APPENDIX 2: RESPONSES TO FREQUENT QUESTIONS RECEIVED DURING THE PUBLIC EXTERNAL REVIEW PHASE

QUESTION	ANSWER
Diagnosis	
What is the justification for lowering the diagnostic threshold of hypertension to ≥130/80 mmHg and the treatment target to <130 mmHg?	Cardiovascular risk begins to increase when BP exceeds 115/75 mmHg.[1,2] Therefore, definitions of hypertension are based on pragmatic decisions, reflecting interpretations of what level of cardiovascular risk is considered unacceptable within specific populations. Since 2015, hypertension in Canada is diagnosed when the AOBP is ≥135/85 mmHg,[3] a threshold selected as it corresponds to a mean daytime ABPM of 135/85 mmHg and a routine office BP measurement of 140/90 mmHg,[4,5] which represent the traditional cut-offs to define hypertension. However, in Hypertension Canada's 2020 guidelines, the AOBP threshold for people with diabetes mellitus was removed due to a lack of definitive evidence.[6] This omission created uncertainties for primary care providers managing elevated blood pressure in patients with diabetes. This Committee's mandate was to provide up-to-date, evidence-based guidelines specifically for primary care providers, where the vast majority of hypertension is managed. They result from a need to simplify and streamline hypertension care to facilitate implementation.[7] One common request from primary care providers in creating these guidelines was to provide a single BP threshold by which to define hypertension and a single BP target with treatment. Unlike previous Hypertension Canada guidelines but consistent with other international guidelines[8,9] and based upon updated evidence regarding the benefits of more intensive BP lowering,[10-13] the current primary care guidelines have adopted a BP threshold of ≥130/80 mmHg to define hypertension and a systolic BP target of <130 mmHg with treatment.
Why is only one threshold provided for office, ambulatory, and home BP measurements?	When measured properly with a standardized technique, AOBP measurements readings are, on average, comparable to both mean awake ABPM readings and home BP readings.[14-16] An outcomes-derived approach suggests that an AOBP measurement of 130/80 mmHg is associated with a cardiovascular risk comparable to a daytime ABPM or home BP reading of 130/80 mmHg.[17] This approach, using identical thresholds for AOBP, daytime ABPM, and

	HBPM, aligns with the latest guidelines from Hypertension Canada and other expert societies. [4,6,8,9,16]
Treatment	
Should treatment be initiated in all people with hypertension regardless of their cardiovascular risk?	Yes. However, treatment of hypertension includes both non-pharmacologic (lifestyle) and pharmacologic interventions. We recommend healthy lifestyle changes for all adults with hypertension. Based on the existing evidence, we recommend initiation of pharmacotherapy for all adults with hypertension with BP ≥140/90 mmHg and for adults at high cardiovascular disease risk with systolic BP 130-139 mmHg. We do not recommend initiation of pharmacotherapy for adults with hypertension with systolic BP 130-139 mmHg who are not at high cardiovascular disease risk. In this population, we emphasize optimizing healthy lifestyle changes and reassessment of BP and cardiovascular disease risk within 3-6 months.
Why is there no recommendation regarding a diastolic BP target?	No diastolic BP target is provided as the presence of a diastolic BP >80 mmHg when the systolic BP is <130 mmHg (isolated diastolic hypertension) is infrequent and does not appear to significantly increase the risk of adverse events.[18-20] While optimizing lifestyle interventions is important in these individuals, the evidence to support initiation and/or increase of pharmacotherapy is lacking and decisions to this regard should be made through a shared-decision making process.
Is the treatment algorithm and/or target for elderly individuals (>80 years)?	Health status can vary widely among individuals of the same age, and while frailty can occur at any age, it is not synonymous with advanced age. This committee's mandate was not to categorize individuals as "elderly" or "not elderly" based on an arbitrary age cut-off. Most older adults can still benefit from some degree of BP control, similar to that of younger populations. In SPRINT, individuals aged >75 years and/or those who were frail experienced significant benefits from intensive BP reduction, with no increase in adverse events.[21,22] Even those with orthostatic hypotension, a common concern in older adults, also benefit from more intensive BP treatment.[23,24] Setting a higher BP target for older adults could therefore lead to suboptimal reduction of cardiovascular risk. Nonetheless, individualization of care should be prioritized over any set BP target with considerations beyond age, including goals of care, frailty, fall risk, symptomatic orthostatic hypotension, and comorbidities.
Why is the BP target in individuals at high risk of	Recent trials favor intensive BP treatment in high-risk individuals. The first, SPRINT, included only non-diabetic individuals and showed that targeting a systolic BP <120 mmHg resulted in significant benefits in terms of cardiovascular risk prevention with few adverse

cardiovascular disease not <120 mmHg?	events.[10] STEP showed that in older adults from China, targeting a systolic BP between 110-130 mmHg was beneficial compared to a target of 130-150 mmHg.[11] ESPRIT showed results similar to SPRINT but in a Chinese population including people with diabetes.[12] Lastly, BPROAD demonstrated the benefits of intensive BP lowering in individuals with diabetes. [13] Overall, only in the ESPRIT trial was the mean achieved systolic BP lower than 120 mmHg. This suggests that, even in highly controlled clinical trial settings, achieving a systolic BP below 120 mmHg is challenging. Taking these factors into account, the Committee concluded that recommending a target systolic BP of <130 mmHg for all individuals, including those at high cardiovascular risk, is reasonable. This recommendation is consistent with other international guidelines.[8,9] This does not exclude the possibility of targeting a lower BP in specific individuals. Providers can pursue a systolic BP of <120 mmHg in accordance with Hypertension Canada's 2020 guidelines.[6]
Should all people treated for hypertension be switched to the recommended regimen?	No, switching to the recommended treatment protocol is not required. It is reasonable for individuals with well-controlled BP to continue with their current medication regimen. This treatment algorithm was developed to be applicable to most patients with hypertension, but clinical discretion must still be applied on a case-by-case basis. A list of reasonable alternatives is provided.
Why are specific drugs suggested in the treatment algorithm, rather than drug classes?	The hypertension treatment algorithm for primary care is based in the HEARTS framework from the World Health Organization. One of the core principles of HEARTS is to provide simplified directive treatment algorithms to promote a standardized, cost-effective, and evidence-based approach to hypertension management.[25] All HEARTS treatment algorithms outline the specific medications and dosages to be used, as well as the recommended order for their administration. This approach has been shown to quickly improve hypertension control rates and involves implementing a standardized, population-based antihypertensive treatment protocol.[26-28] It ensures the availability and affordability of high-quality antihypertensive medications.
Could starting a single-pill combination lead to excessive BP reduction?	Since 2017, Hypertension Canada recommends single-pill combination as an acceptable first-line therapy for hypertension regardless of the initial BP level.[29] On average, initiation of a low-dose single pill combination results in a 14 mmHg decrease in systolic BP. However, the degree of BP reduction is proportional to the starting BP level. In a large trial from Ontario, initiation of single-pill combinations in participants with an average starting BP of

	155/88 mmHg resulted in a 23/10 mmHg BP reduction.[30] On the opposite end, in a large trial testing a triple pill combination, the BP reduction was 9/5 mmHg in participants with an average baseline BP of 138/86 mmHg.[31] In regard to potential harms from use of single-pill combinations in the initial management of hypertension compared with standard-dose monotherapy, meta-analysis data showed no difference in adverse events for single-pill combinations compared with free-drug combination use (odds ratio 0.80 [95% CI 0.58-1.11]).[32]
What is the justification underlying the choice of irbesartan/HCTZ as a first-line treatment?	Multiple factors were considered for drug selection. These include efficacy, tolerability, cost, coverage, availability, and protection from future drug shortages in Canada. Pharmaceutical companies did not have any influence in the process. All single-pill combinations were carefully considered, and this Committee's conclusions were that irbesartan/HCTZ provided the best alternative. Importantly, irbesartan/HCTZ is universally covered in Canada and identified as a pan-Canadian select molecule by the pan-Canadian Pharmaceutical Alliance, which aims to guarantee Canada's access to affordable generic drugs. Of all available combinations, this one is amongst the least expensive and has a wide availability from generic manufacturers. For example, olmesartan/HCTZ, candesartan/HCTZ, lisinopril/HCTZ, and perindopril/indapamide are all 25-50% more costly and have poorer availability than irbesartan/HCTZ. Telmisartan/HCTZ was initially considered but concerns were raised during the public review phase of the guidelines in regard to possibility of splitting the Telmisartan/HCTZ 80/25 mg pill due to its hygroscopicity. Other pills combining a long-acting ARB and a long-acting CCB (telmisartan/amlodipine), or a long-acting ARB and a thiazide-like diuretic (azilsartan/chlorthalidone) were considered but were not selected due to their high cost and poor availability.
Can irbesartan/HCTZ pills be cut in half?	Yes. As a general rule, pills that are sold without protection from humidity, are not coated, and do not contain extended-release formulation can be cut in half.
Why is an angiotensin receptor blocker suggested over an angiotensin-converting enzyme inhibitor?	Most observational data suggest the effects of ACEIs and ARBs on cardiovascular risk are similar while ARBs provide better safety and tolerability profiles.[33,34] In absence of direct comparative studies, all major guidelines consider ACEI and ARB as acceptable and interchangeable first-line therapies. [6,8,9,35]

Why is a single pill combination including HCTZ recommended whereas the prior guidelines recommended favoring long-acting thiazides such as indapamide and chlorthalidone?	In Hypertension Canada's 2020 guidelines, the use of long-acting thiazide-like diuretics is preferred over other thiazides such as HCTZ. his preference was supported by meta-analyses of randomized trials and observational data indicating that long-acting thiazide-like diuretics provide greater blood pressure reduction and cardiovascular event prevention, despite the fact that all direct comparative trials were small.[36,37] Since then, new data has emerged bringing arguments against this preference. In 2022, a large randomized-controlled trial showed that in individuals already taking HCTZ, switching to chlorthalidone did not lead to improved cardiovascular outcomes nor lower BP, while resulting in an increased risk of hypokalemia.[38] This new data suggest thiazides and long-acting thiazide-like diuretics may be interchangeable in terms of cardiovascular disease prevention and BP control. Nonetheless, and following this Committee's preference for long-acting agents, recommending a first-line single pill combination including a long-acting thiazide-like diuretic would have been preferable. However, in Canada, only two renin-angiotensin system blockers are combined to either chlorthalidone or indapamide; however, the first (perindopril/indapamide) is 35% more costly than the recommended combination, and the second (azilsartan/chlorthalidone) is not reimbursed by most provincial public insurance providers. If developed in the future and cost-effective within Canada, a single-pill combination of a long-acting ARB plus a long-acting thiazide-like diuretic (i.e., chlorthalidone or indapamide) may be preferable.
What is the place of beta-blockers in hypertension treatment?	Beta-blockers appear less effective than the other classes of antihypertensive medications to reduce the risk of stroke and are more likely to be stopped due to adverse events or side effects.[39] Overall, they have a less favorable benefit-to-risk ratio and are not recommended as first-line therapy for hypertension unless a specific clinical indication is present, such as heart failure, angina, post-myocardial infarction, or for heart rate control.[40,41] As fourth-line agents, beta-blockers were shown to be less effective in reducing BP than spironolactone.[42] Therefore, a combination of all three recommended first-line agents (thiazide/thiazide-like diuretics, ACEI/ARB, dihydropyridine CCB) then spironolactone should be used before beta-blockers are initiated, unless a specific indication for beta-blocker use is present or one of the previous agents are contra-indicated or not tolerated.

Are routine blood tests recommended for all people who start combination therapy and/or after each dosage change?	Routine blood testing should be performed during the initial evaluation after a diagnosis of hypertension to assess risk and screen for end-organ damage (outlined in Appendix 1, Supplementary Table 1). Such testing is necessary to predict whether an individual is at high cardiovascular risk which is factored in when deciding at what BP threshold to initiated pharmacotherapy for hypertension.
Will recommending specific antihypertensive drugs lead to back-order issues?	Without a robust national drug manufacturing base, Canada will remain vulnerable to shortages and back-order issues. In jurisdictions where HEARTS was implemented, the use of a standardized treatment protocols did not result in back-order issues. In the Kaiser Permanente Northern California jurisdiction, where the underlying principles of HEARTS were first used, prescriptions of the recommended drug slowly increased over the years. As not all adults with hypertension will be switched to the recommended regimen here in Canada, we anticipate irbesartan/HCTZ use will also slowly increase. The use of a standardized treatment algorithm also facilitates provincial/territorial planning and predictable bulk purchases. If supply issues arise, other agents on the list of acceptable alternatives can be provided. Hypertension Canada will monitor such issues and if necessary, adapt its algorithms.
How were conflicts of interests managed regarding drug selection?	Please see Hypertension Canada' policy on management of competing interests for full details. Pharmaceutical companies were not involved in any process regarding the creation of these guidelines. Great care was used not to select an agent where issues of monopoly could arise. For example, telmisartan/amlodipine is currently only manufactured by one generic manufacturer.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ABPM, ambulatory blood pressure monitoring; AOBP, automated office blood pressure; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; HCTZ, hydrochlorothiazide.

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