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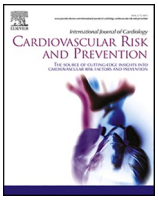

# Commentary: "*Lower is Better*" — SPRINTing to STEPping up hypertension research? An historical perspective on hypertension trials

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The recent publication of the US-based Trial of Intensive versus Standard Blood-Pressure Control (SPRINT) [1] and the Chinese Intensive Blood-Pressure Control in Older Patients with Hypertension (STEP) [2] mark the culminating point of over four decades of clinical trials in hypertension and high-risk patients. Over this time span emphasis moved from diastolic blood pressure in the very early Veteran Administration trials in the 1970s, over combined hypertension, and in the 1990s onwards to isolated systolic hypertension. Over time, there was a steady shift of the age band of interest to more elderly patients and to lower blood pressure targets. A recently published meta-analysis [3] included 358,707 patients from 51 trials, aged 21–105 years (median, 65 years; interquartile range, 59–75 years). It showed no evidence for any clinically meaningful heterogeneity of relative risk reduction by blood-pressure lowering therapies across different baseline blood-pressure categories in any age group. Per 5-mm Hg systolic blood pressure reduction, the hazard ratios of major cardiovascular events were 0.82 (95% confidence interval, 0.76–0.88), 0.91 (0.88–0.95), 0.91 (0.88–0.95), 0.91 (0.87–0.96), and 0.99 (0.87–1.12) in the age bands <55 years, 55–64 years, 65–74 years, 75–84 years and ≥85 years with similar patterns of relative risk reduction per 3-mm Hg lower diastolic blood pressure [3]. However, the reductions in absolute risk produced by blood-pressure lowering increased with advancing age. This meta-analysis [3], the post-trial evidence from SPRINT [1] and from the Systolic Hypertension in Europe Trial (Syst-Eur) [4] consolidated the concept that the benefits generated by antihypertensive treatment increased with earlier initiation of the pharmacological management of hypertension and lower blood pressure targets, as endorsed by the current American College of Cardiology/American Heart Association (ACC/AHA) guideline.

Starting from the 1990s, the convincing results of the earlier hypertension trials and the market introduction of novel blood-pressure lowering drug classes initiated the move from placebo-controlled to actively controlled trials and from primary to secondary prevention studies. This initiated a fervent debate focusing on whether the benefits observed in the hypertension trials were due to the pleiotropic properties of the newer *vs* the older drugs or to blood-pressure lowering "*per se*". Remarkably, a meta-regression analysis based on randomized controlled trials published before 2001, predicted a relative risk reduction associated with a 10-mm Hg difference in systolic blood pressure of around 25% for a composite cardiovascular endpoint [5]. In line with these analyses [5], the hazard ratios for cardiovascular events were 0.73 (0.63–0.86) in the intervention period of SPRINT (intensive *vs* standard treatment difference in systolic blood pressure, 13.1 mm Hg) [1] and 0.74 (0.60–0.92) in STEP (9.3 mm Hg) [2], supporting the idea that the achieved blood-pressure reduction rather than specific drug properties is the main driver of the benefit resulting from the pharmacological management of hypertension. To some extent this controversy became theoretical, because given the current ACC/AHA blood pressure targets, most patients will require three drug classes to achieve hypertension control.

Are SPRINT [1] and STEP [2] heralding the grand finale of clinical trials in hypertension or will they inspire the next generation of hypertension specialists to address research issues that stillneed to be answered over the next decade. A few examples follow, but by no means represent a complete list. What is in this digital age the long-term benefit of hypertension treatment managed via smartphone-based applications as pioneered in STEP [2] and other studies, such as the Urinary Proteomics Combined with Home Blood Pressure Telemonitoring for Health Care Reform Trial (NCT04299529) [6]. This investigator-initiated study sponsored by the Alliance for the Promotion of Preventive Medicine (UPRIGHT-HTM; URL: www.appremed.org) will enroll patients in Europe, sub-Saharan Africa and South America. The hypothesis being tested is that early knowledge of urinary proteomic risk profile on top of the home blood pressure monitored by a smartphone application as in STEP [2], will lead to more rigorous risk factor management and result in benefit [6]. A major issue still to be addressed is how to design and test strategies for the detection and management of hypertension including remote technologies, which would be practicable and efficient in low-income countries currently transiting from a disease burden dominated by communicable, maternal, neonatal, and nutritional causes to non-communicable disorders, mainly driven by hypertension and its cardiovascular complications. Building on the 2001 meta-analysis [5], re-analysis of the trial data already available and mounting randomized trials in asymptomatic patients with stage-A heart failure (only risk factors present) might assess the role of the blood-pressure reduction produced by sodium-glucose cotransporter (SGLT2) inhibitors in the

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prevention of death, recurrent hospitalization and renal dysfunction in patients with symptomatic heart failure, irrespective of ejection fraction and the presence *vs* absence of type-2 diabetes? Would SGLT2 inhibitors or other novel drugs, such as selective aldosterone receptor antagonists (finerenone) or angiotensin receptor neprilysin inhibitors (sacubitril/valsartan) qualify to replace spironolactone as the fourth-line drug in the management of resistant hypertension? Although stroke is the complication closest associated with the blood-pressure level, why did SPRINT [1], in contrast to STEP [2] and Syst-Eur [4], not demonstrate benefit for this devastating endpoint. And finally, how to manage hypertensive patients with a history of ischemic or hemorrhagic stroke, who were excluded from SPRINT [1] and STEP [2]?

Based on these examples and the observation that hypertension remains the direct cause of half of the worldwide cardiovascular mortality, the obvious perspective must be that trials of blood-pressure lowering therapies should keep their mainstay position in supporting human longevity in years and quality of life. In doing so, the focus should shift from treating established and often irreversible disease at out-patient clinics and hospital wards to true prevention in a digitally-enabled patient-centered way in the home environment under guidance of clinical risk markers and biomarkers predicting the transition from silent to symptomatic disease [6]. If clinical trials would validate such approach, this would be a game changer revolutionizing the management of public health and supporting the sustainability of health care in aging populations.

## Declaration of competing interest

None of the authors reports a conflict of interest.

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