

## Recommendations for Intensive Blood Pressure Lowering in High-Risk Patients, the Canadian Viewpoint

Raj Padwal, Doreen M. Rabi, Ernesto L. Schiffrin

Recent publication of the Systolic Blood Pressure Intervention Trial (SPRINT) in close temporal proximity to 2 meta-analyses affirming the benefits of intensive blood pressure (BP) control collectively signify the need to reevaluate BP targets in hypertensive patients at high risk for cardiovascular events.<sup>1-3</sup> This commentary discusses how this recent evidence has affected Canadian clinical practice guidelines, describes the process used to update these guidelines in light of this evidence, and outlines the major issues deliberated by Canadian Hypertension Education Program (CHEP) Task Force members during this process.

### Evidence for Intensive BP Reduction in High-Risk Patients

In the SPRINT trial, which studied 9361 subjects aged  $\geq 50$  years at increased risk for cardiovascular events, intensive systolic BP control (to  $< 120$  mmHg) reduced the incidence of cardiovascular events and mortality by 25% (5.2% versus 6.8%; hazard ratio 0.75; 95% confidence interval 0.64–0.89) compared with standard systolic BP control (135–139 mmHg).<sup>1</sup> Furthermore, a meta-analysis of 55 randomized controlled trials (265 576 subjects) demonstrated that the reduction in cardiovascular events realized from a 10-mmHg systolic BP reduction is similar across different quintiles of baseline systolic BP ( $< 130$ , 130–139, 140–149, 150–159,  $\geq 160$  mmHg).<sup>2</sup> In a second meta-analysis of 14 treat-to-target trials (44 989 subjects), a 7-mmHg mean systolic BP reduction (from 140 to 133 mmHg) led to a 14% (95% confidence interval 0.78–0.96) reduction in major cardiovascular events.<sup>3</sup> In aggregate, these data support the implementation of intensive BP control in high-risk patients.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Medicine, University of Alberta, Edmonton, AB, Canada (R.P.); Mazankowski Heart Institute, Edmonton, AB, Canada (R.P.); Departments of Medicine, Community Health and Cardiac Sciences, University of Calgary, Calgary, AB (D.M.R.); Department of Medicine and Lady Davis Institute for Medical Research, Jewish General Hospital, McGill University, Montreal, QC, Canada (E.L.S.).

Correspondence to Raj Padwal, Clinical Epidemiology, Clinical Pharmacology and General Internal Medicine, Professor and Director, Hypertension Clinic, University of Alberta, 5-134A Clinical Sciences Bldg, 11350-83rd Ave, Edmonton, AB T6G2G3, Canada. E-mail rpadwal@ualberta.ca

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### The Hypertension Canada Recommendations Process

Canadian hypertension clinical practice guidelines are crafted and disseminated by the multidisciplinary 75-member CHEP Recommendations Task Force, a process that is funded by Hypertension Canada.<sup>4</sup> CHEP has produced annually updated recommendations for the diagnosis and management of high BP since 1999.<sup>5</sup> The CHEP process consists of the following:

1. A Cochrane librarian conducts literature searches in collaboration with Task Force members. These searches are designed to inform the creation of new (draft) recommendations.
2. Any of the 15 CHEP subgroups may produce  $\geq 1$  draft recommendations in a given year.
3. Draft recommendations are independently vetted and graded by members of the Central Review Committee, comprised of methodological experts who have no industry-related potential conflicts.
4. Refined draft recommendations are presented at a 1-day consensus conference held in October of each year.
5. A new recommendation must be ratified by  $\geq 70\%$  of Task Force members before being adopted. Implementation and dissemination of new and old recommendations follows.

Because the data assessing the merits of intensive BP reduction were published after the 2015 CHEP consensus conference, a special process enabling expedited review of these data was organized. The relevant CHEP subgroups, Central Review Committee members, and CHEP Chairs met in person, virtually, and by teleconference to discuss the need for a new recommendation. Once consensus to move forward was reached, a draft recommendation was crafted and disseminated to the entire Task Force. A virtual consensus conference was held to enable discussion, debate, and refinement of the recommendation. An electronic vote was then held, by which ratification was achieved.

### The 2016 CHEP Recommendation on Intensive BP Reduction and Discussion Points

The new recommendation, published within the 2016 CHEP clinical practice guidelines,<sup>6</sup> is summarized in the Table. Certain aspects of the new recommendation deserve emphasis and discussion.

### Risks of Intensive BP Lowering

The CHEP Task Force debated extensively the issue of generalizability of the SPRINT results to the Canadian hypertensive population. Partly as a result of these deliberations, the final recommendation was crafted to closely follow the inclusion and exclusion criteria of the SPRINT trial. Notwithstanding

**Table. The 2016 CHEP Recommendation for Intensive BP Lowering in High-Risk Individuals**

Recommendation
For high-risk patients (panel 2), aged $\geq 50$ y, with systolic BP levels $\geq 130$ mm Hg, intensive management to target a systolic BP $\leq 120$ mm Hg should be considered. Intensive management should be guided by automated office BP measurements. Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups (Panel 3).
Clinical indications defining high-risk patients as candidates for intensive management
Clinical or subclinical cardiovascular disease
OR
Chronic kidney disease (nondiabetic nephropathy, proteinuria $< 1$ g/d, estimated glomerular filtration rate 20–59 mL/min per 1.73 m <sup>2</sup> )
OR
Estimated 10-year global cardiovascular risk $\geq 15\%$
OR
Age $\geq 75$ y
Patients with $\geq 1$ clinical indications should consent to intensive management.
Generalizability of intensive blood pressure lowering: cautions and contraindications
Limited or no evidence
Heart failure (ejection fraction $< 35\%$ ) or recent myocardial infarction (within last 3 mo)
Indication for, but not currently receiving, a $\beta$ -blocker
Frail* or institutionalized elderly
Inconclusive evidence
Diabetes mellitus
Prior stroke
eGFR $< 20$ mL/min per 1.73 m <sup>2</sup>
Contraindications
Patient unwilling or unable to adhere to multiple medications
Standing SBP $< 110$ mm Hg
Inability to measure SBP accurately
Known secondary cause(s) of hypertension

BP indicates blood pressure; CHEP, Canadian Hypertension Education Program; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and SPRINT, Systolic Blood Pressure Intervention Trial.

\*Frailty was not a specific exclusion criterion in SPRINT; therefore, inclusion of frailty here is based on expert consensus.

the relatively low incidence of serious adverse effects reported in SPRINT, the Task Force felt the risks of intensive BP control would undoubtedly be greater in conventional clinical practice. Accordingly, Task Force members felt securing patient consent for intensive BP reduction through a shared decision-making process to be an integral and necessary prerequisite to implementing intensive BP control.

### The Need for Automated Office BP Measurements

BP measurements in the SPRINT trial were taken with an Omron HEM 907 automated office device, with the mean of

3 readings used for clinical decision-making.<sup>1</sup> CHEP strongly endorses use of automated office BP (AOBP) measurements and considers AOBP to be the preferred method of in-office BP measurement.<sup>6</sup> AOBP is preferred because it automates BP measurement, thereby mitigating many known sources of BP measurement error, including the white coat effect, failure to take serial readings, and the failure to use the mean of these readings to guide therapeutic initiations and titrations.<sup>7</sup> Because manual BP measurements are often spuriously elevated,<sup>7</sup> failure to use AOBP when implementing the SPRINT trial results in clinical practice risks overaggressive BP reduction. One practical barrier to the use of AOBP devices is cost—units are currently approximately priced between 500 and 750 USD.

### Use of Long-Acting Antihypertensive Agents and Protocolized Care

The SPRINT formulary, published as an appendix to the main trial, is notable because it primarily contains long-acting drugs.<sup>1</sup> In addition, SPRINT care protocols mandated that monthly therapeutic adjustments be made if BP was not yet at target in the intensive arm. These care elements, together with enrollment of relatively adherent and nonresistant hypertensive subjects, probably explains the ability of the SPRINT investigators to achieve a 120 mmHg systolic BP target using only 2.8 agents, on average. As the new CHEP recommendation is implemented in primary and specialty care clinics across Canada, it will be important to emphasize these important facets of the SPRINT trial. Use of case managers and protocolized case management may be one way to optimize implementation of intensive BP reduction.

### BP Targets in Diabetes Mellitus

Subjects with diabetes mellitus were excluded from SPRINT, and therefore, this trial does not directly inform BP targets in this patient population. The CHEP Task Force has thus maintained 130 mmHg systolic and 80 mmHg diastolic BP targets in patients with diabetes mellitus. Although there are no studies testing a systolic BP goal of  $< 130$  mmHg, the rationale for these targets has been discussed elsewhere and is underpinned by data from meta-analyses (for systolic BP) and the Hypertension Optimal Trial (for diastolic BP).<sup>8</sup> Potential shortcomings of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, often cited as evidence against intensive BP lowering in diabetes mellitus, have also been discussed in detail.<sup>8,9</sup> ACCORD, which used a complex factorial design, was likely underpowered to detect clinically important outcome differences; furthermore, interpretation is clouded by interaction between treatment strategies.<sup>8,10</sup> Overall, the CHEP Task Force did not feel that the results of SPRINT could be confidently extrapolated to patients with diabetes mellitus. In the opinion of the present 3 authors, the question of whether intensive systolic BP lowering to  $\leq 120$  mmHg should be pursued in this patient population remains unresolved. As shown in the Table, the consensus of the majority of the members of the CHEP Task Force was to recommend caution when extending the recommendation of intensive BP lowering to patients for who evidence of benefit of intensive BP lowering was inconclusive, including diabetic people.

### BP Targets in the Very Elderly

In performing expedited review of the SPRINT trial and related literature, the CHEP Task Force did not examine specifically the broader impact of these data on other CHEP recommendations. Time and capacity constraints were major considerations in this decision. Performing expedited review of a focused issue (ie, SPRINT) was relatively straightforward; in contrast, modifying or eliminating existing recommendations was felt to require more extensive reflection and deliberation. Because CHEP updates annually, it was felt that these discussions were best not rushed. In particular, the current CHEP recommendation endorsing a systolic BP treatment threshold of  $\geq 160$  mmHg for initiation of pharmacotherapy, with a BP target of  $< 150$  mmHg, in patients  $\geq 80$  years of age remains unaltered for now. This recommendation is based largely on the Hypertension in the Very Elderly Trial (HYVET) and additional data from meta-analyses.<sup>11,12</sup>

SPRINT targeted enrollment of individuals aged  $\geq 75$  years, and results in this subgroup were consistent with the overall findings. Although the new CHEP 130/120-mmHg intensive BP threshold/target may at first seem incongruent with the preexisting more conservative 160/150-mmHg threshold/target, it was felt that use of a more intensive BP recommendation in appropriate patients did not preclude use of a more conservative target in patients deemed unsuitable for intensive BP control. Stated another way, CHEP endorses application of the intensive BP recommendation to patients aged  $\geq 80$  years if deemed appropriate. If not felt to be appropriate, application of the 160/150 mmHg recommendation based on the above cited evidence is suggested. Because further SPRINT subgroup analyses are published, including further details of outcomes in very elderly patients, the issue of which systolic BP target is most appropriate in very elderly patients in whom intensive BP reduction is not deemed suitable may require revision. The 2 major options include making no changes and continue to recommend the 160/150-mmHg thresholds/targets or to default to the general threshold/target of 140 mmHg in this population. This issue will be discussed extensively in October 2016, the date of the next Task Force consensus conference.

### Concluding Remarks

Here we have presented the process whereby the 2016 CHEP guidelines have adapted to the publication of SPRINT, deemed to be a well-conducted trial providing definitive evidence of the benefit of intensive BP lowering in the management of hypertension in high-risk patients. The CHEP process is a highly rigorous one, firmly evidence-based, and has allowed the rapid response to new practice-changing data that needs

to be rapidly implemented when, as in SPRINT, it provides life-saving information. This process might be a model for other organizations internationally to adapt to rapidly changing information that can improve patient outcomes.

### Disclosures

R. Padwal is the immediate past Chair of the CHEP Recommendations Task Force and is a Member of the Board of Hypertension Canada. D. Rabi is the current Chair of the CHEP Recommendations Task Force. E.L. Schiffrin is President of Hypertension Canada and Chairman of the Board of Hypertension Canada. The present work represents the opinions of the authors and not the organizations mentioned.

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