Blood Pressure Targets for Older Patients—Do Advanced Age and Frailty Really Not Matter?

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ABSTRACT

In 2017, Hypertension Canada removed advanced age and frailty as considerations for caution when deciding on intensive therapy in their guidelines for the diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Dementia is not mentioned. In this commentary, we review why advanced age and frailty were removed, and examine what is currently known about the relationship between hypertension and both incident and prevalent dementia. We make the case that the presence of frailty (especially when severe) and dementia should be considered when deciding on intensive therapy in future iterations of Hypertension Canada guidelines.

Key words: hypertension, clinical practice guidelines, frailty, dementia, old age

INTRODUCTION

In this commentary, we focus on Hypertension Canada guideline recommendations that specifically deal with treatment indications and blood pressure (BP) targets in older patients. From 2016 onwards, the influence of the Systolic Blood Pressure Intervention Trial (SPRINT)[(1)] can be seen with a call to consider intensive therapy (target systolic BP <120 mmHg) in high-risk patients. The 2017 guidelines removed both advanced age (i.e., ≥80) and frailty as treatment considerations. We will describe what led to these changes and how solid the underlying evidence for them might be. Then we'll address the presence of dementia, which is currently not mentioned. We believe frailty should be a treatment consideration, and dementing illnesses need to be addressed in future iterations of the guidelines. We advocate for a more explicitly individualized approach in the management of hypertension in older patients who range in health status from the very fit to the severely frail.

Hypertension Canada Guidelines

Both the 2016[(2)] and 2017[(3)] Hypertension Canada guidelines advised treatment for average diastolic BPs of 100+ and/or systolic BPs of 160+ in those without macrovascular target organ damage or other cardiovascular risk factors (see Table 1). If either were present, treatment was strongly considered for those with diastolic BPs of 90+ and/or systolic BPs of 140+. Suggested treatment goals were <140 systolic and <90 diastolic except for high-risk patients where a target of <120 systolic would be a consideration. Among the high-risk criteria listed was age ≥75. In selecting patients for intensive therapy, the 2016 guidelines[(2)] suggested that: SPRINT inclusion and exclusion criteria be considered (they form the basis of the clinical indications, cautions, and contraindications for intensive therapy recommended by Hypertension Canada); risks and benefits be carefully weighed with caution used for clinical conditions where this is limited evidence supporting a lower systolic BP target; automated office BP (AOBP) readings be used to guide therapy (in a systematic review and meta-analysis routine office systolic BP readings were found to be on average 14.5 mmHg higher than AOBP determinations);[(4)] and, patients should be prepared for more clinical encounters, more monitoring, and greater medication use if offered intensive therapy (SPRINT patients were followed monthly until target BP was achieved and were on an average of 2.7 medications). Indications, cautions, and contraindications for intensive therapy in the 2017 guidelines remained the same, other than that the mention of frailty was removed[(3)] (Table 1).

The 2016 Hypertension Canada guidelines included both advanced age (i.e., ≥80) and frailty as considerations when deciding on either the initiation of hypertension therapy or the target BP[(2)] (see Table 1). Advanced age and frailty as treatment considerations were then removed from the 2017 guidelines.[(3)] Frailty was deleted because of post hoc analyses of HYpertension in the Very Elderly Trial (HYVET)[(5,6)], which had a target BP of <150/80, and SPRINT.[(7)] Both had used frailty indices (FIs) to assess the status of participants. The analyses mentioned didn't find evidence that frailty influenced treatment outcomes. Based on their review of these two papers, the authors of the 2017 guidelines concluded that older persons with hypertension benefitted from BP reduction regardless of baseline frailty. The only concern raised with intensive therapy was a significant risk of renal dysfunction.

It was noted that both HYVET and SPRINT excluded individuals with limited life expectancy, dementia, or requiring institutional care. As for advanced age (i.e., ≥80), the rationale for its removal as a treatment consideration was less clearly stated. Mention was made of a systematic review and meta-analysis published in 2016 that showed intensive BP reduction was as beneficial in reducing major cardiovascular events in older adults as compared to younger ones, but this paper defined "older" as ≥62 years of age.[8]

Dementia was not mentioned in the 2016, 2017 or 2018 guidelines.[2,3,9] The 2018 ones didn't alter the 2017 recommendations mentioned in the preceding paragraph.[9] No update of Hypertension Canada guidelines was released in 2019.[10]

Advanced Age and Frailty

As noted, the reason for removing advanced age as a factor requiring consideration in the 2017 guidelines is unclear. The only paper directly referenced used 62 as the age with which to

TABLE 1.

Comparison of 2016 and 2017 Hypertension Canada recommendations[2,3]

Indications For Treatment	*2016*	*2017*
In patients *without* macrovascular target organ damage or other cardiovascular risk factors	Indication for treatment: Average SBP ≥160 or average DBP ≥100 mmHg (Grade A[a])	Indication for treatment: Average SBP ≥160 or average DBP ≥100 mmHg (Grade A)
In patients *with* macrovascular target organ damage or other independent cardiovascular risk factors (Diastolic)	Indication for treatment: Average DBP ≥90 mmHg (Grade A)	Indication for treatment: Average DBP ≥90 mmHg (Grade A)
In patients *with* macrovascular target organ damage or other independent cardiovascular risk factors (Systolic)	Indication for treatment: Average SBP ≥140 mmHg (Grade C for 140-160; Grade A for >160)	Indication for treatment: Average SBP ≥140 mmHg (Grade B for 140-160; Grade A for >160)
Comments about older patients	Antihypertensive therapy should be considered in all patients meeting above indications regardless of age (Grade B) but caution should be exercised in "elderly patients who are frail" and "in the very elderly (aged ≥80 years) who do not have diabetes or target organ damage, the SBP threshold for initiating drug therapy is ≥160" (Grade C)	Age and frailty distinctions were removed from the 2017 guidelines for the treatment of uncomplicated hypertension because of suggestive evidence of benefit in treating those with baseline SBP of 140-160 though there might be increased risk of renal dysfunction (caution recommended for older patients with orthostasis)
Treatment Targets	*2016*	*2017*
Adults with hypertension without compelling indications for specific agents	Treatment Target: SBP <140 mmHg (Grade C) DBP <90 (Grade A)	Treatment Target: SBP <140 mmHg (Grade C) DBP <90 (Grade A)
High-risk patients* aged ≥50 years with SBP levels ≥130 *≥1 of: clinical or subclinical cardiovascular disease OR chronic kidney disease OR estimated 10-year global cardiovascular risk ≥15% OR age ≥75	Intensive therapy to target a SBP ≤120 should be considered. Therapy should be guided by automated office BP measurements. Caution recommended where there is limited or no evidence (includes "frail or institutionalized elderly individuals"), inconclusive evidence or contraindications (includes patients with a standing BP <110 mmHg).	Intensive therapy to target a SBP ≤120 should be considered. Therapy should be guided by automated office BP measurements. Caution recommended where there is limited or no evidence (includes "institutionalized elderly patients" with frailty removed), inconclusive evidence, or contraindications (includes patients with a standing BP <110 mmHg).
Additional comments about older patients	*"In the very elderly (age ≥80 years), the SBP target is <150" (Grade C).*	*Recommendation for different BP goal in very elderly patients removed.*

[a]Grade A: Recommendation based on randomized controlled trials (RCTs) or systematic reviews (SRs) with high levels of internal validity and statistical precision where study results can be directly applied to patients; Grade B: Recommendation based on RCTs, SRs or pre-specified subgroup analyses of RCTs that have lower precision or there is a need to extrapolate; Grade C: Recommendation based on trials with lower levels of internal validity and/or precision, unvalidated surrogate outcomes, or from non-randomized observational studies; and, Grade D: Recommendation based on expert opinion alone.

divide older from younger patients.[7] The relevant section of the 2017 guidelines (pages 566–67)[3] does suggest advanced age was being equated with frailty. Observational studies suggest a U-shaped relationship between all-cause mortality and attained BP in patients ≥80 treated for hypertension in routine care. For example, in a large English study, greater mortality risk was seen with both systolic BPs > 154 and <135. The latter finding is possibly explained by residual confounding.[11]

The 2017 Hypertension Canada recommendations about frailty went beyond what the authors of the referenced work suggested. While the HYVET paper concluded frailty should not be used as a criteria for deciding on BP treatment in patients ≥80 years of age, there was also a call for further work on characterizing the benefit-to-risk ratio of therapy among those with dementia and the very old with more severe degrees of frailty as indicated by the presence of disability.[6] The SPRINT investigators urged caution in interpreting their finding of no apparent effect modification by frailty as this analysis was not pre-specified in the trial protocol and the study was possibly underpowered.[7] The strength of the underlying evidence for the contention that baseline frailty should not influence treatment decisions is dependent on whether the full range of frailty was present in sufficient numbers among HYVET and SPRINT participants. In Hypertension Canada guidelines, frailty is dealt with as a categorical variable (i.e., present or not) rather than one with gradations from milder to more severe forms. The exclusion criteria of HYVET and SPRINT barred many potential participants. Among US adults ≥75 with treated hypertension, it was estimated that less than a third (31.3%) would have none of the SPRINT exclusion criteria.[12] Certain of the exclusion criteria found in the Supplementary Appendix to the 2015 SPRINT paper[13] would disproportionately affect those with severe degrees of frailty. Examples where this would be likely are as follows: one-minute standing systolic BP of less than 110; diabetes mellitus; history of stroke; estimated GFR < 20 ml/min /1.73m^2 or end-stage renal disease; symptomatic heart failure within the past six months or left ventricular ejection fraction (by any method) < 35%; life expectancy < than three years or cancer diagnosed and treated within the last two years (except for non-melanoma skin cancer, early-stage prostate cancer, localized breast cancer); unintentional weight loss of >10% in the last six months; dementia; and, nursing home residency.[13]

Data from the studies indicate those with more severe degrees of frailty were under-represented. Median FI scores were 0.17 (interquartile range [IQR] 0.11, 0.24) in HYVET[6] and 0.16 (IQR 0.11, 0.22) in SPRINT.[14] To put these values in perspective, mean electronic FI (eFI) values among primary care patients in the UK between the ages of 65 and 95 are ~0.14.[15,16] Frailty can be categorized as mild (>0.12–0.24), moderate (>0.24–0.36), and severe (>0.36). This is a more nuanced approach than the one used by the SPRINT investigators where frailty was defined as present (if FI >0.21) or not (if ≤0.21) without any range in severity.[14] In HYVET there were more withdrawals among those with higher FI values, and few participants had a FI >0.36.6 Likewise few SPRINT participants had FI values in the severe range.[7] Many, if not most, individuals in HYVET and SPRINT would be categorized as well with treated comorbid disease or vulnerable (categories 3 and 4) on the Clinical Frailty Scale.[17] Because HYVET and SPRINT had a limited number of moderately and few severely frail participants, they were underpowered to comment on the relative benefits and risks of treatment for these segments of the frailty spectrum.[18,19] Even within the truncated frailty range of SPRINT, a FI >0.21 was associated with a higher risk of syncope, hypotension, and falls (though it should be noted that falls were not more common in those receiving intensive compared to standard therapy).[20]

Dementia

Mid-life hypertension is a recognized risk factor for the development of late-life cognitive impairment, and there is promising evidence that its management might lower this risk.[21] While the HYVET-COG did not yield positive results,[22] in the SPRINT MIND trial those assigned to intensive therapy had significantly reduced risks of incident mild cognitive impairment (MCI) and a combined outcome of incident MCI and dementia, though not incident dementia when considered on its own.[23]

An area of practice uncertainty not mentioned in the Hypertension Canada guidelines is the management of hypertension in people with a co-existing dementia. The two conditions frequently occur together, but there is little trial information to guide care as older persons with prevalent dementia have been excluded from most hypertension trials.[24,25] Examples of studies excluding those with a dementia are HYVET and SPRINT. Their exclusion from the latter study means we have no data on the relative effects of intensive therapy compared to standard in the setting of a dementia. While reasonable to assume that patients with dementia would experience equivalent cardiovascular morbidity and mortality benefits, it is unclear whether they would be more prone to adverse effects arising from the treatment of hypertension or what would be the impact of this treatment on cognition. Some, though not all, observational studies indicate lower systolic BPs in cognitively normal and impaired older patients being treated for hypertension are associated with accelerated cognitive decline.[26-28] This might be related to the development of orthostatic hypotension (OH) with treatment, as OH has been shown to increase the risk of subsequent cognitive impairment.[29] The association may also reflect reverse causation. Epidemiological studies show that BP begins dropping two to five years before the diagnosis of a dementia[30] and continues to drop as the dementia progresses,[31] with declines in cognition possibly more pronounced among those being treated for hypertension.[32] The decline in BP immediately prior to and during the course of a dementing illness would suggest caution in the choice of BP target and the need for close monitoring of BP in treated hypertensive patients with a dementia.

Concluding Comments

William Osler is quoted as saying, "It is much more important to know what sort of a patient has a disease than what

sort of disease a patient has." An individualized approach taking into account the values and goals of the older patient, as well as their overall health status (e.g., comorbidities, life expectancy), should be utilized in deciding on the intensity of hypertension therapy.[33] In the absence of frailty, disability, and significant multi-morbidity, BP targets should be considered independent of the person's age.[19] There is also evidence that intensive therapy in carefully selected individuals with mild degrees of frailty is beneficial.[6,7] We don't believe, though, the benefits of intensive therapy have been proven for those with more severe degrees of frailty, and would encourage Hypertension Canada to re-evaluate their conclusions that baseline frailty does not matter when deciding on the intensity of therapy. In their annual updates, we would also suggest that the emerging evidence of the role of BP control in preventing age-related cognitive decline be noted, and the lack of data on the management of hypertension among those with a dementia be included. In addition to the points already raised, there are particular challenges in, for example, obtaining informed consent and ensuring adherence to therapy in this particular patient population. As a minimum, dementia should be included in the list of conditions where we have limited or no evidence when contemplating intensive BP lowering therapy.

CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

REFERENCES

1. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015; 373(22):2103–16.
2. Leung AA, Nerenberg K, Daskalopoulou SS, *et al*. Hypertension Canada's 2016 Canadian hypertension education program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol*. 2016;32(5):569–88.
3. Leung AA, Daskalopoulou SS, Dasgupta K, *et al*. Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. *Can J Cardiol*. 2017;33(5):557–76.
4. Roerecke M, Kaczorowski J, Myers MG. Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension: a systematic review and meta-analysis. *JAMA Intern Med*. 2019;179(3):351–-62.
5. Beckett NS, Peters R, Fletcher AE, *et al*. Treatment of hypertension in patients 80 years of age and older. *N Engl J Med*. 2008;358(18):1887–98.
6. Warwick J, Falaschetti E, Rockwood K, *et al*. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC Med*. 2015;13(1):78.
7. Williamson JD, Supiano MA, Applegate WB, *et al*. Intensive vs. standard blood pressure control and cardiovascular disease outcomes in adults aged >/= 75 years: a randomized clinical trial. *JAMA*. 2016;315(24):2673–82.
8. Xie X, Atkins E, Lv J, *et al*. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet*. 2016; 387(10017):435–43.
9. Nerenberg KA, Zarnke KB, Leung AA, *et al*. Hypertension Canada's 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children. *Can J Cardiol*. 2018;34(5):506–25.
10 Daskalopoulou SS, Feldman RD, McAlister FA, *et al*. The history of hypertension guidelines in Canada. *Can J Cardiol*. 2019;35(5):582–89.
11. Delgado J, Masoli JAH, Bowman K, *et al*. Outcomes of treated hypertension at age 80 and older: cohort analysis of 79,376 individuals. *J Am Geriatr Soc*. 2017;65(5):995–1003.
12. Bress AP, Tanner RM, Hess R, *et al*. Generalizability of SPRINT results to the US adult population. *J Am Coll Cardiol*. 2016;67(5):463–72.
13. Supplement to: The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103-16. Available from: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1511939/suppl_file/nejmoa1511939_appendix.pdf
14. Pajewski NM, Williamson JD, Applegate WB, *et al*. Characterizing frailty status in the Systolic Blood Pressure Intervention Trial. *J Gerontol A Biol Sci Med Sci.* 2016;71(5):649–55.
15. Clegg A, Bates C, Young J, *et al*. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing*. 2016;45(3):353–60.
16. Hollinghurst J, Fry R, Akbari A, *et al*. External validation of the electronic Frailty Index using the population of Wales within the Secure Anonymised Information Linkage Databank. *Age Ageing*. 2019;48(6):922–26.
17. Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489–95.
18. Russo G, Liguori I, Aran L, *et al*. Impact of SPRINT results on hypertension guidelines: implications for "frail" elderly patients. *J Hum Hypertens*. 2018;32(8):633–38.
19. Todd OM, Wilkinson C, Hale M, *et al*. Is the association between blood pressure and mortality in older adults different with frailty? A systematic review and meta-analysis. *Age Ageing*. 2019;48(5):627–35.
20. Sink KM, Evans GW, Shorr RI, *et al*. Syncope, hypotension, and falls in the treatment of hypertension: results from the Randomized Clinical Systolic Blood Pressure Intervention Trial. *J Am Geriatr Soc*. 2018;66(4):679–86.
21. Peters R, Warwick J, Anstey KJ, *et al*. Blood pressure and dementia: what the SPRINT-MIND trial adds and what we still need to know. *Neurology*. 2019;92(21):1017–18.
22. Peters R, Beckett N, Forette F, *et al*. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008;7(8):683–89.
23. The SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs. standard blood pressure control on probable dementia—a randomized clinical trial. *JAMA*. 2019;321(6):553–61.

24. Beishon LC, Harrison JK, Harwood RH, *et al*. The evidence for treating hypertension in older people with dementia: a systematic review. *J Hum Hypertens*. 2014;28(5):283–87.
25. Harrison JK, van der Wardt V, Conroy SP, *et al*. New horizons: the management of hypertension in people with dementia. *Age Ageing*. 2016;45(6):740–46.
26. Mossello E, Pieraccioli M, Bulgaresi M, *et al*. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. *JAMA Intern Med*. 2015;175(4):578–85.
27. Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old. Data from the Leiden 85-plus Study. *Age Ageing*. 2018;47(4):545–50.
28. Streit S, Poortvliet RKE, den Elzen WPJ, *et al*. Systolic Blood pressure and cognitive decline in older adults with hypertension. *Ann Fam Med*. 2019;17(2):100–07.
29. Peters R, Anstey KJ, Booth A, *et al*. Orthostatic hypotension and symptomatic subclinical orthostatic hypotension increase risk of cognitive impairment: an integrated evidence review and analysis of a large older adult hypertensive cohort. *Eur Heart J*. 2018;39(33):3135–43.
30. Peters R, Peters J, Booth A, *et al*. Trajectory of blood pressure, body mass index, cholesterol and incident dementia: systematic review. *B J Psychiatry*. 2020;216(1):16–28. [Epub ahead of print]
31. Hanon O, Latour F, Seux ML, *et al*. Evolution of blood pressure in patients with Alzheimer's disease: a one year survey of a French Cohort (REAL.FR). *J Nutr Health Aging*. 2005;9(2):106–11.
32. Joas E, Bäckman K, Gustafson D, *et al*. Blood pressure trajectories from midlife to late life in relation to dementia in women followed for 37 years. *Hypertension*. 2012;59(4):796–801.
33. Supiano MA, Williamson JD. New guidelines and SPRINT results: implications for geriatric hypertension. *Circulation*. 2019;140(12):976–78.

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