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The new US and European guidelines in hypertension: A multi-dimensional analysis

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ABSTRACT

The Systolic Blood Pressure Intervention Trial (SPRINT) compared the clinical outcomes between target systolic blood pressure (SBP) levels between 140 and 120 mmHg or lower. Both,the 2017 ACC/AHA and the 2018 ESC/ESH guidelines in hypertension are derived from the SPRINT trial and advise initiation and/or intensification of treatment at lower blood pressure thresholds. The ACC/AHA guidance supersedes the 2014 Eight Joint National Committee guideline (JNC-8) which advised initiation of treatment when the BP was 140/90 mmHg or higher; in adults 60 years or over, the target was 150/90 mmHg. Compared to JNC-8, the new guidelines lower the SBP target by 10 mmHg in patients under age of 60 years, and by 20 mmHg in the elderly. We performed a qualitative multi-dimensional analysis in order to answer two key questions: will the new guidelines deliver the stated benefits? and, will translation to the clinic be simple, risk-free, and affordable? A major investment by national healthcare administrations will be necessary for the initiation and support of this program but this decision can only be justified by a valid expectation of clinical benefit. At this time, a definitive answer is not available and a "wait and see" attitude appears appropriate and reasonable. In the interim, efforts are best directed to the immediate problem of untreated hypertension worldwide.

1. Introduction

Based on the SPRINT trial, the 2017 American College of Cardiology/American Heart Association (ACC/AHA) and the 2018 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines in hypertension have lowered the detection threshold and treatment targets for hypertension [1–3]. The objective of this revision was to enhance the safety and efficacy profile of intervention and to deliver this benefit to a larger population. Although well-intentioned, downward revision of the definition of disease may involve an overlap with the normal, however defined. In this context, the overlap population risks labeling, diagnostic drift, and the consequences of overtreatment. Labeling has serious and long-term consequences. Healthy individuals are now patients, and face increasing payments on account of a pre-existing condition, hypertension, that was not there yesterday. The elderly, and especially the frail elderly are more concerned about immediate adverse events, especially falls, rather than uncertain future benefits. In the US alone, implementation of the ACC/AHA guidelines will result in an additional 30 million individuals (from 72 to 103 million), about half the adult US population, to be labeled hypertensive [1,2].

Hypertension is highly prevalent in the adult population in the United States, especially among persons older than 60 years of age, and in 2015, affected approximately 1 billion adults worldwide [4]. Lowering of the diastolic blood pressure (DBP) has resulted in a decrease in complications and an increased survival. In order to explore additional benefit, attention is now being directed towards lowering of the systolic blood pressure (SBP). The hypothesis that a lower SBP target (e.g., <

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ACP, American College of Physicians; AAFP, American Association of Family Physicians; ARR/RRR, Absolute risk reduction/Relative risk reduction; CV, CVD, cardiovascular, cardiovascular disease; IT/ST, Intensive treatment, ST standard treatment; JNC-7, 8, US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 2003, 2014; ESH/ESC, European Society of Hypertension/European Society of Cardiology; SBP, DBP, Systolic blood pressure, diastolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial

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120 mmHg) would further prevent cardiovascular disease risk was designated by the US National Heart, Lung, and Blood Institute as the most important hypothesis to be tested.

The over-riding determinant of cardiovascular health is a person's age. By 2030, approximately 20% of the population will be aged 65 or older. In this age group, cardiovascular diseases (CVD) will result in 40% of all deaths and rank as the leading cause. Vascular damage accumulation during aging leads to an increase in CVD via atherosclerosis, hypertension, myocardial infarction, and stroke. Accordingly, a trial to evaluate intervention in systolic hypertension in older adults is justified and appropriate. However, aging is associated with comorbidities and caution is indicated; aggressive attempts to address cardiovascular risk increases the probability of iatrogenic harm, for example, falls, and the consequences of polypharmacy, especially drug interactions.

In the context of recent advances in diagnosis and therapeutics Benjamin Chin-Yee and his colleagues at the University of Toronto and the Harvard T.H. Chan School of Public Health, Boston, have outlined issues related to societal relevance namely costs, equitable resource allocation, and health disparities. Hypertension has reached an epidemic prevalence worldwide and in addition to the uptake of the newer guidelines, a broader public health and policy audience should discuss benefit/risk of approaches that could divert from other priorities such as social equity, which is a common denominator within and between countries [5]. Here, we evaluate the promise of the new guidelines, in individual and population contexts, against this objective.

2. The SPRINT trial

The Systolic Blood Pressure Intervention Trial (SPRINT) was a controlled, randomized, open-label study in subjects with an on-treatment SBP between 130 and 180 mmHg and an increased cardiovascular risk. 9361 subjects were randomized to an SBP target of < 120 mmHg (intensive treatment group, 4678 subjects) or a target of < 140 mmHg (standard treatment, 4683 subjects) [1]. The primary endpoints were a composite outcome that included myocardial infarction and other coronary syndromes, stroke, heart failure or death from cardiovascular causes. The average age was 68 years, and 28% of the subjects were over the age of 75. The average baseline blood pressure (on treatment) was 140/78, (90% of participants were on treatment) and two-thirds had a SBP < 145 mmHg. Enrollment occurred between 2010 and 2013 at 102 sites in the United States and Puerto Rico, and the maximum follow-up period was 6 years. Patients with diabetes mellitus, prior stroke, cancer, or a medical condition likely to limit survival to < 3 years were excluded. The trial was well-conducted, subjects were balanced between groups, and dropouts were few.

Based on the outcome of this study, the 2014 guidelines on hypertension, JNC-8 [6], was revised. The 2017 ACC/AHA guideline involves initiation of treatment at a SBP > 130 mmHg and a target SBP of 120 mmHg or lower in subjects with intermediate or high cardiovascular risk [2]. The revised guideline applies to all patients irrespective of age. Comparisons with JNC 8 [6], JNC 7 [7] and the ESH/ESC [8] guidelines are provided below Table 1.

According to the ACC/AHA 2017 guidance, BP is categorized as normal, elevated, or stages 1 or 2 hypertension. Normal BP is defined as < 120/ < 80 mmHg; elevated BP 120–129/ < 80 mmHg; hypertension stage 1 is 130–139 or 80–89 mmHg, and hypertension stage 2 is ≥140 or ≥ 90 mmHg.

3. Analysis

The ACC/AHA guideline based on SPRINT is puzzling, problematic, and perplexing. In SPRINT, target SBP levels of 140 and 120 mmHg or lower were compared relative to clinical outcomes [1]. The ACC/AHA target SBP of 130 mmHg is therefore not evidence-based [2]. Our analysis, which is limited to summary data, is directed to primary care physicians and follows the principles of Evidence Based Medicine, namely, in understanding the results, assessing the credibility of the evidence, the way that the results are communicated, and determining how best to apply them to daily practice.

Table 1
Evolving hypertension guidelines [1–3,6–8].

Guideline/trial	Target population, age in years	Treatment goal, mm Hg
JNC 7 (2003)	< 60	< 140/90
ESH/ESC (2013)	< 80	< 140/90
	> 80	< 150/90
JNC 8 (2014) (endorsed by ACP and AAFP, 2014)	< 60	< 140/90
	> 60	< 150/90
SPRINT trial (2015)	> 50	< 120/–
ACC/AHA (2017)	General population	< 130/80
ESH/ECC (2018)	< 65	< 130/ –
	> 65	Less aggressive

Abbreviations: JNC, US Joint National Committee, ESH, European Society of Hypertension, ESC, European Society of Cardiology, ACP, American College of Physicians, AAFP, American Association of Family Physicians, ACC, American College of Cardiology, AHA, American Heart Association.

3.1. Methodology – blood pressure measurements

SPRINT used a novel BP method that involved unattended measurements in a quiet environment. In general, BP values using this method are generally lower than conventional measurements performed in doctor's offices. This makes interpretation and comparisons with earlier trials difficult.

3.2. Analytic frame

The achievement of statistical significance for the primary outcome is a necessary requirement for the adoption of a new treatment guideline, but it is not sufficient [9]. The totality of trial results will be carefully examined by stakeholders, including payers, journal editors and reviewers, clinical experts, guidelines committees, physicians, and also patients. The determination of whether the findings provide evidence that is sufficient to modify medical practice requires careful interpretation of the trial data and comparisons with the clinical record of earlier guidelines. Here we address some of the points raised by Stuart Pocock and Gregg Stone (London School of Hygiene and Tropical Medicine and Columbia University Medical Center, New York) that are relevant to SPRINT and the derived guidelines: *The Primary Outcome Is Positive — is that good enough* [9]? Table 2.

Here our focus is three-fold, namely on items 7, 8, and 11 in Table 2, the clinical consequences that could result from the adoption of the new guidelines, and the impact on national healthcare administrations on individual and public health.

In closing, we request readers to respond to two questions:

- will the new guidelines deliver the stated benefits in the clinic? and

Table 2
Assessment of clinical trials [9].

1. Does a *P* value of < 0.05 provide strong enough evidence?
2. What is the magnitude of the treatment difference?
3. Is the primary outcome clinically important and internally consistent?
4. Are secondary outcomes supportive?
5. Are the principal findings consistent across important subgroups?
6. Is the trial large enough to be convincing?
7. Was the trial stopped early?
8. Do concerns about safety counterbalance positive efficacy?
9. Is the efficacy-safety balance patient-specific?
10. Are there flaws in trial design and conduct? Randomized groups, double blind?
11. Will the findings apply to my *next* patient?

Table 3
Primary outcome, serious adverse events and deaths [1].

	Intensive therapy (n = 4678)	Standard therapy (n = 4683)	P Value
Primary outcome - %	5.2	6.8	< 0.001
Serious adverse events - %	4.7	2.5	< 0.001
Deaths	155	210	< 0.003
Cardiovascular deaths	37	65	< 0.005

- will translation be simple, risk-free, and affordable?

3.3. Analysis

3.3.1. Data on efficacy and safety

3.3.1.1. Efficacy. In this open-label trial, a lower rate of the primary composite outcome of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes was noted with intensive treatment. (5.2% vs 6.8%, hazard ratio 0.75, 95% CI, 0.64 to 0.89, P < .001, ARR -1.6%, RRR -24%) Table 3**.**

3.3.1.2. Safety. Serious adverse events (SAE's) were presented in two formats in separate locations (Table 3**)** in the paper [1], Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events, and table S5 in the supplementary appendix, Serious Adverse Events and Conditions of Interest Classified as Possibly or Definitely Related to the Intervention (supplementary information).

Separate formats are confusing to the reader and hinder appraisal of causality and interpretation of possible harms. For example, the incidence of SAE's in Table 3 of the paper, describes an incidence of 38.3% in the IT group vs 37.1% in the ST group (hazard ratio, 1.4 and P value, 0.35). Thehe incidence of SAE's that are possibly or definitely related to the intervention, as reported in table S5 of the supplementary appendix, was 4.7% in the IT group vs 2.5% in the ST group (Hazard ratio 1.88, P value, < 0.001) [1]. However, in the text, nor in the study protocol it was clearly defined how the category 'possible or definite SAE" was defined. Probably this definition is identical to the predefined list of SAE's, which was considered likely to occur with antihypertensive treatment. It would have been more logical to report these SAE's in the main paper and present the overall SAE comparison in the appendix, as many of the latter may be unrelated with the treatment and by chance are having similar incidence in both groups. In general, it is difficult to exclude the absence of a relationship between an intervention (lowering of the BP) and SAE's in a clinical situation that includes possible comorbidities and polypharmacy and attendant drug interactions. John Ioannidis, at Stanford University, and his colleagues at the CONSORT group have provided a framework for better reporting of harms in randomized trials [10].

SAE's were defined as an event that was fatal or life threatening, resulting in significant or persistent disability, requiring or prolonging a hospitalization, or was an important medical event that the investigator judged to be a significant hazard or harm to the participant that may have required medical or surgical intervention to prevent one of the other events listed above. 4.7% of the intensive-treatment group and 2.5% of the standard-treatment group had SAE's that were classified as possibly or definitely related to the intervention, which is a relative increase of 88% (hazard ratio, 1.88; P < .001) (supplementary appendix, table S5 in Ref. [1]). Serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure, but not injurious falls or bradycardia, occurred more frequently in the IT group than in the ST group. It is difficult to explain why *orthostatic* hypotension was less common in the IT group. Despite a higher rate of serious adverse events in the IT group, there was an excess of deaths in the ST group (P < .003). Age at death would be useful information, but cannot be extracted from the SPRINT report.

3.3.2. Basis for clinical outcomes

The immediate and projected clinical outcomes in the SPRINT trial may be attributed to differences in the decrement in the BP, as well as between-group values at termination of the trial. Table 4**.**

4. Concerns

4.1. Trial-related

4.1.1. Interim analyses and clinical context

Well-executed and planned interim analyses are critical to the credibility of conclusions of a clinical trial. The design of trials usually includes a strategy for early stopping if an interim analysis reveals large differences between the treatment group and controls related to benefit or harm, or no difference – futility [11]. The responsibility for premature termination lies with the Drug Safety and Monitoring Board (DSMB), which oversees statistical data as well as clinical safety [12,13]. Termination based on futility or an excess of adverse events in the intervention group is understandable and appropriate; however, premature termination related to efficacy in the intervention group raises the concern whether the treatment benefit is over-estimated [14–16]. Uncertainty is an unavoidable feature of interim analyses [14], and a trial that aims to make a substantive revision to a national guideline for a common and serious disease demands high credibility.

In SPRINT the stopping procedure was based on planned biannual analyses (March/October). During the trial, the primary outcome exceeded the monitoring boundary in March 2015 (planned). Exact stopping rules were not published before the pretermination decision was made. Despite a lack of evidence of overwhelming efficacy in the IT group, nor imminent danger to the ST group, an urgent and unplanned analysis was performed in August. A planned analysis in October 2015 may have confirmed a trend or identified a "random high." Table 5.

Based on a lower rate of the primary composite outcome in the IT vs the ST group SPRINT was prematurely terminated after a median follow-up of 3.26 years (planned average of 5 years). The outcome was reported in *relative terms*, as a 25% reduction in the primary composite outcome, a 43% reduction in death from CV causes, and a 27% reduction in death from any cause [17,18]. The outcome in *absolute terms* were: a reduction of 1.6% in the primary composite outcome, a reduction of 0.6% in death from CV causes, and a reduction of 1.2% in

Table 4
Average blood pressure at entry (90% on treatment) and at termination of the study [1].

	Intensive therapy (n = 4678)	Standard therapy (n = 4683)
Entry. SBP mm Hg (note 90% on treatment)	140 ± 16	140 ± 15
Average number of medicines – at entry	1.8 ± 1.0	1.8 ± 1.0
Termination. SBP, mm Hg	122	135
Average number of medicines – at termination	2.8 ± ?	1.8 ± ?
Termination. Decrement in SBP in each group, mm Hg	18	5
Termination. Between-group difference in SBP, mm Hg	13	

Abbreviation: SBP: systolic blood pressure, ± : standard deviation,?: not reported.

Table 5
Group sequential boundaries and interim testing [1].

Date	Planned analysis	Z score	Bounds	One-sided nominal alpha for bound	Cumulative stopping probability under null
October 2013	Yes	1.08	± 5.956	< 0.0001	< 0.0001
March 2014	Yes	0.219	± 4.402	< 0.001	< 0.0001
October 2014	Yes	1.405	± 3.681	0.0001	0.0002
March 2015	Yes	3.413	± 3.217	0.0006	0.0014
August 2015	**No**	**3.936**	**± 2.819**	**0.0024**	**0.0053**
(October 2015)	**Yes, but not done**	**–**	**–**	**–**	**–**

Modified from: supplementary appendix, fig. S3. Group Sequential Boundaries and Interim Testing [1]. Bold on this data indicates the SPRINT trial was stopped prematurely.

death from any cause.

However, clinical context was missing. The IT group had a lower relative risk of the primary outcome by 25% (absolute reduction, 5.2 vs 6.8 = −1.6%) while the ST group had an increase in serious adverse events by 88% (absolute increase (4.7 vs 2.5 = +2.2%). In the aggregate, the price for a reduction of the primary outcome by 25% was an increase in serious adverse events by 88% [19].

Stopping rules insist on *equally spaced*, *planned* interim analyses in order to protect against the temptation to terminate at the very first sign of possible efficacy – a random high. In the absence of overt benefit or harm with intensive or imminent harm with standard therapy, a *simple, prudent, and credible strategy would be to avoid premature termination* [11,16,20]. The risk of *premature* termination is a *premature* declaration of superiority, and in this case, questionable net treatment benefit. Looking back, there was no urgency for the interim analysis in August, and this datapoint may have been modified by chance, not justifying the conclusion of secure evidence for a trial that aimed for changing a national guideline.

4.1.2. Generalizability of results

Clinical trials that are destined to be the basis for practice guidelines should be designed in order to be generalizable to the clinic. In the SPRINT trial, individuals younger than 50 years and diabetics were excluded. At entry, 90% of participants were on at least two drugs, and by conventional criteria, likely had moderate hypertension; the remaining 10% were on no medicines. For the same SBP of 130 mmHg, a healthy 40 year old adult is quite different from a 50 year old hypertensive being treated with two antihypertensive drugs. Overall, based on the SPRINT eligibility criteria, the trial population included just about 20% of patients seen in practice [19,21]. When treatment guidelines, proposing a universal target for intervention, namely a SBP > 130 mmHg, is applied over a broad and heterogeneous demography, there is an important and vital requirement for clinical judgement. Further, few doctor's offices have research grade facilities that allow for unattended BP measurements in a quiet environment.

4.1.3. Cardiovascular risk models

Changing (inter)national hypertension guidelines as aimed for by the SPRINT trial relies on cardiovascular risk models that translate trial results to population outcomes. The rationale for the development of complex multifactorial risk models for this aim is that CVD is associated with multiple risk factors. Here, a combination of several seemingly modest risk factors can outweigh the risk from a single highly elevated factor [22]. The strategy for risk factor intervention in national prevention programs relies on the use of contemporary risk prediction models [23,24]. About 363 risk prediction models have been developed for cardiovascular disease in the past decades, the most utilized are the Framingham risk score - 1991, SCORE - 2003, and QRISK- 2007 [23]. The majority reflect demography from earlier eras and usually overestimate the risk of cardiovascular disease; few are externally validated. All risk models use the 10 year risk for CV *events*, with the exception of SCORE, which estimates 10-year risk of CV *mortality*. The strongest predictor of cardiovascular risk in any risk model is age. Pylypchuk and colleagues' using a national database from New Zealand, have improved existing risk prediction for cardiovascular disease by adding relevant predictors that address socioeconomic status, ethnicity, and comorbidities [25]. Contemporary risk models are necessary to reflect demography, to lessen overtreatment of the healthy majority, and to identify vulnerable high-risk subpopulations that might otherwise be undertreated [25]. Most subjects are at low risk of cardiovascular disease, which explains why outdated risk models based on old cohorts overestimate risk.

Age, sex, smoking, lipid status and blood pressure are the key risk factors for cardiovascular disease. *In this scheme, age also captures the element of duration of exposure*. The aim of risk scores is to describe the potential impact of risk factors on future morbidity and mortality in individuals and the justification to intervene earlier with risk factor modification. Changes in the secular trend of CV risk (a decrease), and in the environment, alter the relative contribution of conventional risk factors and suggest new ones. Several new candidates have been proposed: family history of heart disease, sedentary lifestyle, central obesity, social deprivation, and ethnicity (namely, Southeast Asians). In the past, adding new candidates to the primary five risk factors has not resulted in appreciable change in prediction [22,26], but this may change.

A key concern is the problem of communicating future risk to younger individuals with emergent risk factors but a low risk score. In calculating risk, age is a relevant issue at both extremes of age. (It is interesting to note that the American guideline, in contrast to the European one, emphasizes functionality rather than chronological age in managing high BP in older adults.) Younger adults will have a very low estimated CV death risk and older adults will have a much higher estimated risk, even when CV risk factors are low [27]. Marie Therese Cooney and her colleagues explain that with current risk models, even a 40-year-old man who is severely hypertensive, severely hypercholesterolemic, and a smoker will be assigned to a low-risk category [26,27].

Julia Hippisley-Cox and her colleagues at Nottingham University, UK, developed and validated version 2 of the QRISK cardiovascular disease risk algorithm (QRISK2) in order to provide better estimates of cardiovascular risk in patients from different ethnic, and socio-economic groups in England and Wales and to compare its performance with the modified version of Framingham score recommended by the National Institute for Health and Clinical Excellence (NICE). The population of interest covered 531 practices in England and Wales with 2.3 million patients aged 35–74 (over 1.6 million person years) who experienced 140,000 cardiovascular events. They incorporated ethnicity, social deprivation, and other clinical conditions into the QRISK2 algorithm for risk of cardiovascular disease and found that it improved the accuracy of identification of those at high risk in a nationally representative population. At the 20% threshold, QRISK2 was more efficient and equitable tool for treatment decisions for the primary prevention of cardiovascular disease. The validation was performed in a similar population to the population from which the algorithm was derived [28]. The updated QRISK3 risk prediction model (2017) includes additional clinical variables namely, chronic kidney disease, a measure of systolic blood pressure variability (standard deviation of

repeated measures), migraine, corticosteroids, SLE, atypical antipsychotics, severe mental illness, and erectile dysfunction. This version will better identify patients at most risk of heart disease and stroke [29]. Although algorithms makes prediction more accurate, capturing multiple dimensions of the evolution of disease, especially with aging, resists exact formulaic prescriptions. Thierry Christiaens advises that we rethink how to use risk models in clinical practice in order to avoid labeling and overtreatment of healthy older people [30]. We await an improved risk model that can capture the clinical judgement of experienced general practitioners.

Accordingly, based on this, and the prevalence of risk factors that affect nearly half the adult population, leadership in treatment is best assumed by general practitioners and supported by public health. The reasoning is simple – when reduced to basics, the treatment of hypertension, a highly prevalent disease, is properly *preventive medicine* directed to the reduction of complications, namely heart attack and stroke. Here, public health, epidemiology, and experienced front-line physicians are more relevant than academic expertise in the treatment of high-risk individuals [31,32]. The vast majority of deaths in a community come from those at lower levels of risk, simply because they are more numerous compared to high-risk individuals, who develop fewer events in absolute terms [27].

4.2. Clinical consequences

4.2.1. Syncope and falls

The careful reader may rightfully ask why we show concern for falls when the incidence between the groups were small and equal [1]? We show concern because syncopal attacks are a predisposition for falls, and the incidence of syncope was higher in the Intensive treatment group. It is difficult to reconcile observational studies that report an increased risk of falls with aggressive antihypertensive treatment and the SPRINT trial which did not find an excess of falls with lowered BP levels [33]. Few events cause more regret to a physician than an avoidable fall in an elderly patient.

A composite presentation on the incidence of hypotension, syncope and falls in the SPRINT trial is presented in Table 6.

Syncope is defined as a state of loss of consciousness due to cerebral hypoperfusion and is characterized by a rapid onset, short duration, and spontaneous complete recovery. The syndrome involves a loss of awareness, amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration. Comorbidity, especially in older patients, influences the incidence of this event which is usually accompanied by falls. Specifically, polypharmacy involving cardiovascular medications, and psychotropics (neuroleptics and antidepressants) and dopaminergic drugs increases the risk of syncope and falls. Despite the lack of large controlled trials and an overall modest quality of studies, there is strong consensus that reduction or discontinuation of hypotensive drugs and psychotropic drugs clearly outweighs the undesirable effects (e.g. complications) of hypertension. If unwitnessed falls are not due to “slips or trips on steps and curbs”, it is likely that a syncopal event has occurred [34]. The term “injurious fall” is not helpful. Falls are falls, and the same fall on the stairs or on a hard floor as opposed to a carpeted one is more likely to cause serious injury-location matters more.

With the current emphasis on intensive BP control, the potential for overtreatment and treatment-related adverse events is an important consideration. In addition to poor balance, impaired vision, and side-effects of medications, aggressive BP control is associated with substantial risk. Falls often cause severe injuries, decreased mobility, and loss of independence, and is one of the most costly health conditions among older adults. Judy Stevens and Robin Lee at the US Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Atlanta, Georgia, estimated the number of medically treated falls that could be prevented and the direct medical costs involved. Preventing falls can benefit older adults substantially by improving their health, independence, and quality of life [35]. In 2015, in the US, > 28,000 older adults died and 3 million more were treated in emergency departments for nonfatal fall injuries. In 2015, total medical expenditures for falls totaled $50 billion, making falls one of the most costly health conditions among people aged 65 years and older [36–39].

Falling is the most frequent cause of injury in older adults in the United States; approximately one-third of older adults fall each year. Several causes of falls are recognized [40], including an excessive reduction of the BP. However, the causality between the BP and dizziness, syncope, falls, fractures and orthostatic hypotension, is not well defined [41–49]. Lewis Lipsitz and his colleagues state that conflicting data on the relationship between antihypertensive medications and falls in elderly people may lead to inappropriate undertreatment of hypertension in an effort to prevent falls [48]. According to Rose Anne Kenny, at Trinity College Dublin, falls are the leading cause of emergency admissions, loss of functional ability, independence, quality of life, and injury-related death. In the UK, as many as 250,000 falls and > 1000 fractures are recorded each year [50].

In a US study in Medicare beneficiaries, Mary Tinetti and her colleagues at the Yale University School of Medicine, analyzed 4961 hypertensive adults older than 70 years over 3 years [51]. They found that antihypertensive medications were associated with greater risk of serious fall-related injuries, especially in those with prior fall injuries. In this cohort, 446 participants (9%) experienced serious fall injuries, and 837 (17%) died. Serious fall injuries included hip and other major fractures, traumatic brain injuries, and joint dislocations. In older adults with multimorbidities, the potential harms vs benefits is best considered before intensifying antihypertensive treatment [51]. In the elderly, the initiation of antihypertensive therapy has been associated with greater risk of hip fractures during the ensuing 45 days [52]. Since about 90% of individuals in the SPRINT trial were on stable antihypertensive therapy at entry [1], the trial could not have captured fall risk associated with the initiation of therapy. *The effect of serious injuries, such as hip fracture and head injury, on function and mortality is comparable to that of cardiovascular events.* The low risk of fall injuries reported in clinical trials of healthy older adults may not reflect the higher risk in older adults with multimorbidities and could reflect selection bias [51]. Therefore physicians are advised to be cautious and to recognize, that in elderly patients with a BP at or under 150/90 mmHg, competing concerns are the avoidance of immediate harm and a possible gain in life expectancy. This concern was recognized in JNC-8, where a higher BP was advised in patients older than 60 years. Table 1.

The Irish Longitudinal Study on Aging (TILDA) is a large-scale, nationally representative study of 8178 community living individuals aged 50 and above. Donal Sexton and his colleagues at Trinity College Dublin used data from TILDA to compare baseline rates of injurious falls and syncope in community-dwelling older adults with the rates in the standard care group of SPRINT. Before adopting an intensive strategy to lower the SBP in the elderly, it is prudent to determine if individuals meeting inclusion criteria for SPRINT outside the clinical trial context are similar to trial participants, especially with regard to risk for adverse outcomes. In TILDA, participants 75 years of age or older who met inclusion criteria for SPRINT had rates of injurious falls and syncope approximately 5-fold higher than the standard care group in SPRINT [53,54]. Table 7 Given the high baseline rates of falls and syncope, any increase in these rates due to intensive treatment of hypertension could result in harm. What is striking is that the number of injurious falls in older adults in Ireland and the US is far higher than that noted in SPRINT. The discrepancy between the incidence of falls in matched subjects between SPRINT and TILDA remains unresolved [55,56].

In the management of hypertension general practitioners face a dilemma – the pressure to conform: should therapy be intensified in elderly patients who exceed the SPRINT threshold or not [57]? Experts in hypertension, citing clinical trials, state that they have not observed an excess of falls and fall-related injuries in older patients receiving

Table 6
Incidence of hypotension, syncope, and injurious falls[a] in two formats. Modified from [1].

Format 1. Serious adverse events, conditions of interest, and monitored clinical events [1, Table 3]

	Intensive treatment (N = 4678)		Standard treatment (N = 4683)		Hazard ratio	P value
	Subjects	%	Subjects	%		
Serious adverse events	1793	38.3	1736	37.1	1.04	0.25
Conditions of interest						
Hypotension	110	2.4	66	1.4	1.67	0.001
Syncope	107	2.3	80	1.7	1.33	0.05
Injurious fall	105	2.2	110	2.3	0.95	0.71
ER visit/Serious adverse event						
Hypotension	158	3.4	93	2.0	1.70	< 0.001
Syncope	163	3.5	113	2.4	1.44	0.003
Injurious fall	334	7.1	332	7.1	1.00	0.97

Format 2. Serious adverse events and conditions of interest classified as possibly or definitely related to the intervention[b] [1, Supplementary Table S5]

	Intensive treatment (N = 4678)		Standard treatment (N = 4683)		Hazard ratio	P value
	Subjects	%	Subjects	%		
Serious adverse events	220	4.7	118	2.5	1.88	< 0.001
Conditions of interest						
Hypotension	83	1.8	37	0.8	2.52	< 0.001
Syncope	64	1.4	28	0.6	2.15	0.006
Injurious fall	19	0.4	13	0.3	1.99	0.21
ER visit/Serious adverse event						
Hypotension	125	2.7	58	1.2	2.24	< 0.001
Syncope	94	2.0	44	0.9	2.13	0.005
Injurious fall	36	0.8	23	0.5	2.22	0.05

[a] Injurious fall defined as a fall that resulted in evaluation in an emergency department or that resulted in hospitalization. Here, the term "injurious fall" is not helpful. Falls are falls, and the same fall on the stairs or on a hard floor as opposed to a carpeted one is more likely to cause serious injury- location matters more.
[b] The constellation of hypotension, syncope and falls are related to antihypertensive drugs. Therefore excluding a relationship to the intervention is difficult.

Table 7
Comparison of the rates of syncope and injurious falls between SPRINT and TILDA.

	SPRINT – USA	TILDA – IRELAND
Syncope, %	2.4	5.5
Injurious falls, %	5.5	27.3

Abbreviation: TILDA, The Irish Longitudinal Study on Aging.

intensive BP therapy [58,59]. Kaycee Sink and her colleagues analyzed the predictors of serious adverse events involving syncope, hypotension, and falls in the Systolic Blood Pressure Intervention Trial. Participants randomized to intensive SBP control (< 120 mmHg) had a greater risk of hypotension and possibly syncope, but not falls. The greater risk did not vary according to age [60].

However observational studies suggest caution against overtreatment due to the risk of falls. With regard to falls, it should be noted that clinical trial data is limited to the selection of participants whereas observational studies reflect reality [61,62]. In older patients, falls can be conceptualized as a sentinel expression of the failure of a complex system and explains why even multifactorial falls prevention programs have not succeeded. Accordingly, in the frail elderly, any small stressor will precipitate falls in these individuals. [63] This may explain why the initiation and intensification of BP medicines is associated with an increased risk of serious fall injuries among older adults in the short term, and in the absence of orthostatic hypotension, infrequent during long-term stable therapy and in clinical trials [64,65]. Falls can result in serious injuries, such as skull, spine, hip, shoulder and forearm fractures, and *the effect on morbidity and mortality is comparable to that of cardiovascular events.* The potential harms vs benefits of intensifying therapy, especially in older adults with multiple comorbidities should be carefully evaluated [66,67].

Peter Sever at Imperial College, London, offers a possible explanation for the paucity of falls in SPRINT: One of the main concerns about the methodology used in SPRINT was that the BP was measured in an environment in which there was no doctor or nurse present. This, unattended and more basal blood pressure, has been shown to be equivalent to a routine clinic BP of at least 10 − 15 mm systolic higher − thus reflecting a usual clinic BP < 140 mmHg, rather than a SBP of < 120 mmHg [68]. In SPRINT, BP was measured by an automatic device in an unattended environment [69]. Unattended automatic readings underestimate the standard sphygmomanometer reading in a busy office setting by up to 15 mmHg [70], although not all studies show a difference [71]. Thus, in keeping with Peter Sever, the intensive treatment target of < 120 mmHg tested in SPRINT may correspond to a somewhat higher usual office blood pressure.

In the SPRINT trial, the paucity of expected falls in the intensive treatment group may be explained by noting that 90% of the participants were on treatment at entry, and that falls are usually precipitated at initiation or intensification of treatment [52]. Further, as in SPRINT, BPs were recorded in an *unattended* environment. It is quite likely that the incidence of falls will be a concern if the lower SPRINT targets are implemented in *attended* environments. Older patients should be warned of the risk of falling when beginning or titrating existing antihypertensive medications and to take precautions to minimize risk of orthostatic loss of balance.

4.2.2. Multimorbidity and polypharmacy

Multimorbidity, defined as the co-existence of two or more chronic conditions each lasting > 1 year, is a relevant and clinically important topic, particularly in the management of older adults with cardiovascular disease. Multimorbidity occurs in adults of all ages, but the number and complexity of comorbid conditions commonly increase with advancing age such that cardiovascular disease in older adults typically occurs in a context of multimorbidity. Current clinical practice

Box 1
NICE: framework for multimorbidity [73].

- Guidelines on single health conditions are useful but may not be applicable in the clinic
- Aggressive management of risk factors for future disease is a major treatment burden and can be inappropriate
- Assess whether patients may benefit from an approach to care that takes account of their multimorbidity
- Consider all conditions and treatments simultaneously
- Provide easier access to simple data on the absolute benefit of commonly prescribed treatments

Source: NICE, National Institute for Health and Care Excellence, UK.

and research mainly target single disease-specific care that does not embrace the complexities imposed by concurrent conditions [72]. Clinical guidelines (like the ACC/AHA 2017 and ESH/ESC 2018) are based on randomized clinical trials (like SPRINT) that do not specifically address multimorbidity as a possible effect modifier or risk for (serious) adverse effects. Clinical trials enroll a population with a specific disorder for which the benefits of a specific intervention are assessed. Thus, subjects with multimorbidity usually are not evaluated as subgroup. Most importantly, the SPRINT report did not consider comorbidities, concomitant medications, and possible drug interactions relative to adverse events [1]. Comorbidities lead to polypharmacy and this can be a direct cause of adverse events independent of the level of the blood pressure. For people who are older, and with comorbidities, guidelines on individual diseases are usually uninformative or their uncritical application may cause serious harm. Primary care physicians deal with multimorbidity on a daily basis and authors of guidelines have much to learn from them. Crafting of clinical practice guidelines is a two-way street, and the NICE guideline on multimorbidity is a *nice* example [73,74] Box 1.

Multimorbidity is complicated by polypharmacy – the requirement for 5 or more medications to address comorbid conditions. In practice, polypharmacy is complicated by nonadherence, and drug interactions that can result in serious adverse events. Accordingly, trials directed to the generation of guidelines for index chronic diseases should report on comorbid conditions and concomitant medications. In Sweden, almost half of the individuals aged ≥75 years are exposed to polypharmacy. The most frequently used drugs were cardiovascular drugs, analgesics, and psychotropics [75,76]. The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older Adults is a list of PIMs best avoided in older adults in general and in those with certain diseases, prescribed at reduced dosage or with caution or carefully monitored. Beers Criteria PIMs are associated with poor health outcomes, including confusion, falls, and death [77]. The PIMs list is amenable to polypharmacy reduction strategies [78]. The 2013 ACC/AHA guideline on cardiovascular risk lists antihypertensives, psychotropics (neuroleptics and antidepressants) and dopaminergic drugs as agents that increase the risk of falls [79,80]. However, with the exception of excluding diabetes, the 2017 ACC/AHA guideline in hypertension did not emphasize the relevance of multimorbidity and polypharmacy [2]. This omission makes the interpretation, causality and prevention of serious adverse events difficult. Daniel Forman and his colleagues outline major research gaps and unmet needs of patients with multimorbidities [72]. Gregory Ouellet and his colleagues outline a framework that considers patients' own priorities to achieve optimal treatment outcomes. Here, the objective is to maximize benefits that matter to the patient while minimizing predictable harms.

4.2.3. Diagnostic creep and overtreatment

Diagnostic creep refers to novel interventions that lower the threshold for the detection of disease. A revised definition of disease (lowering the diagnostic threshold) may allow for either earlier detection and treatment of disease or mislabel healthy individuals and increase the size of the disease population. SPRINT used an automatic device in an unattended environment for the measurement of the blood pressure (Omron HEM 907 oscillometric monitor). With this device unattended (undisturbed) recordings display lower values than standard procedures. The BP target in the SPRINT trial was an SBP of 120 mmHg or lower, rather than 140 mmHg, and the net effect of using the new criteria for intervention, when using conventional BP methodology, is “diagnostic creep.” The 2017 guideline has just increased the prevalence of hypertension in the US from 72 to 103 million, or from 32 to 46% of the adult population.

Diagnostic creep rationalizes overtreatment, allows for adverse events in a previously healthy population, and can increase healthcare spending [81–86]. Kevin Riggs and Peter Ubel, at Johns Hopkins University, Baltimore, and Duke University, Durham, make a persuasive plea for professional societies to limit diagnostic creep [87]. In the case of SPRINT, 11 professional organizations endorsed the 2017 ACA/AHA guideline; the only exceptions being the American Association of Family Physicians and the American College of Physicians [88,89].

4.2.4. Labeling

In, “*Now we are sick; labeling and hypertension*” Thomas Pickering draws attention to the law of unintended consequences in the context of screening programs [90]. Most newly labeled hypertensives experience deterioration in the quality of life that is attributable to an undue preoccupation with sickness, depression, decline in energy, general activity, and sexual activity, and an increase in irritability [91]. This implies that “disease” be diagnosed and treated only if there is valid evidence of benefit exceeding harm. In 1978, Haynes and his colleagues noted that in industrial settings that the labeling of subjects as hypertensive resulted in increased absenteeism [92]. After screening they found that absenteeism rose by 80% in the labeled group exceeding the 9% rise in the general employee population. Further, absenteeism rose among those previously unaware of their condition, regardless of whether antihypertensive therapy was started. Timothy Wilt and his colleagues ask: are the harms, costs, and complexity of care associated with a lowered BP target justified by the presumed benefits of labeling nearly half the U.S. population and subjecting them to treatment [93]?

5. European society of hypertension/EUROPEAN society of cardiology guideline – ESH/esc 2018

At 98 pages and 629 references, the ESC/ESH guideline of 2018 steers a narrow course between the ACC/AHA 2017, JNC-7/8, and the ESH 2013 guidelines [3]. The ESC/ESH 2018 target is a BP of 130/80 mmHg (SBP of 140 for those with diabetes or chronic kidney disease). In contrast to the ACC/ASH guideline (and the SPRINT data), B*P* values below 120/80 mmHg are discouraged for reasons of increased risk, and clinical judgement, especially in the elderly is encouraged. The European guideline is less aggressive, especially in the elderly [94]. Table 8.

Also, the ESH/ESC proposal makes a timely and appropriate argument in favor of initial combination therapy using a single pill. Thomas MacDonald and his colleagues [95] in the PATHWAY trial have shown that initial combination therapy achieved target BPs in twice as many participants as initial monotherapy, without any difference in withdrawals due to adverse events. It should be recalled that both the ACC/

Table 8
Key differences between the American and European guideline in hypertension [94].

Guideline	ACC/AHA-2017	ESC/ESH-2018
Threshold for intervention	*All adults:* 140/90 mmHg *CVD/high ASCVD risk score:* ≥130/80 mmHg.	< *80 years:* SBP 140 mmHg or DBP ≥ 90 mmHg. > *80 years:* SBP 160 mmHg or DBP ≥ 90 mmHg.
Treatment target	*All adults:* < 130/80 mmHg	< *18–65 years:* SBP 130 mmHg or lower. Not < 120 mmHg > *65 years:* Less aggressive

AHA 2017 and ESH/ESC 2018 guidelines were prompted by the SPRINT trial which evaluated comparative clinical outcomes between SBP targets of 140 and 120 mmHg or lower, but not 130 mmHg. In any event, overdiagnosis/diagnostic creep remains a key consideration and the socio-economic aspects of lowering a disease intervention threshold in a highly prevalent disorder need to be evaluated. In the US, labeling has the potential to increase the already high premiums for health and life insurance.

6. Sri Lanka triumph trial – 2018

Ruth Webster, at The George Institute for Global Health, University of New South Wales, Sydney, Australia and her colleagues in the TRIUMPH study group conducted an open randomized trial in 700 patients with hypertension requiring escalation therapy, comparing triple therapy with usual therapy [96]. Table 9 Diabetes accounted for 29% of patients. Entry BP was > 140/90 mmHg (> 130/80 mmHg in diabetes or chronic kidney disease). The components of the single formulation were telmisartan 20 mg, amlodipine 2.5 mg, and chlorthalidone 12.5 mg. The primary outcome was the proportion reaching target BP of < 140/90 mmHg or < 130/80 mmHg in diabetics or chronic kidney disease. At 6 months, the response with triple therapy was 70% vs 55% in the group on usual therapy. Adverse events and trial withdrawals were similar between groups. This trial supports the use of low-dose triple therapy in a single pill in patients with mild to moderate hypertension inclusive of relevant comorbidities, namely, diabetes and chronic kidney disease [97].

7. The Oxford/Cambridge primary care study in hypertension-2018

James Sheppard and his colleagues at the primary care centers at Oxford and Cambridge reported on a longitudinal cohort study in mild uncomplicated hypertension(untreated blood pressure of 140/90–159/99 mmHg) [98]. The study compared 19,143 treated patients, aged between 18 and 74, against a similar group of 19,143 untreated patients (age, 55 ± 12, women, 55%, 10,000 white). During a median follow-up period of 5.8 years, no association was found between antihypertensive treatment and all-cause mortality (hazard ratio, 1.02; 95%CI, 0.88–1.17) or between antihypertensive treatment and cardiovascular morbidity (hazard ratio, 1.09; 95%CI, 0.95–1.25). Treatment was associated with an increased risk of adverse events, including hypotension, number needed to harm at 10 years, syncope, electrolyte abnormalities, and acute kidney injury. This study demonstrated that therapeutic intervention in low risk mild hypertension is not associated with benefit. Caution should be exercised in generalizing findings from trials conducted in high-risk patients to those at lower risk [99,100].

8. Umeå University meta-analysis-2018

Mattias Brunström and Bo Carlberg at Umeå University, Sweden conducted a meta-analysis of 16 randomized controlled trials (66,816 participants) with at least 1000 patient years of follow-up, comparing antihypertensive treatment versus placebo, or different blood pressure goals against each other [101]. Mean baseline SBP was 138 mmHg, and mean difference between treatment arms was 5.5 mmHg. The purpose was to estimate the effect of antihypertensive treatment in trials with baseline normotension and low levels of previous cardiovascular disease and to test if the results from SPRINT are compatible with those from other trials. Antihypertensive treatment was associated with a neutral effect on all-cause mortality [relative risk 0.98, 95% confidence interval (CI) 0.92–1.05] and major cardiovascular events (0.97, 0.91–1.03). They concluded that the results from SPRINT differs from other trials with baseline SBP < 140 mmHg and low levels of previous cardiovascular disease. Overall, blood pressure-lowering treatment does not reduce mortality or combined major cardiovascular events in this setting. The totality of evidence does not support general application of SPRINT blood pressure targets [101].

9. Global considerations – health care policy

The worldwide prevalence of hypertension in adults has now crossed 1 billion, and is increasing in low- and middle-income countries [4], and the need for novel, simple, and workable approaches is evident. Katy Bell and her colleagues at the School of Public Health, University of Sydney, and the Centre for Research in Evidence Based Practice, Bond University, Gold Coast, Australia) analyzed the incremental benefits and harms of the 2017 ACC/AHA High Blood Pressure Guideline [102]. Our analysis is aligned with their assessment.

Universal application of the new guidelines do not appear to have major advantages over JNC 7/8 for the vast majority of hypertensives. JNC-8 recognizes that a higher target (150/90 mmHg) may be appropriate for older adults with relevant comorbidities, and could therefore minimize the consequences of polypharmacy. Jordana Cohen and Raymond Townsend at the University of Pennsylvania, describe the logistical problems in transitioning between JNC-7 and the new guideline [103]. Combination therapy as advised by ESH/ESC 2018 appears appropriate and pragmatic, as a public health initiative, in

Table 9
The Sri Lanka TRIUMPH trial. Percent achieving the primary outcome and reduction in blood pressure [96].

	Triple combination pill (n = 349)	Usual therapy (n = 350)
Achieving primary outcome	231/318 = 69.5%	132/329 = 55.3%
Blood pressure at randomization:		
Systolic, mm Hg (SD)	154.2 (11.3)	154.2 (11.6)
Diastolic, mm Hg (SD)	89.5 (9.7)	90.0 (9.7)
Blood pressure decrement:		
Systolic, mm Hg (95% CI)	−29.1 (−31 to −27)	−20.3 (−23 to −18)
Diastolic, mm Hg (95% CI)	−13.9 (−15 to −12)	−9.5 (−11 to −8)

Abbreviations: SD, standard deviation, CI, confidence interval.

Table 10
Europe: treated, controlled and uncontrolled blood pressure by country, The EURIKA study, 2011. Modified from [104].

Country	Access to therapy	Controlled BP (%)	Uncontrolled BP (%)
Austria	Universal	36	64
Belgium	Universal	44	56
France	Universal	46	54
Germany	Universal	36	64
Greece	Universal	48	52
Norway	Universal	35	65
Spain	Universal	41	59
Sweden	Universal	34	66
Switzerland	Universal	37	63
Turkey	Universal	32	68
UK	Universal	43	57

Note: Controlled hypertension defined as a SBP < 140 mmHg and a DBP < 90 mmHg.

addressing hypertension not only in low- and middle-income countries, but also world-wide. A global mindset is appropriate because even in Europe, where the availability of treatment is close to universal, the prevalence of uncontrolled hypertension (BP > 140/90 mmHg) is striking. [104,105] Table 10.

In the context of population health and health policy, Benjamin Chin-Yee and his colleagues explain why developments in clinical medicine have important implications for population health, health disparities, the medicalization of prevention, and the setting of societal priorities for resource allocation [4]. In view of these concerns, reports from Canada, UK, Sweden, France, Germany, Spain, China, India, Australia, and particularly, Japan, indicate serious consideration on these points and the adoption of a wait and see attitude before revising national policies on hypertension [106–120]. Factors being considered beyond the uncertainty of incremental benefit include logistics, costs, and the consequences of labeling. To date, few would agree that the 2017 ACC/AHA and the 2018 ESC/ESH guidelines have had substantial influence within and beyond their regions of origin [93].

In the US, the transition to ACC/AHA 2017 will be neither simple nor easy; implementation will require the adoption of a new model of health care, including team-based care, telehealth, a shift towards self-management, better approaches to patient adherence, and the use of home blood pressure monitoring [121]. Besides questionable benefit, lower treatment thresholds will unquestionably lead to incremental costs and increased risk of adverse events [109]. In this regard, the 261 page SPRINT protocol and a 481 page guideline with 106 recommendations is intimidating and may be both *too much, and not enough of a good thing* [103]. Josep Redon and his colleagues at the University of Valencia, Spain, ask the key question: *why with the surfeit of safe, effective, and affordable drugs is hypertension not 100% controlled worldwide today* [122]?

10. Conclusion – health care policy

The overall objective of SPRINT was to evaluate the clinical outcome of lowering the SBP from 140 to 120 mmHg or lower. This attempt was confounded by using a novel method – unattended BP measurements. The latter has the potential to record lower BP recordings to a variable extent, and accordingly preclude comparisons with earlier trials and guidelines. Revisions of major clinical practice guidelines, especially for a highly prevalent disease, need to be simple, credible, realistic, and persuasive to patients, front-line physicians, and national healthcare organizations; logistics and costs aside individual and societal advantage should be explicit. The net effect of lowering thresholds is a huge increase in labeled prevalence, and does not appear to deliver an individual or population benefit.

Whenever thresholds for intervention in disease are lowered, the primary question for investigators is, *will the expected benefit outweigh immediate harm, and the serious consequences of widespread labeling*? In the SPRINT report, the emphasis has been on future benefit, but the analysis and communication of adverse events is insufficient. These conclusion are based on a meticulous analysis of all published data on the SPRINT trial, however it still has some limitations. We were not able to study original data, though the researchers were asked for access to the data, specifically related to the inclusion of a third of the subjects with a baseline systolic blood pressure below the lower limit of the inclusion criterion (130 mmHg). Another limitation is that we did not have access to the decision making process to start preterm interim analysis, nor the decision to stop the trial after this unplanned interim analysis.

All things considered, the results of the SPRINT trial are not persuasive enough to support the 2017 ACC/AHA and the 2018 ESC/ESH guidelines. Especially in the absence of an assessment of the clinical, labeling, and socio-economic impact. Accordingly, in the absence of trial data comparing the safety and efficacy of SBP targets of 140 vs 130 mmHg, it may be reasonable to pause, remain with JNC-7/8, and the 2013 ESH/ESC guidelines, and allow for professional judgement in the management of mild hypertension, and in the elderly. Time will tell whether the new hypertension guidelines will be adopted, however it is invalid to expect great benefit for the older population [123]. In the interim, front-line physicians are circumspect, and a “wait and see” policy is both pragmatic and prudent. Therapeutic enthusiasm is in order and may be best directed to the immediate problem of untreated hypertension worldwide.

Competing interests

We declare no competing interests.

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