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From 'essential' hypertension to intensive blood pressure lowering: the pros and cons of lower target values

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When towards the end of the Second World War, the 'big three', i.e. Franklin D. Roosevelt, Winston Churchill, and Joseph Stalin, met in Yalta from 4 to 11 February 1945, the US President was already a sick man; not a good basis for the reorganization of Europe's post-war political landscape. Perhaps history might have developed differently would he have been treated as is standard today.

Two months later, on 12 April 1945, Franklin D. Roosevelt's personal physician Admiral McIntyre announced the sudden death of the President and claimed 'Came out of clear sky. There was no indication of imminent danger.'[1] As the media reported the next day. The death of the President had been determined to be due to a cerebral haemorrhage, apparently without any preceding symptoms. Of note, Franklin D. Roosevelt had been known to suffer from so-called 'essential' hypertrension for many years and his blood pressure values steadily rose as his presidency was faced with increasing problems with the advent of the Second World War (*Figure 1*[2]).

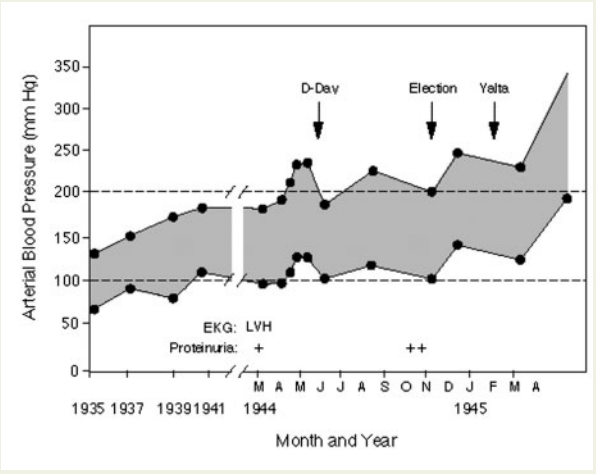

Figure 1 Blood pressure chart of Franklin D. Rososevelt over the years of his presidency (from Messerli[2]).

At that time, high blood pressure was considered 'essential' as it was thought to be necessary in such patients to allow for appropriate perfusion of vital organs. Indeed, as late as in 1937, the Braunwald of the day, Paul Dudley White, stated: 'Hypertension may be an important compensatory mechanism which should not be tampered with, even were it certain that we could control it'. So they did, and allowed Franklin D. Roosevelt's blood pressure to rise steadily until a blood vessel in the brain broke. Then of course, there was little that could be done: neither calcium antagonists nor inhibitors of the renin–angiotensin system were available, beta-blockers were only discovered in the 1960s, and the commonly used diuretics were toxic. At some point, the Presidents' physicians tried Kempner's rice diet obviously without success.

It was the late Edward D. Freis as well as the investigators of the Framingham Study[3] who noted in the early 1960s that high blood pressure was indeed not a good thing, but a risk factor for myocardial infarction, stroke, and death. Shortly after this observation, Freis designed and carried out the first randomized, placebo-controlled, double-blind multicentre trial in cardiovascular medicine to prove that blood pressure lowering would prevent such events. Starting in January 1964 over several years a total of 523 patients with high blood pressure were enrolled and treated with either a combination of a thiazide diuretic, reserpine, and hydralazine, or placebo. Out of the 523 patients, 143 had diastolic blood pressures >115 mmHg. In this subgroup, the trial had to be stopped after only 18 months because of a marked reduction in morbidity and mortality in the treated patients.[4] Indeed, 4 of the 70 patients in the placeb group died and 21 experienced major cardiovascular events, but none of the 73 treated patients died and only one had severe side effects of the drugs. The remaining 380 patients with diastolic blood pressures between 90 and 114 mmHg were followed for ~3 years during

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which 19 died in the placebo group, but only 8 in the active group.[5] As expected, these hypertensives died from myocardial infarction, sudden death, or stroke. Overall, 29% of the untreated hypertensives, but only 12% of those recieving drugs, developed cardiovascular events. Thus, Freis for the first time convincingly demonstrated that blood pressure lowering saves lives and reduces devastating complications such as stroke. Surprisingly, his findings did not make the headlines initially, but eventually changed medicine and led to to the concept that high blood pressure was not 'essential' (the Germans called it 'Erfordernishochdruck'), but rather a cardiovascular risk factor that requires proper treatment.[6]

The question remained of how far blood pressure should be lowered—and it continues to be a controversial issue to this day. What is a normal blood pressure? Is it in the range of 95/65 mmHg as among the Yanamona[7] or 110/70 mmHg as among the Kuna Indians[8] in South America who still live as hunters or gatherers, or is an age-adjusted value good enough for the Western population? In the late 1970s the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-1) considered <160/95 mmHg as appropriate;[9] indeed, in the elderly, values up to 180 mmHg systolic were deemed acceptable. After numerous anti-hypertensive trials, most guidelines recommended values below 140/90 mmHg as target values.[10] Still, in the elderly, higher values were accepted for quite some time, until more recent trials demonstrated that even in this age group and even in the presence of isolated systolic hypertension,[11,12] blood pressure lowering to 150 mmHg systolic or even lower prevented strokes, infarction, and death.[13] Today, therefore, the ESC/ESH Guidelines for the management of hypertension recommends a target blood pressure value of < 140/90 mmHg for all hypertensive patients and suggested even 130/90 mmHg in diabetics, with debatable evidence. Indeed, trials addressing this issue revealed mixed results: for instance, the ACCORD study was essentially neutral[14] and only a subanalysis showed a signal for a reduction of strokes.

Then the SPRINT trial was published in 2015[15] and caused an earthquake in the scientific community, with some welcoming its results enthusiastically, while others heavily criticized its design, conduct, and analysis. The Editors of the *European Heart Journal* therefore felt that they should allow, in a dedicated *Focus Issue on Hypertension*, both sides to speak up and present their arguments for or against an even lower systolic blood pressure target value in future guidelines. Sverre E. Kjeldsen from University of Oslo and Giuseppe Mancia from University of Milan-Bicocca outlining with a great deal of passion the counterarguments,[16] while Vasilios Papademetriou from the Veterans Administration Medical Center and Georgetown University in Washington DC, an investigator of the SPRINT trial, counters their arguments in his article.[17]

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A critical review of the systolic blood pressure intervention trial (SPRINT)

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Introduction

Why are we critical?

The *Systolic Blood Pressure Intervention Trial* (*SPRINT*) was stopped early because of a statistically significant reduction in cardiovascular morbidity and mortality by lowering systolic blood pressure to below 120 mmHg, and the main findings were included in a press release 2 months prior to the full publication. However, as we see it the data are marginal, if at all of clinical relevance, and the unconventional method used in the study for measurement of blood pressure (BP) makes the claim for target BP in regular practice to be below 120 mmHg unsupported and potentially harmful, particularly in the elderly and the patients with high entry BP. Targets for treatment of hypertension could possibly be lower than recommended by current guidelines but unfortunately SPRINT does not provide any support for making changes in BP targets.

Summary of the SPRINT study

Systolic Blood Pressure Intervention Trial enrolled 9361 participants age 50 years and older in about 100 expert medical centres and clinical practices throughout the USA.[1] Systolic Blood Pressure Intervention Trial excluded patients with diabetes and stroke survivors since prior clinical trials sponsored by the US National Institutes of Health (NIH) included those populations.[2,3] Between 2010 and 2013, the SPRINT investigators randomly allocated the study participants into a standard treatment group receiving an average of two different BP medications to achieve a systolic BP target <140 mmHg, and an intensive treatment group receiving an average of three BP medications to achieve a systolic BP target <120 mmHg. The Director of the National Heart, Lung and Blood Institute stopped SPRINT early because a protective effect of treatment in patients randomized to the lower BP target. The preliminary results of SPRINT were announced on 11 September 2015[4] and the study results were quickly and favourably commented upon by the New York Times[5] and the Washington Post.[6] The target systolic BP <120 mmHg apparently had reduced rates of the composite primary outcome that included myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes by 25% and the risk of death from all causes by 27%, as compared to the target systolic BP of <140 mmHg. The primary results of the trial were presented at the Scientific Sessions of the American Heart Association in Orlando on 9 November 2015 and published on the same day.[7] The SPRINT Study was released with an accompanying statement from the Editor of *New England Journal of Medicine*[8] saying that 'This clinical trial will change practice, and we are proud to publish it and to defend the importance of the expedited peer-review and publication process that it has undergone. The report is now in the public domain, and the investigators' data interpretation, analysis, and clinical discussion are open to examination and comment'.

The call from the Editor of *New England Journal of Medicine*

The purpose of this critical review is just to do so and respond to the call from the Editor of *New England Journal of Medicine*[8]—now a couple years after the publication when contents and consequences are better understood. We will review the clinical endpoints and potential differences between the two target groups. A clinical relevant difference in endpoints is a prerequisite for promoting the study and the outcomes, and a clinical relevant difference in endpoints is needed in order to recommend the findings for providing the basis for changing guidelines and clinical practice. *Second*, what is the importance of the unattended automatic office BP measurement technique[9] that was used in SPRINT? A new technique for measurement of BP has several implications including comparison with standard BP measurement regarding the exact mmHg, feasibility for clinical practice (can it be used?), and we need to know whether BP taken with a new method predicts cardiovascular complications to hypertension and thus whether it at all is worthwhile to persuade? *Third*, while NIH and the SPRINT investigators promote target systolic BP of 120 mmHg in the elderly, it is our opinion that this target may be harmful, and it may potentially increase mortality in the elderly and in patients with high baseline BP. At best, it may lead to side effects so frequently that patients who need antihypertensive medication stop taking them and run into complications because of their untreated state.

Marginal endpoint findings in SPRINT

The primary endpoints in SPRINT

Seventy-six less patients were reported to have encountered a primary endpoint in the intensive vs. the standard BP arm. Thirty-eight, exactly 50% of these patients, were reported to have had a primary endpoint because of incident heart failure. A proper assessment of these numbers is critical for the meaning of SPRINT.

A strict, administrative, and even a political view would claim that the study was prospective and randomized and that the components of the primary endpoint are irrelevant for the overall interpretation.

This may potentially explain the actions of the NIH leadership when they unexpectedly had a 'positive' study at an early stage. They surprisingly stopped the study with these low numbers and released the data.[4,7] Was this a proper thing to do?

The primary endpoint included incident heart failure which has always been considered a 'soft' endpoint in hypertension research because of requirement of both clinical symptoms and objective signs of the diagnosis, and because it is not a specific disease itself but may represent multiple cardiac diseases in an advanced stage. 'Hospitalization for heart failure' is also a soft endpoint because criteria for hospitalization differ markedly from one place to another and these criteria are not always well defined.

The diagnostic criteria for heart failure are not universal or 'hard' as they tend to be for myocardial infarction, cerebral stroke, electrocardiogram-documented arrhythmias, and mortality. For a double-blinded study this may not have been important because both arms are equally affected. However, in an open study like SPRINT investigator bias may easily explain some cases of incident heart failure, and particularly so in a study like SPRINT in which the 9361 participants had very high risk of getting heart failure.[7] Additionally, the changes in the specific first line treatment with diuretics may open up or conceal the typical symptoms of heart failure in high-risk hypertensive patients with latent or mild degree of this endpoint. In other words, an apparent difference is explained by a systematic error like in a previous large outcome trial.[10]

As many as 3136 patients were randomized into SPRINT with baseline BP 130–≤132 mmHg. For the 1553 patients who then needed elevation of BP towards 140 mmHg, some medication was down-titrated or discontinued (*Figure 1A*). And as the protocol[7] strongly recommended to first make changes in diuretics, chlorthalidone, or furosemide, such heart failure protective or symptoms hiding drugs in patients with high-risk hypertension were discontinued in this arm, and they must have been intensified in the 1583 patients with baseline BP 130 to ≤ 132 mmHg in the other arm in order for them to get BP down towards 120 mmHg (*Figure 1B*). Here, we have the second and maybe even stronger explanation for the 38 patient-difference in incident heart failure between the two arms. We find it very likely that the difference in patients with incident heart failure appeared as a consequence of the SPRINT design and the finding should therefore be considered to be an artefact. And it does not matter whether the changes in diuretic treatment caused some new cases of heart failure or just masked or de-masked symptoms of heart failure; the difference appeared because of the study design.

And without the 38 patients with incident heart failure the difference in the primary endpoint would not be significantly different between the two treatment arms. The study leadership had found no reason to stop the study early if realizing that the primary endpoint was driven by an artefact. In a well-designed open protocol, the cases of incident heart failure had counted as secondary endpoints and SPRINT had run its full course with a chance of showing a difference in cerebral stroke and possible other endpoints which would have been expected with a difference of approximately 15 mmHg in systolic BP between the two arms.

The mortality findings in SPRINT

At the time when SPRINT was stopped prematurely, there was a rather small but statistically significant difference of 55 less fatal cases in the intensive arm. However, these were equally split into 28 and 27 cardiovascular and non-cardiovascular deaths, respectively.[7] The intensive arms had 25% more visits in order to up-titrate the antihypertensive medication, reach the systolic BP target <120 mmHg and detect patients with side effects. It is commonly known that patients with side effects hesitate to take their antihypertensive medication. Surprisingly high numbers of side effects appeared in the intensive arm compared to the conventional arm.[7] Thus, more frequent visits to the investigator site were needed to perform the study and retain the patients. Despite these efforts, a record-high 245 patients were lost to follow-up; in our opinion this large number is an indicator of suboptimal quality of the follow-up performance and retention efforts of patients in the study. This is in contrast to many randomized and controlled hypertension trials performed elsewhere and maybe particularly so regarding outcome trials in the country of Sweden. As examples we mention the STOP studies which had no patients lost to follow-up.[11,12] In any case, an equal distribution of cardiovascular and non-cardiovascular deaths between the two arms indicate an unspecific effect of the intervention which was only expected to lower cardiovascular mortality.

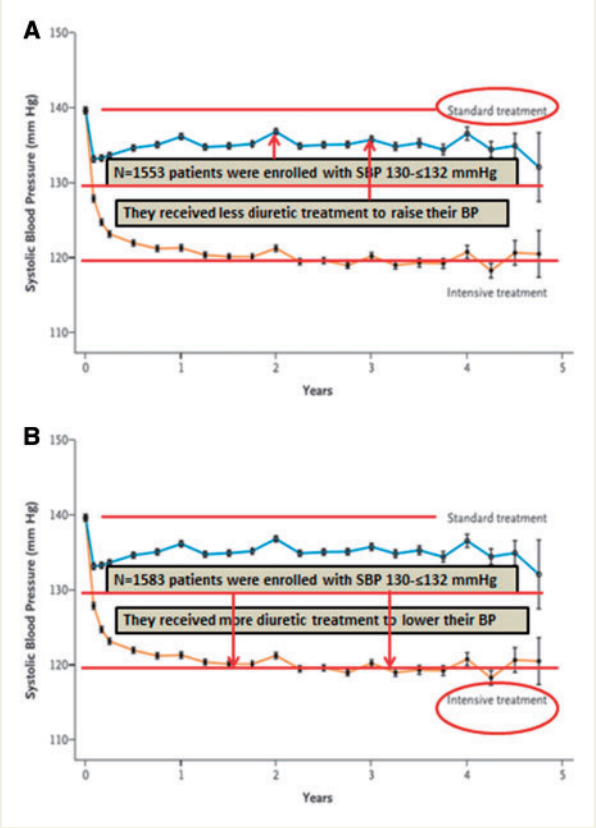

Figure 1 (*A*) Patients randomized to standard treatment, including more than 1500 patients with slightly elevated enrollment blood pressures of 130-≤132 mmHg, needed less medication to achieve higher target blood pressures and (*B*) Patients randomized to intensive treatment, including more than 1500 patients with slightly elevated enrollment blood pressures of 130-≤132 mmHg, needed more medication to achieve lower target blood pressures.

The side effects in SPRINT

Patients with serious side effects such as acute renal failure outnumbered the patients with the primary endpoint or mortality. For

example, there were 84 more patients with acute kidney injury or renal failure in the intensive arm, 80 more patients with serum sodium <130 mmol/L and 40 more patients with serum potassium <3.0 mmol/L, 65 more patients with hypotension, and 50 more patients with syncope; all these increases were statistically highly significant. As mentioned above, it is well known that side effects cause patients with hypertension to stop taking their medication, or in a clinical trial—'drop out'. The SPRINT investigators expected a 2% drop out rate per year; after an average follow-up of 3.26 years their drop-out rate was approximately 10.5% which was considerably higher than expected, 489 vs. 497 in the two arms, respectively. This high discontinuation rate suggests that the SPRINT investigators were not able to retain more patients in the intensive arm despite 25% more visits to the study sites.

The blood pressure measurements in SPRINT

Unattended automated office blood pressure

The original SPRINT publication[7] did not contain any description of the method that the investigators used to measure BP. As standardization of BP measurements is critically important in a study of BP targets, we summarized the issue based on numerous small hints and details in various papers and concluded that, for the first time ever in an outcome trial, 'unattended automated office BP' measurements were taken.[9] All investigators used the Omron 907 model (Omron Healthcare, Lake Forest, IL, USA), which was also available in a previous NIH supported Study,[2] but in that study the staff stayed in the room and activated the device at the end of the 5 min period of rest. There has been an extensive discussion in the literature and at meetings what actually took place in SPRINT but in the publication of the elderly subgroup analysis, co-authored by the entire study leadership, the method for BP measurements is described *sans fraise* as 'BP was determined using the mean of three properly sized automated cuff readings, taken 1 min apart after 5 min of quiet rest *without staff in the room*'[13] as we first time described.[9]

Already in the Hypertension Optimal Treatment (HOT) study published 20 years ago,[14] a sub-sample of 926 treated hypertensive patients who measured their BP at home using the same semi-automatic device as the investigators used at office visits were devoid the classical 'white coat effect' in as much as the average BPs were almost identical at home and in the office. Similar BP measurements technique was applied in several other large studies for the purpose of standardization.[9] However, in SPRINT the protocol for unknown reasons for the first time utilized the full capacity of the Omron 907: The device was preset to measure BP after 5, 6, and 7 min and all staff then left the room and did not re-enter until after measurements. It appears that before study start there were training sessions at all sites, and a demonstrating video was posted at the study web-site though removed around the time of the main publication.[7]

Validation of unattended automated office blood pressure

The unattended automated office BP measurement technique has been promoted in Canada[15] through 15 years and it has recently quite extensively been validated against office and standard home BP measurements.[16] Unattended automatic office BP averaged 16/8 mmHg lower than standard office BP in 353 treatment hypertensive patients.[16] Also in 29 patients who met the inclusion and exclusion criteria of SPRINT, unattended BPs like in SPRINT were taken following standard office measurements and averaged 13/4 mmHg lower.[17] A sub-study of 24-h BP measurements in SPRINT[18] investigating approximately 450 participants in each arm who were representative for the whole SPRINT population, showed that the unattended automated office BP in SPRINT averaged 7 mmHg lower that daytime 24-h systolic BP in the intensive arm while when taking standard office BP we are used to see the opposite. If we thus circumvent the SPRINT situation adding 14 mmHg and consider the daytime part of 24-h systolic BP to be equal to standard home systolic BP, SPRINT sub-study data are almost identical to the findings in the studies that validated the measurements techniques mentioned above[16,17] and that found differences of 16 and 13 mmHg for systolic BP, respectively.

Further, in an accompanying editorial Parati *et al.*[19] compared 24-h systolic BP in SPRINT with similar BP in ELSA[20] and PAMELA[21] and found from the regression line that the true standard office systolic BP in SPRINT could have been approximately 130 mmHg in the intensive arm and 150 mmHg in the less intensive arm. ELSA and PAMELA were meticulously done scientific studies. If slightly less meticulously measurements had been done in regular clinical work and patients being seated for 5 min before measurements, 5 mmHg more should probably be added suggesting that SPRINT compared standard office readings of approximately 135 vs. 155 mmHg. Adding 15 mmHg would be compatible with the comparison of home BP measurements with the unattended automated office BP techniques in the study of 353 treated hypertensive patients.[16] Comparisons of such target-BPs would be of limited interest in most patients maybe except for in the very elderly above the age of 80 years.

It should also be mentioned that unattended automatic office BP has hardly ever been validated against cardiovascular endpoints. There is one study in Ontario, Canada[22] in which 6183 people had their BP taken like this in pharmacies and after an average of 4.6 years there was a weak relationship with cardiovascular complications. Interestingly, when applying the unattended automatic office BP in Ontario most elderly hypertensive people have systolic BP control below 130 mmHg and approximately 40% below 120 mmHg.[23] Thus, we may believe that possibly the Canadians report unnaturally good BP control and avoid facing the real problem by simply bypassing hypertension in many people when applying this method.[24]

The SPRINT subgroups that should have the most conservative target blood pressures

The elderly subgroup in SPRINT

Twenty-eight % of the SPRINT participants qualified and were included because of their high age and they averaged 80 years at the outset. All the weaknesses described above also applied to this group.[13] The difference in the primary endpoint was made up

of 46 patients in favour of the intensive arm, but it was reduced to a difference of 26 cases when patients with non-fatal heart failure are kept out. And 133 cases of total 180 fatal events in difference between the two arms were non-cardiovascular again pointing towards an unspecific effect of intensive follow-up rather than intensive treatment of hypertension. Direct 'translation' from standard measurements of office BP[16] indicates that in the elderly approximately 140 mmHg was compared with 160 mmHg on average in the two arms. We cannot easily see how this could change our current recommendation of a target systolic BP between 140 and 150 mmHg based on the outcomes of the HYVET study[25] in the people above the age of 80 years.

We may further envision a scenario, that could arise if the recommendations of SPRINT would be implemented world-wide, e.g. the well-known 'u-shape phenomenon' in BP treatment, the increasing number of hospital admission due to syncope, renal failure, hypotension, and so forth. This scenario is foreseen by a study from Ireland recently published.[26] In a community-based prospective cohort with contemporaneous follow-up of comparable duration, participants 75 years of age or older who met inclusion criteria for SPRINT had rates of injurious, falls, and syncope approximately five-fold higher than the standard care group in SPRINT. Given the high baseline rates of falls and syncope, any increase in these rates due to intensive treatment of hypertension could result in harm.[26]

SPRINT subgroup with high baseline blood pressure

The strongest evidence supporting the construct that the effect of more intensive vs. standard systolic BP lowering on outcomes is related to baseline systolic BP comes from a recent *post hoc* analysis of data from the SPRINT study.[27] In an analysis of patient-level data that developed prediction models to determine the intensity of BP control best suited to individual patients to maximize benefit and reduce risk, Patel *et al.*[27] found that in contrast to the absence of an interaction between randomized treatment and tertiles of baseline systolic BP found in the main SPRINT analyses,[7] patients with major adverse cardiovascular events or death had higher mean systolic BP and there was a significant interaction between intensive systolic BP lowering and baseline systolic BP. In their subsequent multivariable risk model for major adverse cardiovascular events, intensive systolic BP lowering was associated with an odds ratio of 1.12 (95% CI 1.02–1.22) for every 10 mmHg increase in baseline systolic BP. Thus, based on these analyses,[27] SPRINT patients with higher baseline systolic BP did better with more conservative systolic BP goals.

Recent analyses of other randomized clinical trials in response to SPRINT

It may be important to re-analyse other databases in light of SPRINT to see whether target systolic BP below 120 mmHg would reduce cardiovascular complications or even visualize the J-curve with increments of cardiovascular events or serious adverse events with very low target BP. This has now been done and with the low BPs targets, in all studies using conventional office measurements, there is either increased risk or no benefit.

First, in high-risk patients aged 55 years or older with a history of cardiovascular disease, 70% of whom had hypertension, mean achieved systolic BP less than 120 mmHg during treatment was associated with increased risk of cardiovascular outcomes except for myocardial infarction and stroke.[28] Similar patterns were observed for diastolic BPs less than 70 mmHg, plus increased risk for myocardial infarction, and hospital admission for heart failure. Very low BP achieved on treatment was associated with increased risks of several cardiovascular disease events. The authors concluded[28] that the lowest BP possible is not necessarily the optimal target for high-risk patients, although it is not possible to rule out some effect of reverse causality.

The analysis in patients with diabetes and hypertension came to the conclusion that attaining a usual systolic BP target between 120 and 140 mmHg demonstrated a clear benefit for lowering the burden of cardiovascular risk.[29] Achieving a more intensive target systolic BP target of less than 120 mmHg did not appear to attenuate the risk. These findings support the contention of a less aggressive approach toward lowering BP among individuals with diabetes mellitus.

Regarding patients with coronary heart disease and hypertension,[30] the authors concluded that their findings favour achieving systolic BPs of 120 to <140 mmHg and avoidance of the extremes of systolic BPs due to high mortality risks, some of which appears linked with a concomitant low diastolic BP. Adapting strategies to achieve systolic BPs < 120 mmHg in hypertensive patients with coronary artery disease would be premature, as the cardiovascular impact of diastolic BP lowering requires further prospective study.

Recently reported, in patients with left ventricular hypertrophy there was a statistical significant interaction between baseline systolic BP and the average achieved systolic BP during treatment for all-cause mortality.[31] In the patients with the highest baseline systolic BP at 160 mmHg and above, mortality increased if average systolic BP during follow-up fell into the tertile of participants with the lowest average systolic BP during follow-up.

In a thorough meta-analysis of 17 trials that enrolled 55 163 patients with 204 103 patient-years of follow-up which included SPRINT,[32] the authors concluded that BP targets of <140 and <150 mmHg ranked #1 and #2, respectively, as the safest target for the outcome of serious adverse effects, and that cluster plots for combined efficacy and safety showed that a systolic BP goal of <130 mmHg achieved the optimal balance between efficacy and safety.

Potential limitation of our *post hoc* SPRINT criticism

The SPRINT Study has been in the public domain for almost 2 years, and we admit that we have used approximately 1 year and 10 months longer than the time that was available for the SPRINT authors to analyse, interpret, and write up their data from 11 September and until the presentation and publication on 9 November 2015.[7] We do not feel particularly well in extensively criticizing the work of American colleagues even without having access to the data base like the SPRINT investigators and their Data and Safety Board. However, the situation has been complex in light of the interpretations of the previous prospective and randomized clinical trials aiming to identify the optimal target BP.[2,3,33] The most correct characterization of these trials is probably that they were statistically underpowered. When all participating patients were randomized to rather low BP targets, and additional treatments given according to randomization in factorial design in two of them,[2,33] the overall event rate became

low and differences between groups difficult or almost impossible to detect. Further, regarding incident heart failure and mortality in SPRINT differences in our opinion can be explained by features in the study design as explained above.

It has not been obvious to us from the first moment that we disagree with the characterization *landmark study* as claimed in the initial press release.[4] Our criticism has thus been limited by available information in the first months following the publication, and it has been a puzzle to accumulate the information needed to express our opinions including the description of the method used to measure BP.[9]

Possibly, we are also biased in the sense that we are influenced by data from previous research and in particular the inconclusive results of the previous three large randomized studies.[2,3,33] The European Guidelines recommendations[34] regarding target BP have also been floating for certain groups of patients including patients with high risk such as those who participated in the SPRINT Study.

Summary and outlooks

As we see it the SPRINT data are marginal, if at all of clinical relevance, and the unconventional method used in the study for measurements of BPs makes the claim for target BP in regular practice to be around 120 mmHg unsupported. The publications of 'unadjusted' SPRINT data in the prestigious US medical journals may be harmful for the patients of the readers who do not catch that the BP targets in SPRINT should be translated to approximately 135 vs. 155 mmHg (140 vs. 160 mmHg in the elderly) in regular clinical practice. If not implementing such an adjustment for a new and different BP measurement technique, the optimistic expressions of saving thousands of life by applying 120 mmHg as systolic BP target may be inverted to increased mortality and particularly so in the elderly and in the patients with the highest baseline BPs. And the clinical field which we considered as 'clinical hypertension research and practice' will be weakened and consequently suffer for many years to come.

When responding to our criticism, please check whether NIH is focusing on the critical issues. 1) In the unblinded SPRINT Study the difference in mortality was unspecific (equal number of cardiovascular and non-cardiovascular deaths) and detected by 25% more follow-up visits in the intensive arm. 2) The difference in the primary endpoint was a consequence of the study design with heart failure included in the primary endpoint and more heart failure preventing or concealing drugs given in the intensive arm.

Conflict of interest: S.E.K. reports modest personal honoraria from ABDiiBRAHiM, Bayer, MSD, and Takeda within the past 3 years. Giuseppe Mancia reports no conflict.

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SPRINT is a landmark trial: results should be adopted in clinical practice

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Introduction

The Systolic Blood Pressure Intervention Trial (SPRINT) is a land mark trial that will influence the practice of hypertension for many years to come. SPRINT was a randomized, prospective, well-designed and run interventional trial, not industry sponsored, not specific drug targeting study, blood pressure (BP) lowering dependent study, conducted by highly trained professional personnel and paid by the US tax payers money. The study[1] showed in an indisputable way that targeting systolic BP level <120 mmHg (achieved 121.4 mmHg) better protects from cardiovascular events and death than targeting systolic BP <140 mmHg (achieved 136.2 mmHg). The study published in the NEJM,[1] received worldwide recognition, and stared up the stagnant waters of the hypertension field creating interest all over the word about controlling high BP again. Nevertheless, it also stared up the interest of sceptics who disputed the results. Two of our esteemed colleagues indeed wrote the current article heavily criticizing SPRINT in an attempt to discredit the SPRINT results.[2] In a way this is reminiscent of the original land mark trials in hypertension, the VA co-op studies designed and spearheaded by our own Eduard D. Fries in the early 1960s.[3,4] At that time many clinicians thought that essential hypertension was 'essential' to perfuse tissue and vital organs and lowering it would be detrimental. The conventional wisdom at that time was that, it made no sense and perhaps it was even unethical to treat patients with mild to moderate hypertension. Vital organs, in particular with diseased perfusing arteries, needed higher pressures. The VA co-op studies proved once and for all that hypertension was not 'benign' and that treatment with orally effective drugs could dramatically reduce morbidity and mortality, in patients with severe hypertension[2] and of course in patients with mild to moderate hypertension.[3]

Although the early findings were broadly accepted, adoption of the results was difficult. 'It took a great number of publications to convince clinicians there was nothing essential about essential hypertension' and 'It has been a long fight to convince people of this', said Ed Freis. Yet the VA co-op studies revolutionized the treatment of hypertension from doing little or nothing to actively pursuing hypertension treatment and control. In so doing, the study results helped to save untold thousands of lives and reduce the incidence of stroke, heart failure, and renal failure in the process.

Of note, subsequent analysis of the study results demonstrated benefits from a diastolic BP of 105 mmHg and above. It took more than three decades, hundreds of studies, and hundreds of thousands of patients to demonstrate benefit by lowering diastolic BP < 90 and/or systolic <140 mmHg.[5–8]

Fast forward and in November 2015 results of the SPRINT trial[1] are published, demonstrating that compared to <140 mmHg, targeting <120mmHg results in an impressive reduction of cardiovascular events and mortality. No surprise, the sceptics are still there, ready to deprive middle age and older patients with hypertension a longer, happier, and complication-free life. The main argument made: the methods used in SPRINT to measure BP were new and by extension inaccurate, resulting in lower than expected levels of BP and thus underestimating terminal values, i.e. the authors of the counter piece insinuate that although the final values in the two groups were

136.2 vs. 121.4 mmHg, the true values, measured in clinical practice should have been 135 and 160 mmHg.

For the rest of the article of this counterpoint (ref. Kjeldsen), I want to make clear that I am not a spokesman for the SPRINT study, although I was an investigator and local primary investigator, and part of several publications. I therefore have my own bias. Nevertheless, I will try to objectively oppose the arguments made as best as I can:

The authors of the article[2], my opponents, present a fair summary of the SPRINT results, but present the premature termination of the study as suspect and the call from the editor of the NEJM, as part of a conspiracy and fraud. The authors[2] are well known seasoned and accomplished investigators and they comprehend the weight of their statements. Consequentially they should know that the study was terminated prematurely, because it met the pre-defined criteria of premature discontinuation for ethical reasons, i.e. it was unethical to continue the study, because patients in the standard treatment group would have suffered unnecessarily higher number of cardiovascular events.

They go on to question the motivation of the editor of the *New England Journal of Medicine* in publishing the results with an abbreviated review process. We all know the reason: the study was and is important, it is destine to change many minds and practices in hypertension and the *New England Journal of Medicine* editor wanted to make it known as soon as possible.

Furthermore they question the decision to stop the study prematurely, but the decision was based on interim analysis and predefined parameters using 'group sequential stopping boundaries defined with the use of the Lan–DeMets method with an O'Brien–Fleming-type spending function. The fine-ray model for the competing risk of death was used as a sensitivity analysis',[1] supplement). The decision was neither premature nor inappropriate. The intent was to protect the patient interest.

The authors list a series of provocative arguments against the findings of SPRINT trying to discredit the results. I will try below to present the counter arguments based on evidence and not on speculations and opinions.

The primary endpoint was reduced by an impressive 25% with a *P*-value of <0.001. For the record: Everyone knows that means one in a thousand that the finding is a play of chance. It is highly statistically significant and clinically relevant. The authors furthermore feel that it was primarily driven by the incident heart failure events and thus less reliable. They also claim that 'A strict, administrative and even a political view would claim that the study was prospective and randomized and that the components of the primary endpoint are irrelevant for the overall interpretation'.

I fully agree with my opponents that the study was well designed, prospective, and randomized (although not blinded), and thus the primary endpoint is what counts and not its components. That's how it usually works. Obviously, the study was not powered to assess changes in all the components of the primary endpoint not even many of the secondary endpoints, so the authors should not make a big deal of it. In fact they hold the opposite opinion about the results of the much smaller ACCORD BP trial (which was under-powered) and consider the results negative despite the fact that there was a significant reduction in stroke (a secondary endpoint) with intensive therapy, both in the main study[9] and in a subgroup analysis,[10] and they still consider the study negative.

They go on stating that incident heart failure is a 'soft' endpoint and diagnosis is based on objective signs and symptoms and operator dependent, but they forget that all the local primary investigators of SPRINT were selected to be seasoned scientists and good clinicians that are able to reliably make the diagnosis of heart failure. Furthermore, the criteria used were obviously the same for patients in the standard and intensive groups. Hospitalization for heart failure is also a 'soft' finding, perhaps for outside observers and statisticians, but for the patients who huff and puff and get admitted to the hospital for treatment with infusion therapies for heart failure, admission is indeed a very 'hard' endpoint and tantalizing experience. Because it is very relevant to patients quality-of-life (one of the main reasons we treat patients), it has always been included as a component of the primary endpoint and as a secondary endpoint. That been said it does not take away from the argument that it may introduce bias. Indeed if the local primary investigator was responsible for admissions and had a knowledge of patient randomization, it would make that argument valid; but, at least in the USA, the responsibility for patient admissions belongs to the emergency room physician who has no knowledge of patient randomization. This is particularly true and important for SPRINT, because the medication administered to the patient was readily available and the emergency room physician had no reason to inquire about randomization. Thus, the argument that somehow there was favouritism and more patients in the standard arm were admitted with diagnosis of heart failure is not sustainable.

The argument made that some heart failure events were due to down-titration or discontinuation of diuretics is also untrue. Here is the story with diuretic use (personal communication): thiazide diuretic use was about the same in both arms during screening, i.e. about 39%. In the standard group at randomization, a small number of the participants who had not been taking a diuretic previously were started on a thiazide diuretic, and an equal number of participants who had been taking one stopped taking it. Overall there was no decrease in percentage of diuretic use after randomization and no change in the number of medications, although numerically there were more patients who started a diuretic than discontinued one. Consequently there was a slight decrease in systolic BP (from 140 to 136 mmHg) after randomization. In the intensive group, BP medication was generally increased as per protocol. As such the use of all kinds of BP medication increased, including thiazide diuretics. In 33% of participants in the intensive group who had not been taking a thiazide a diuretic was started; 7% who had been taking one stopped. Overall, then the percentage taking a thiazide diuretic increased from 38% to 56%. In the intensive group, there was an increase in total medication from 1.8 to 2.7 per patient including utilization of calcium channel blockers (mainly amlodipine) which would have led to more oedema and possibly more 'false diagnosis' of incident heart failure in the intensive group. Thus, the argument is counterproductive and indeed works the other way around.

My opponenets claim that in the 1553 patients who needed loosening up of their medications to allow BP to increase towards the level of 140 mmHg, the medication decrease was mostly the diuretic. This is not based on the facts: As stated above, this is not true and there was no overall increase in diuretic use or in any medicine in the standard group participants. The bumps shown on their graphs are merely an artefact. The only recommendation to

the local primary investigators was to change when possible hydrochlorothiazide to chlorthalidone, which if in any case, would have increased the diuretic effect, as chlorthalidone is twice as effective as hydrochlorothiazide.

The mortality findings in SPRINT

The point made on mortality rates is not clear to me either. My opponents state that 'At the time when SPRINT was stopped prematurely there was a rather small, but statistically significant difference of 55 less fatal cases in the intensive arm. However, these were equally split into 28 and 27 cardiovascular and non-cardiovascular deaths, respectively'. Fifty five fewer deaths in the intensive group means 55 more patients alive. Every life counts and every death is devastating, even if it is not cardiovascular. Yet the causes of death are clearly stated in the supplementary table S3 of the paper as discussed by the authors. The results worked exactly as they should, namely a markedly more pronounced reduction in CV deaths in the intensive group. Indeed, in the intensive group there were 37 deaths due to CV causes and in the standard group 65 (a 27% highly significant reduction with a $P = 0.0003$). Deaths due to cancer, as expected were equal in both groups, i.e. 49 and 52, respectively. Thus, their argument is again not based on the facts.

They also complain about the number of patients lost to follow-up and state that there were a lot more than in Swedish trials. This is certainly true, but patients in the USA are a lot more mobile than in Sweden, they move around and do not necessarily bother to reconnect with the study centres. It is not a weakness of the investigators or the study it is a factor of demographics.

Yes, patients in the intensive group had—as expected—more biochemical side effects, mostly related the use of more diuretics, but they survived in greater numbers and had longer and happier lives. Although patients in the intensive group had more episodes of hypotension and syncope, they had no more injurious falls, indicating that the adverse effects were transient, mild, and inconsequential. The serious adverse event that had the most visibility was the acute kidney injury. Overall, there were 88 episodes in the intensive group and 34 in the standard group (which was significant with a $P < 0.0001$). In the elderly, 75 and 54 events were noted, respectively (with a borderline $P = 0.07$). These results have been analysed in separate manuscripts[11,12] and the indications are that even these patients benefitted from lower overall cardiovascular events and death. Interestingly there was no increase in chronic kidney disease in patients with baseline kidney disease,[13] but there was some derangement, mostly functional in patients without chronic kidney disease.[12] This functional or cosmetic change did not reduce the beneficial effects of intensive treatment.

Blood pressure measurements

SPRINT was one of the most carefully done studies that I have ever participated in (since the late Edward D. Freis' era). The study provided a standardized device to all centers (Omron Healthcare, Lake Forest, IL, USA Omron 907 model), used in all sites and the personnel was trained for its appropriate use. The method for measuring BP in the SPRINT study was designed to obtain a true baseline BP of the patient, unaffected and uninfluenced by external factors, such as environmental noise, white coat effect, smoking and caffeine, patient posture, observer influences, and inadequacies. Timing and measurements were pre-programmed and automated and the results printed for accuracy. Human error and sloppiness has been taken out of the equation. Thus, the SPRINT BP measurements were truly optimal. Patients were seen in a quiet room, seated for at least 5 min, with the back supported, legs uncrossed, and not speaking as all these factors are known to influence BP levels. The device was programmed to start taking BPs 5 min after activation and take three measurement 1 min apart. Thus, measurements were taken at minutes 5, 6, and 7 after device activation. The personnel were asked to leave the room, so to provide privacy and to return after the three measurements were completed. Unattended BP was measured in many cases, but not all. In a good percentage of cases, the nurse had stayed in the room (relevant data will be presented at the upcoming AHA meeting). Now, Kjeldsen and Mancia, make a big deal about the methods used for BP measurements in SPRINT: 'However, in SPRINT the protocol for unknown reasons for the first time utilized the full capacity of the Omron 907: The device was pre-set to measure BP after 5, 6 and 7 min and all staff then left the room and did not re-enter until after measurements'. They insinuate that this distorted the study results and therefore the study is not credible. In support of their argument, the authors refer to a sample 926 patients from the *Hypertension Optimal Treatment* (HOT) study[13] who had similar clinic BPs and average home BPs measurements. I do not see how this strengthens their argument. Certainly, HOT was a well-designed and well-run study. Although it used a semi-automated device, personnel were instructed to take three BPs 1 min apart, with the patient seated in a quiet room for 3–5 min. Thus, in a way the instructions were very similar to SPRINT to the extent that the HOT study personnel followed the instructions measurements were good and reliable and correlated precisely with average home BP measurements. I am certain that BPs would have been very similar, had they used the SPRINT device and measurements taken attended or unattended. Similar guidance has been given to study personnel for many years now in many well-done studies. In our renal denervation study[14] in 46 patients, we performed repeatedly all three modalities of BP measurement, i.e. office, home, and ambulatory BP monitoring. Office BPs were measured using very similar guidance to SPRINT. We used an automated device with printout, patients were seated for 3–5 min in a comfortable room with back supported, legs uncrossed, and not talking. Home BPs were taken for the last 2 weeks prior to each visit, and ambulatory BP monitoring performed at the same day as the office visit. At 12 months (ignore baseline BPs as there are too many confounders), home and office BPs were identical and day time BP from Ambulatory Blood Pressure Measurement (ABPM) within 2 mmHg from both office and average home BP. It seems that the authors are confusing BPs taken for study purposes to measurements taken casually in clinic; indeed, the latter measurements are very different, the clinic is busy, noisy, the nurse is in a hurry, patients do not wait for 5 min and not always does the nurse check BPs three times as required. It is a well-known fact that in the clinic setting the more you check the BP, the lower it gets. Thus, you can make no sense out of BPs unless measurements are standardized and the procedure is faithfully followed. The innovation in SPRINT was the fact that the device was programmed to wait 5 min before starting checking BPs and not the fact that the nurse walked out of

the room. That made no difference. In other words, BP measurements in SPRINT were built in a safeguard so the study nurse had to adhere to the guidance we always give to study personnel. Otherwise results can vary widely. Indeed, we routinely encounter patients referred to us for BPs of 220 mmHg and by the time they get to clinic and get measurements the right way, the values are down to 160 mmHg systolic. Perhaps the authors are concerned about the part that the personnel left the room and measurements were taken 'Unattended'. However, neither the authors nor anyone else has data comparing head-to-head attended and unattended BP measurements taken in close proximity, during the same visit, using the SPRINT device. Actually we do have such data (unfortunately as of yet unpublished) that show no difference what so ever between attended and unattended SPRINT measurements. In summary then, I would like to make a suggestion here: instead of fighting the BP methods followed in SPRINT, let's put all of our efforts forward to teach everyone how to always measure BP the SPRINT way. It will eventually come to that, and we certainly would help a lot of patients.

In contrast, my opponents make the point that unattended automated office BP has been validated in Canada against usual office values and ambulatory BP monitoring. In the referenced study[15] they state: 'Unattended automatic office BP averaged 16/8 mmHg lower than standard office BP in 353 treated hypertensive patients (15) and by 13/4 against ambulatory BP measurements'. What they fail to say is that in the said study, unattended automated BP was measured six times after 5 min rest (remember the more times you check it the lower it is!) and the usual office BP measurement used the auscultatory and not the automated way (which introduces a bias, including white coat effect, and apprehension to the patient). Of note, auscultatory pressures are always higher than automated pressures no matter what.

My opponents also only partially quote the results of the SPRINT ABPM sub-study. 'The unattended automated office BP in SPRINT averaged 7 mmHg lower than daytime 24-h systolic BP in the intensive arm'. True, but they omit to say that the difference between unattended office BP and day time systolic BP in the standard group was only 3 mmHg and the 24 h average systolic was 3 mmHg higher in the intensive group and 2 mmHg lower in the standard group.[16] Furthermore, there is BP variability, from day-to-day and even from minute-to-minute. The ABPM SPRINT sub-study was a cross sectional study done around the 27 month visit, which means that the clinic pressures and the ABPM might have not been contemporaneously recorded. They further refer to data from Gianfranko Parati's paper[17] and the ELSA and Pamela studies[18,19] and they conclude, using difficult to follow calculations, that 'If slightly less meticulously measurements had been done in regular clinical work and patients being seated for 5 min before measurements, 5 mmHg more should probably be added suggesting that SPRINT compared standard office readings of approximately 135 vs. 155 mmHg'. They failed to point out however that at lower levels of achieved BP the correlations of office with ambulatory BP values were much better. In the ELSA study for example, the office BP of 120 mmHg correlated exactly with 120 mmHg measured by ambulatory monitoring.[18] Furthermore, we need to remind ourselves that none of the outcome data we have is based on 'standard office readings'. Indeed, standard office readings vary widely depending who is doing the reading and how meticulous they may be. My standard office reading the other day measured by an automated validated device, in my doctor's office was 155 mmHg, the first time, 145 the second time and 135 mmHg the third time. When I returned to clinic and it was measured properly in triplicate after 5 min rest it was 124 mmHg. Thus, using standard office measurements I would have been diagnosed as hypertensive and been treated who knows by how many antihypertensive so far.

My opponents further argue that unattended automated blood pressure has never been validated against cardiovascular outcomes. Well now it has. Along with the Canadian study, we have established a robust data base showing that measurements done the SPRINT way can predict precisely cardiovascular outcomes. Instead of trying to discredit the results perhaps, we should all try to teach young (and older) physicians to adopt modern methods of diagnosing and treating patients with hypertension. That will benefit not only us all, but mostly our patients.

Subgroup analysis

The elderly

Based on their arguments discussed above, my opponents declare that 'Direct "translation" from standard measurements of office BP indicates that in the elderly approximately 140 mmHg would truly have been 160 mmHg on average in the two arms with so-called standard measurements'. The SPRINT study, randomized 1317 patients over the age of 75 years to a target BP < 120 mmHg and 1319 patients to a target BP < 140 mmHg.[20] The achieved BP was 123.4 mmHg in the intensive elderly group and 134.8 mmHg in the standard elderly group, slightly higher pressures than the overall population. It is difficult to follow their argument that these BPs should have been translated arbitrarily into 140 and 160 mmHg, respectively. Undoubtedly, lower BPs in the intensive group translated into substantial clinical benefits, i.e. a 33% reduction in the primary endpoint, a 38% reduction in heart failure, a 40% reduction in cardiovascular death and a 33% reduction in all-cause mortality. Impressively benefits were evident among all subgroups of patients older than 75 of age, the fit, the less fit, and even the frail. Furthermore, serious adverse events were similar between patients randomized to the intensive and standard groups (637 vs. 637). Again and as expected, some adverse events occurred slightly more frequently in the intensively treated group (such as hypotension, syncope, electrolyte abnormalities, and acute kidney injury, but with no statistical significance) and they were mostly inconsequential. In contrast and unexpectedly, injurious falls occurred more frequently in the standard group as compared to the intensive group, but the difference was not statistically significant (5.5% vs. 4.9%, P = NS). Furthermore, gait speed, a component of frailty, although it had a declining course during the study, was not different between the two groups. Thus, the interpretation of these probably counterintuitive findings is that intensive treatment does not affect patient's gait speed or frailty (*Figure 1*).[21]

With these data at hand, I cannot see why we should deprive the elderly of longer and happier lives! Kjeldsen and Mancia refer to a study from Ireland[22] and speculate that if and when the data are adopted world-wide, hospitalizations from hypotension, syncope and injurious falls may increase and intensive therapy may result in harm.

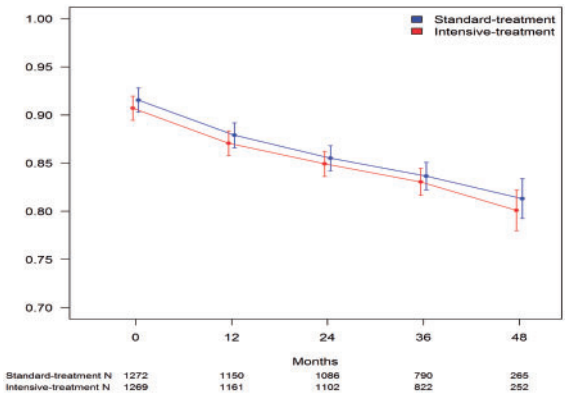

Figure 1 On treatment, gait speed and frailty changes in standard and intensive group participants in the Systolic Blood Pressure Intervention Trial (SPRINT). There was no difference in the rate of decline between groups.

Let me remind them that dead people do not become hypotensive, do not develop syncope and do not fall. Instead why not refocus on taking care of the elderly, training them and their physicians on how to take care of them and help them live comfortable long lives. In fact, a recent publication[23] by our own group by Adam Bress applied the SPRINT eligibility criteria to the 1999–2006 National Health and Nutrition Examination Survey and linked them with the National Death Index through December 2011. The study authors concluded that if fully implemented in eligible USA adults, intensive treatment of systolic BP the SPRINT way could prevent around 107 500 deaths per year, but could result in an increase in serious adverse events. The authors caution and we agree that careful patient selection and monitoring are important because intensive treatment is associated with an increased risk of hypotension, syncope, electrolyte abnormalities, and acute kidney injury.

In their effort to uncover supporting evidence concurring with their point of view Kjeldsen and Mancia move further by stating: 'The strongest evidence supporting the construct that the effect of more intensive vs. standard systolic BP lowering on outcomes is related to baseline systolic BP comes from a recent post-hoc analysis of data from the SPRINT study'[24] . . . Patel *et al.*[24] found patients with major adverse cardiovascular events or death had higher mean systolic BP and there was a significant interaction between intensive systolic BP lowering and baseline systolic BP. In their subsequent multivariable risk model for major adverse cardiovascular events, intensive systolic BP lowering was associated with an odds ratio of 1.12 [95% confidence interval (95% CI) 1.02–1.22] for every 10 mmHg increase in baseline systolic BP. Thus, based on these analyses,[21] SPRINT patients with higher baseline systolic BP did better with more conservative systolic BP goals'. Again, this is beyond me how it supports the authors' point of view. In fact the authors of the above study (Patel *et al.*) explain: 'Intensive BP treatment was associated with a mean of 2.2 ± 2.6% lower risk of MACE including death compared with standard treatment (range 20.7% lower risk to 19.6% greater risk among individual patients) and they continue 'We found a significant treatment interaction with age in our model for MACE including death, suggesting that older patients were more likely to benefit from intensive BP treatment, possibly because of them being at increased cardiovascular risk. In contrast, although we found that while older patients were more likely to have serious adverse events, these were not greater in those with more intensive BP control, as there was no significant treatment interaction of age with serious adverse events. Although a higher BP goal may be appropriate for some patients at advanced age, our results suggest that many of these patients may benefit from intensive treatment'. And they explain further that 'The interaction of BP treatment with patient's baseline systolic BP, suggesting higher risk of MACE or death with intensive treatment in patients with higher baseline systolic BP may result from a larger morbidity/mortality reduction with standard BP treatment'. They conclude: 'To translate the findings from SPRINT to clinical practice, we developed prediction models to tailor the intensity of BP control based on the projected risk and benefit for each unique patient. This approach should be prospectively tested to better engage patients in shared medical decision making and to improve outcomes'. This is a nice but complex paper, I recommend it to interested readers.

Thus in summary, the SPRINT study not only helped all of us establish appropriate targets of therapy it also helped clarify a number of other issues lingering in the field of hypertension. Recent publications from SPRINT helped in that respect:

(1) A study by Beddhu *et al.*[11] examined SPRINT participants without evidence of CKD at baseline. Results indicated that incident CKD event occurred in 3.7% of participants in the intensive group and 1.0% in the standard group at 3-year follow-up, with a hazard ratio (HR) of 3.54 (95% CI 2.50–5.02), but the corresponding percentages for the composite of death or cardiovascular event were 4.9% and 7.1% at 3-year follow-up, with a HR of 0.71 (95% CI 0.59–0.86). The authors conclude that intensive SBP lowering increased risk for incident CKD events, but this was outweighed by cardiovascular and all-cause mortality benefits.

(2) Similarly Cheung *et al.*[12] published the results from patients with CKD at baseline: the study found that among patients with CKD and hypertension without diabetes, targeting a SBP < 120 mmHg

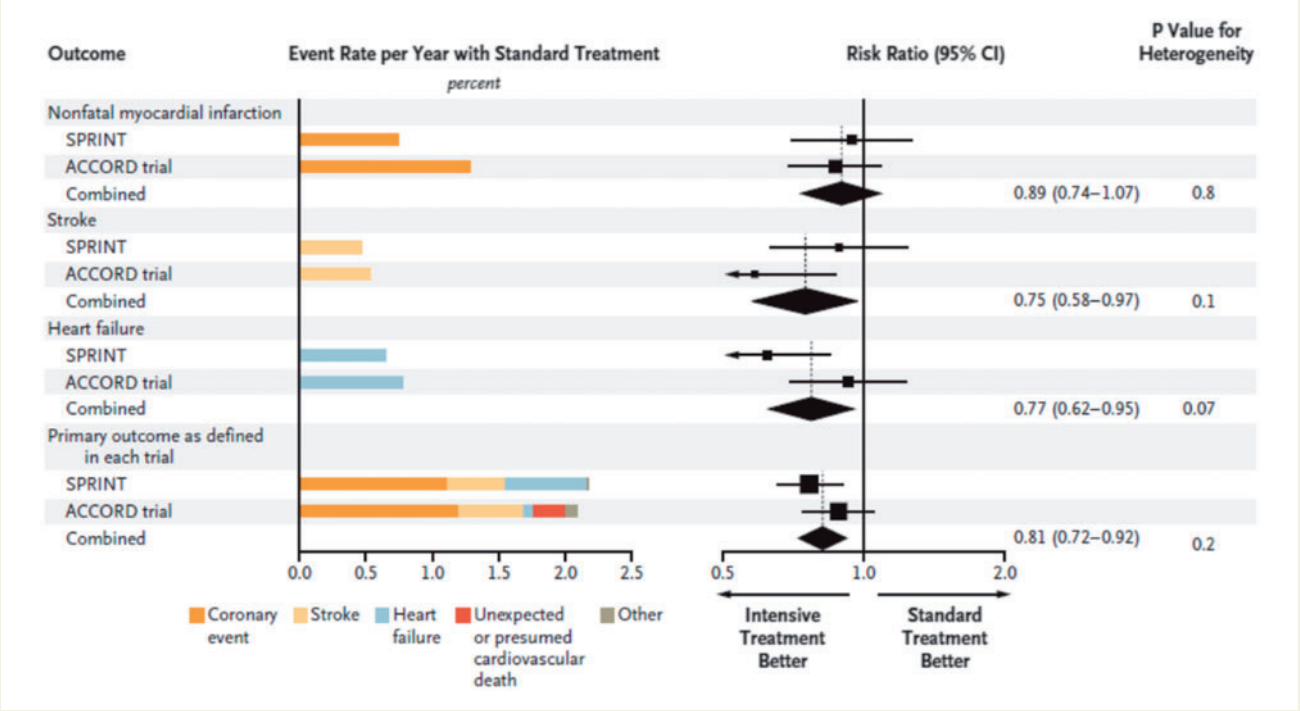

Figure 2 Health outcomes in Systolic Blood Pressure Intervention Trial (SPRINT) and ACCORD trials. Results were concordant, but not always statistically significant.

compared with <140 mmHg reduced rates of major cardiovascular events and all-cause death without evidence of deleterious effect on any of the main kidney outcomes.

(3) Another important study[25] examined the effect of intensive BP treatment in patients with pre-diabetes. In this study, we found that beneficial effects of intensive BP treatment were similar among those with pre-diabetes and fasting normoglycaemia. These results will naturally lead to re-examination of the 'negative' results of the ACCORD-HTN trial which seems to have been underpowered (*Figure 2*).

(4) Finally we assessed the impact of visit-to-visit office BP variability as a predictor of cardiovascular events and death in the SPRINT population.[26] We defined OBPV as the coefficient of variation of the systolic BP using measurements taken during the 3-, 6-, 9-, and 12-month study visits. Use of thiazide-type diuretics or dihydropyridine calcium channel blockers was associated with lower OBPV whereas angiotensin-converting enzyme inhibitors or angiotensin receptor blocker use was associated with higher OBPV. There was no difference in OBPV in participants randomized to standard or intensive treatment groups. We found that OBPV had no significant associations with the composite end point of fatal and non-fatal cardiovascular nor with heart failure or stroke. The highest quintile of OBPV (vs. lowest) was associated with all-cause mortality (adjusted HR 1.92; 95% CI 1.22–???3.03) although the association of OBPV overall with all-cause mortality was marginal ($P = 0.07$). Our results suggest that for now clinicians should continue to focus on office BP control rather than on OBPV.

SPRINT was a monumental, land mark study that provided undisputed evidence that intensive treatment of BP extends the lives of middle age and older men and women without diabetes. That serves well the main purpose of medicine and medical practice 'to take care of people and help them live longer'. The other aim of medicine is to make patients feel better. Intensive therapy, the SPRINT way, provides several clues to that effect. Indeed, prevention of non-lethal events, stroke, heart attacks, and heart failure improves quality-of-life, but adverse events especially those events associated with symptoms can hinder quality-of-life. Nevertheless, it is obvious as well that patient selection, especially among the elderly is crucial. Intensive therapy is not for everyone. Health care professionals should be careful not to inflict side effects and in particular symptoms such as lightheadedness or syncope because of low BP. Medications should be adjusted to make patients comfortable. Achieving a balance between longevity and quality-of-life is important. What SPRINT has taught us is that we can achieve both. Patients and in particular older patients need appropriate care and close follow-up. We can provide it and help them live longer and happier lives.

The views expressed in this article are those of the authors and do not necessarily represent the official position of the National Institutes of Health (NIH), the Department of Veterans Affairs, the U.S. Government, or the SPRINT Research Group.

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