/00027), ERAPERMED2022-248–SIGNAL (AC22/00028), RICORS program to RICORS2040 (RD21/0005/0001, RD24/0004/0001, RD24/0004/0015) co-funded by European Union and SPACKDc PMP21/00109, FEDER funds, COST Action PERMEDIK CA21165, supported by COST (European Cooperation in Science and Technology); PREVENTCKD Consortium Project ID: 101101220 Programme: EU4H DG/Agency: HADEA. KitNewCare, Project ID: 101137054, Call: HORIZON-HLTH-2023-CARE-04, Programme: HORIZON. DG/Agency: HADEA.PICKED Project ID 101168626 HORIZON-MSCA-2023-DN-01-01 MSCA Doctoral Networks 2023.

CONFLICT OF INTEREST STATEMENT

A.O. has received grants from Sanofi and consultancy or speaker fees or travel support from Astellas, AstraZeneca, Bioparto, Boehringer Ingelheim, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Sobi, Menarini, Lilly, Chiesi, Otsuka, Novo-Nordisk, Sysmex, Vifor Fresenius Medical Care Renal Pharma and Spafarma, and is Director of the Catedra UAM-Astrazeneca of chronic kidney disease and electrolytes. He has stock in Telara Farma.

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Abbreviations: CKD, chronic kidney disease; HCP, healthcare professional; NICE, National Institute of Health and Care Excellence. **References:** 1. Vafseo 300 mg film-coated tablets Summary of Product Characteristics (SmPC). Available at: <https://www.medicines.org.uk/emc/product/15656/smpc> (Accessed March 2025). 2. NICE Guidance TA1035. Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease. Available at: <https://www.nice.org.uk/guidance/ta1035> (Accessed March 2025).

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