Lessons learned from Systolic Blood Pressure Intervention Trial

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Purpose of review
The optimal blood pressure (BP) goal during treatment of hypertension has been controversial. In this report, recent articles that elaborate on this issue are reviewed.

Recent findings
Results from the Systolic Blood Pressure Intervention Trial (SPRINT) have suggested substantial benefits from more intensive BP lowering than is recommended in current US BP management guidelines.

Summary
Increasing evidence suggests that intensive BP lowering provides a cost-effective means to improve health in many adults with high BP. SPRINT provides the most convincing confirmation, but experience in other trials, alone and in pooled analyses augments and broadens the evidence base to patient groups who were not included in SPRINT. Implementation trials to document feasibility and effectiveness of SPRINT-like interventions in routine practice, including in resource-constrained settings, are warranted.

Keywords
clinical trials, high blood pressure, hypertension, prevention

INTRODUCTION
Results from the Systolic Blood Pressure Intervention Trial (SPRINT) have revitalized support for the ‘lower is better’ approach in management of high blood pressure (BP).

RISK AND PREVALENCE OF HIGH BLOOD PRESSURE
Observational studies consistently identify a strong, positive and continuous relationship between level of BP and risk of cardiovascular disease (CVD), with no suggestion of a threshold for risk [1]. In a 2012 study conducted by the Global Burden of Disease Study Group, high BP accounted for more deaths than the next two most important risk factors (tobacco smoking and acute respiratory infections) combined [2]. In the most recent worldwide survey [3\textsuperscript{**}], 31.1\% of all adults (1.39 billion) had hypertension (SBP ≥140 mmHg, or DBP ≥90 mmHg or use of BP-lowering medication). This is substantially higher than the estimate from 10 years earlier [4], due largely to an increased prevalence in highly populated low-income and middle-income countries.

NONPHARMACOLOGICAL AND PHARMACOLOGICAL MANAGEMENT OF HIGH BLOOD PRESSURE
Several nonpharmacological interventions are effective for prevention and management of hypertension [5]. Last year, Hypertension Canada added increased dietary intake of potassium as one of their nonpharmacological recommendations for lowering of BP [6\textsuperscript{*}]. Low-dose BP-lowering drug therapy is also effective in prevention of hypertension [7,8], with the recent Brazilian PREVER-Prevention trial documenting a beneficial effect of such treatment on left ventricular mass [9\textsuperscript{**}]. Antihypertensive drug therapy is not only effective in lowering BP but has...
been repeatedly shown to reduce the risk of CVD [10–12].

**SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL MAIN RESULTS**

However, the optimal target for BP during treatment of hypertension has been uncertain. The SPRINT compared the value of intensive treatment (Intensive) with a SBP goal of less than 120 mmHg with standard treatment (Standard) to a SBP goal of less than 140 mmHg in 9361 adults aged at least 50 years who had a baseline SBP between 130 and 180 mmHg and were at increased risk for CVD [13**]. The trial was stopped early, for benefit, after a median follow-up of only 3.26 years. During follow-up, average SBP was 121.5 mmHg in the Intensive group and 134.6 mmHg in the Standard group. The SPRINT primary outcome (a CVD composite) and all-cause mortality were 25 and 27% less common, respectively, in the Intensive group. The overall pattern for benefit was noted in six groups of special interest, defined on the basis of age (≥75 versus <75 years), sex, race, presence or absence of CVD, presence or absence of CKD and starting level of SBP. There was no overall difference in the rate of serious adverse events in the two treatment arms, albeit such events were more common in the Intensive group among those with hypotension, syncope, electrolyte abnormalities and those with acute kidney injury or acute renal failure.

**INTERPRETATION OF THE SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL MAIN RESULTS**

How should the SPRINT findings be interpreted? It is generally accepted that SPRINT was a carefully conducted study that provided convincing evidence of CVD and all-cause mortality benefit in the Intensive group, with only modest evidence of adverse consequences due to the treatment. However, there are caveats in the generalization of the SPRINT findings. First, the SPRINT hypothesis was tested on the basis of group experience. The average achieved SBP in the Intensive group was 121.5 mmHg [13**]. Assuming a close to normal BP distribution, this would correspond to only about half of the individuals in the Intensive group achieving an SBP less than 120 mmHg. In contrast to the group goal used in SPRINT, BP performance indicators assess the percentage of individuals whose BP is below a designated cut-point (usually <140 mmHg [14**]. In a group with an average SBP of 121.5 mmHg, one would expect a relatively high percentage of individuals to have an SBP less than 140 mmHg. Second, the landmark BP-lowering trials that provide a scientific underpinning for treatment of hypertension have all been efficacy rather than effectiveness trials, testing therapy in selected high-risk groups and frequently employing methods that are different to those employed in many clinical practices [15]. As in most antihypertensive drug treatment trials, the SPRINT cohort was relatively old (average age of 68 years) and at high risk for CVD (average 10-year Framingham CVD risk of 20.1%). This differs from the general population but approximates the patient profile seen in clinical practice [16]. The SPRINT cohort did not include adults with diabetes mellitus or stroke, but a sizable percentage had CKD (28.3%) and were aged at least 75 years. In addition to enrollment considerations, landmark trials, including SPRINT, have tended to be more adherent to recommendations for BP measurement than is typical in clinical practice. For instance, in the Medical Research Council Trial of Treatment of Mild Hypertension, systematic measurement errors were minimized by requiring 10 min of quiet rest prior to BP readings, use of a proper cuff size, patient positioning, choice of random-zero sphygmomanometers and employment of a slow deflation rate [17]. In addition, random errors were minimized by using the average of four readings, two at each of two successive visits, to estimate BP. In SPRINT, a 5-min period of quiet rest, proper patient positioning, correct cuff size and use of an automated device (Omron model 907) were employed to minimize systematic error during BP measurement, and averaging of the readings was employed to minimize random error. Use of a SPRINT-like BP measurement method is highly desirable when implementing the trial’s intensive BP-lowering strategy in clinical settings [18].
SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL AND EVIDENCE-BASED MEDICINE

Despite the challenges of generalizing experience from landmark trials, these studies provide the best scientific underpinning for clinical decision-making. Evidence-based medicine has been classically described as the ‘conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients’ [19]. Best evidence, its clinical applicability and patient preference are typically considered to be the three core elements of evidence-based medicine. Clinicians in consultation with patients are best positioned to determine applicability of the SPRINT experience in deciding on intensity of treatment and frequency of follow-up.

CONSISTENCY OF THE SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL RESULTS

Some have claimed that SPRINT is an outlier trial [20]. The findings in SPRINT, however, are consistent with experience in other studies. In 19 other randomized controlled trials, participants have been randomly assigned to different BP treatment goals [21**]. Although the individual trials have had insufficient statistical power to determine whether more is superior to less-intensive therapy, there has been a fairly consistent pattern for greater benefit in more intensively treated groups. The overall pooled estimates for relative risk (RR) [95% confidence interval (CI); P value] were 0.86 (0.78–0.96; P = 0.005), 0.87 (0.76–1.00; P = 0.042) and 0.78 (0.68–0.90; P = 0.001) for CVD, myocardial infarction and stroke, respectively. Meta-analyses have identified similar benefits using the larger number of trials that allow for a comparison of BP differences between treatment arms (antihypertensive drug versus placebo, more versus less-intensive treatment and lower versus higher BP target). A recent meta-regression analysis, based on 123 trials, identified decrements in RR proportional to the magnitude of the reduction in achieved BP [22*]. For a 10 mmHg lower SBP, the RR (95% CI) was 0.80 (0.77–0.83), 0.83 (0.78–0.88) and 0.73 (0.68–0.77) for CVD, coronary heart disease and stroke, respectively. Further, the observed reduction in CVD risk in BP-lowering trials is quite consistent with cohort study experience [23]. For a 7 mmHg difference in SBP, observational studies predict a stroke incidence disparity of approximately 20% [1]. This is almost identical to what has been observed in randomized controlled trials in which participants with hypertension were assigned to different BP targets [21**] or had a difference in BP between the treatment arms [22*] and even in secondary-prevention BP-lowering trials in participants without hypertension [24].

SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL AND DIABETES MELLITUS

SPRINT did not include patients with diabetes, but meta-analyses of other trials suggest that the benefits of more intensive BP management apply to patients with diabetes, and experience in the Action to Control Cardiovascular Risk in Diabetes is consistent with SPRINT [25–27]. Based on SPRINT and other trials, it is likely that the benefits of intensive therapy also apply to patients with CKD and probably to adults with other comorbidities leading to a high risk of CVD [13**,26].

INTENSIVE BLOOD PRESSURE LOWERING IN SENIORS

During the past 12 months, numerous SPRINT-related articles have been published. Among the most important was a detailed report of experience in the 2636 SPRINT participants aged at least 75 years (mean = 79.9 years) at baseline [28**]. This group would be expected to be particularly vulnerable to risks during intensive BP lowering. Similar to the overall trial experience, intensive compared with standard therapy resulted in a significantly lower hazard ratio (95% CI) for both the CVD composite primary outcome (0.66, 0.51–0.85) and all-cause mortality (0.67, 0.49–0.91). In subgroup analysis, those classified as more frail at baseline or having a slower gait had especially high event rates but seemed to derive substantial benefit from more intensive treatment, with no evidence of treatment effect modification. Serious adverse events were common but not different in the Intensive (48.4%) and Standard (48.3%) groups. The only participants with significantly more serious adverse events during intensive therapy were those with hyponatremia or frailty.

Experience in the Hypertension in the Very Elderly Trial (HYVET) is consistent with SPRINT [29]. HYVET randomized 3845 participants aged at least 80 years (mean age = 83.6 years) with hypertension (SBP at baseline was 173 mmHg, with almost two-thirds being treated for their hypertension) to active treatment or placebo, supplemented as needed by active therapy or matching placebo. The target SBP/DBP was less than 150/80 mmHg. After 2 years, SBP in the active treatment group was 143.5 mmHg, 15 mmHg less than in the placebo group. The trial was stopped early due to a significant 21% reduction in total mortality (P = 0.019) and a close to significant
30% reduction in the primary outcome of all strokes ($P = 0.055$) in the active treatment group compared with placebo [29]. Like SPRINT, the biggest relative benefit was a 64% reduction in incidence of heart failure ($P = 0.0001$). In HYVET, serious adverse events were less common ($P = 0.001$) in the active treatment group (358 events) compared with placebo (448 events).

**SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL COST-EFFECTIVENESS**

Based on Markov modeling, it was estimated that the SPRINT Intensive treatment cost $23,777 per quality-adjusted life-years gained [30\textsuperscript{*}]. The authors’ conclusion was that ‘Intensive blood pressure management is cost-effective at typical thresholds for value in healthcare and remains so even with substantially higher adverse event rates’.

**SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL, CLINICAL PRACTICE GUIDELINES AND UNDERLYING CARDIOVASCULAR DISEASE RISK**

Two national BP guidelines were updated during 2016 [6\textsuperscript{*},31,32\textsuperscript{*}]. In May, Hypertension Canada recommended consideration of intensive treatment to an SBP target 120 mmHg or less in selected patients aged more than 50 years with an SBP more than 130 mmHg [6\textsuperscript{*}]. A similar recommendation was included in the July 2016 update of the National Heart Foundation of Australia BP guideline [31,32\textsuperscript{*}]. Both considered the evidence for such a recommendation to be persuasive but had caveats regarding patient selection, BP measurement and monitoring. In an editorial commenting on the updated Australian guidelines, the importance of underlying CVD risk for BP treatment decisions was emphasized [33\textsuperscript{*}]. This has been echoed in other recent publications that have suggested consideration of more intensive BP lowering in adults who would not meet the SPRINT inclusion and exclusion criteria but have an SBP between 120 and 139 mmHg and are at increased risk for CVD [18,34,35\textsuperscript{*}]. Based on NHANES, extension of BP treatment to US adults with an SBP 120–139 mmHg and a high risk for CVD (≥15% 10-year risk of CVD, using pooled cohort equations [36]) would reclassify 5.8 million as being eligible for antihypertensive drug therapy and identify an additional 8.5 million who are already under treatment but would be eligible for more intensive therapy [34\textsuperscript{*}]. Conduct of additional SPRINT-like trials could replicate the original findings, determine the value of the SPRINT intensive intervention in high-risk adults with hypertension who were not included in the original trial, test the intervention in regions where nonischemic CVD predominates and ascertain the practicality of implementing SPRINT-like interventions in routine practice, including in resource-constrained settings [37\textsuperscript{*}].

It has long been recognized that traditional risk prediction tools are very age-dependent and not generally relevant in younger adults, even in those with a substantial burden of biologic risk factors [38\textsuperscript{*}]. Based on lifetime risk considerations, it has been suggested that the SPRINT target of less than 120 mmHg (coupled with a DBP target of <80 mmHg) should be the BP goal for all adults aged at least 18 years [39\textsuperscript{*}].

**SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL AND THE HEART OUTCOMES PREVENTION EVALUATION-3 BLOOD PRESSURE TRIAL**

During 2016, results from the Heart Outcomes Prevention Evaluation (HOPE)-3 trial were published [40,41\textsuperscript{*},42\textsuperscript{*}]. HOPE-3 employed a factorial design and almost 6 years of follow-up to test the efficacy of lipid lowering and BP reduction, alone and in combination, compared with placebo in a cohort of 12,705 adults at intermediate risk for CVD. Lipid lowering, alone and in combination with BP lowering, resulted in a significant reduction in CVD events [40,42\textsuperscript{*}]. In contrast, BP reduction on its own had no significant effect on either of the two coprimary CVD composite outcomes [41\textsuperscript{*}]. The most plausible explanation for the difference in the HOPE-3 BP and SPRINT results is that the two trials tested fundamentally different interventions in quite distinct study groups. SPRINT examined the effect of an intensive stepped care BP reduction strategy in adults with hypertension who were at high risk for CVD, whereas HOPE-3 investigated the effect of a modest reduction in BP using a fixed-dose drug regimen in younger adults who were predominantly normotensive and had a much lower risk for CVD [43\textsuperscript{*}]. The SPRINT experience is more relevant for management of hypertension in clinical settings [43\textsuperscript{*}]. However, the overall HOPE-3 BP trial results are consistent with the ‘lower is better’ experience in other BP-lowering trials [23\textsuperscript{*}], and in subgroup analysis, a nominally significant reduction in CVD was noted in the subgroup with the highest tertile of baseline BP and CVD risk [41\textsuperscript{*}].

**CONCLUSION**

SPRINT and other BP-lowering trials provide strong support for the ‘lower is better’ philosophy during treatment of hypertension, especially in those at high risk for CVD. However, the specific target for
BP during treatment in clinical practice is best determined by practitioners in consultation with their patients. If a patient's BP is to be treated intensively, care must be exercised to ensure that BP is measured according to guideline recommendations, and careful monitoring is essential during dose titration and during subsequent follow-up. The SPRINT results have already led to guideline recommendations for more intensive management of high BP in Canada and Australia. Publication of a new US BP management guideline is expected in 2017.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
■ of outstanding interest

7. Hypertension Canada’s annual update of its clinical practice guideline, including four new recommendations and revisions to two preceding recommendations.
Hypertension


   Interesting report of an analysis, based on the SPRINT experience, which suggested that the benefits associated with an intensive BP reduction strategy are very cost-effective.


   Summary of an update to the Australian BP practice guideline, with six key changes since the previous BP guideline in 2010.


   Provides results of the Heart Outcomes Prevention Evaluation-3 (HOPE-3) BP treatment trial.


   Provides an explanation for the differences in treatment effect noted in SPRINT and the HOPE-3 BP-lowering trial.