Hypertension

High Risk, Pregnancy and Children 2019

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"Seek simplicity, and mistrust it."
Alfred North Whitehead

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Abbreviations and Definitions

ABPM	Ambulatory blood pressure monitoring
ACEi	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AE	Adverse event
ALT	Alanine aminotransferase
AOBP	Automated office blood pressure
aPTT	Activated partial thromboplastin time
ARB	Angiotensin ll receptor blocker
ARI	Absolute risk increase
ARR	Absolute risk reduction
ASA	Acetylsalicylic acid
ASEM	ASpirina en EMbarazo (Aspirin in Pregnancy)
ASPRE	The Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention Trial
AST	Aspartate aminotransferase
B-blockers	Beta-blockers
BMI	Body Mass Index
Booking	First antenatal visit, usually early in pregnancy
BP	Blood pressure
CCB	Calcium channel blockers
CDC	Centers for Disease Control and Prevention
CHIPS	Control of Hypertension in Pregnancy Study
CI	Confidence interval
CKD	Chronic kidney disease
CNS	Central nervous system
CV	Cardiovascular
DBP	Diastolic blood pressure
DIC	Disseminated intravascular coagulation
DM	Diabetes mellitus
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
FHR	Fetal heart rate
HBPM	Home blood pressure monitoring
HDP	Hypertensive disorders of pregnancy

HELLP	Hemolysis elevated liver enzymes and low platelets
HF	Heart failure
HR	Hazard ratio
INR	International normalized ratio
IUGR	Intrauterine growth restriction
LDH	Lactate dehydrogenase
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
NICE	The National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NMSC	Non-melanoma skin cancer
NNT	Number needed to treat
NNH	Number needed to harm
NSAIDS	Nonsteroidal anti-inflammatory drugs
NS	Not statistically significant
NSHA	Nova Scotia Health Authority
OR	Odds ratio
PRES	Posterior reversible encephalopathy syndrome
RCT	Randomized controlled trial
RIND	Reversible ischaemic neurological deficit
RR	Risk ratio or relative risk
RRI	Relative risk increase
RRR	Relative risk reduction
RUQ	Right upper quadrant
SBP	Systolic blood pressure
SOGC	Society of Obstetricians and Gynaecologists of Canada
TIA	Transient ischemic attack
WBC	White blood cell
WHO	World Health Organization

INTRODUCTION

According to Hypertension Canada, hypertension is one of the most common chronic conditions affecting Canadians across their lifespan.

It affects approximately

- 2% of children and adolescents
- 7% of pregnant women
- 25% of the adult population

Hypertension has broad effects on the health of patients because of its association with obesity, chronic kidney disease, cardiovascular disease and death.

Management of hypertension in all ages center on behavioral changes in addition to pharmacotherapy, and is highly informed by the patient's cardiovascular risk.

A strong emphasis is placed on cardiovascular risk assessment

- To engage and educate patients in risk reduction strategies
- For the purpose of therapeutic decision-making.

The purpose of this document is to review and discuss the recommendations and supporting evidence for the management of hypertension in

- High risk patients
- Pregnant women
- Children and adolescents

Throughout this document, clinical questions, table and figure numbers and references apply to an individual section.

Useful Links

American Academy of Pediatrics BP measurement video: https://www.youtube.com/watch?v=JLzkNBpqwi0&feature=youtu.be

British and Irish Hypertension Society: https://bihsoc.org/

- Lists of BP monitors validated in various patient populations: http://www.bhsoc.org/bp-monitors/bp-monitors/

Canadian Paediatric Society: https://www.cps.ca/

- Greig Health Record: https://www.cps.ca/en/tools-outils/greig-health-record

CDC growth charts: https://www.cdc.gov/growthcharts/clinical_charts.htm

Dabl Education Trust:

- Lists of BP monitors validated in various patient populations: http://www.dableducational.org/sphygmomanometers.html

Hypertension Canada: https://hypertension.ca/

- Hypertension Canada Guidelines and Hypertension 2020 Highlights, available at: https://guidelines.hypertension.ca/chep-resources/

Mother To Baby: https://mothertobaby.org/

National Heart, Lung, and Blood Institute's 2004 Normative Blood Pressure Tables: Blood Pressure Levels for Boys and Girls by Age and Height Percentile: https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf

Reproductive Care Program of Nova Scotia: http://rcp.nshealth.ca/

- Nova Scotia Prenatal Record and Companion Document: http://rcp.nshealth.ca/chart-prenatal-forms
- Nova Scotia Rourke Baby Record: http://rcp.nshealth.ca/chartforms/nova-scotia-rourke-baby-record

The Society of Obstetricians and Gynaecologists of Canada (SOGC): https://www.sogc.org/

- SOGC 2014 Guidelines on the Diagnosis, Evaluation and Management of HDP, available at: https://doi.org/10.1016/j.preghy.2014.01.003
- Executive Summary: https://www.jogc.com/article/S1701-2163(15)30588-0/pdf

HYPERTENSION IN HIGH RISK ADULTS

Summary Statements:

Question 1: What blood pressure measurement techniques should be used to diagnose hypertension?

According to the 2018 Hypertension Canada Guidelines

- Automated office blood pressure (AOBP) measurements are the preferred in-office technique for diagnosing hypertension as compared to non-automated office blood pressure (non-AOBP) measurements (Grade D).
- The use of both office blood pressure measurements, along with either ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM), should be used for diagnosing hypertension (Grade C).

Question 1a: What is the evidence for the diagnostic accuracy of different blood pressure measurements?

- ABPM is considered the reference standard in diagnosing hypertension since observational trials suggest that elevated ABPM is associated with an increased risk of CV events (independent of office blood pressure).
- HBPM is considered an alternative to ABPM in diagnosing hypertension since observational trials suggest that elevated HBPM is also associated with increased risk of CV events (independent of office blood pressure). HBPM has fewer studies to support its use compared to ABPM.
- A systematic evidence-based review found that office based measurements (both AOBP and non-AOBP) have lower diagnostic accuracy when compared to ABPM as the reference standard.

Question 1b: How do office-based measurements, AOBP and non-AOBP, compare for diagnosing hypertension?

- AOBP measurements are often promoted as more accurate since they may minimize many non-AOBP measurement errors, including those related to provider hearing deficits, terminal digit preference and rapid deflation.
- AOBP devices use proprietary algorithms to calculate systolic blood pressure (SBP) and diastolic blood pressure (DBP); therefore, it is important to use AOBP devices that have been validated for accuracy.

- One particular method of office blood pressure measurement has not been **consistently** found to be more accurate than another in clinical trials; neither when compared directly with each other nor when compared with ABPM.
  - Trials have found slight variations in mean BP measurements when using different office blood pressure techniques (i.e. AOBP vs. non-AOBP).
  - Trials have also found differences in mean BP measurements when comparing different AOBP devices.
  - **These variations do not occur in a consistent pattern.** For example, some studies have reported lower mean BP while other trials have reported either higher or similar mean BP levels when an AOBP device is compared to a mercury sphygmomanometer.

Question 1c: Is there evidence for improving the diagnostic accuracy of non-AOBP measurements?

- Using standardized techniques improves the accuracy of non-AOBP measurements including taking multiple measurements (i.e. three readings and taking an average of reading 2 and 3). Using standardized techniques bring non-AOBP measurements more in line with ABPM.
- Multiple BP measurements over time (i.e. serial office visits) have better positive predictive value for hypertension than a single measurement using non-AOBP measurements.

Question 2: What is the evidence to treat to a target SBP < 120 mmHg in adults with high risk of cardiovascular disease?

- According to the 2018 Hypertension Canada Guidelines
  - Intensive management is promoted for high risk patients and the BP targets in this high-risk group is a systolic BP < 120 mmHg based on AOBP measurements (Grade B).
    - The definition of high-risk patients used in the guidelines are the same as the patient population included in the SPRINT trial.
  - Starting therapy at a SBP ≥ 130 mmHg (using AOBP measurements) is recommended (Grade B).
- The SPRINT trial was a large open label RCT that compared a BP target < 120 mmHg to a standard target of < 140 mmHg in a population > 50 years of age **with** high CV risk (Framingham risk > 15%) but **without** diabetes, stroke, HF, or ESRD.
- Patients in the SPRINT trial were a treated population (> 90% already treated with antihypertensives), with a mean BP of 140/78 mmHg at the start of the trial, and a Framingham risk of ~20%.

- The primary outcome of fatal and non-fatal CV events (MI, other ACS, stroke, HF or death from CV cause) occurred at a significantly lower rate in the intensive treatment arm compared to the standard treatment arm resulting in a NNT of 63 over 3.3 years.
- Serious AE related to treatment with antihypertensives occurred at significantly higher rates in the intensive treatment arm compared to the standard treatment arm over the same time frame resulting in a NNH of 46 over 3.3 years.

SPRINT Bottom Line

- A target SBP of < 120 mmHg vs. a target SBP < 140 mmHg results in a trade-off between benefit and harm.
  - For every 50 people treated to a target SBP < 120 mmHg for 3.3 years instead of a SBP < 140 mmHg there will be approximately one less CV event (mostly HF or death) BUT there will be approximately one more treatment related serious adverse event (mostly acute kidney injury).
- The risks and benefits for each individual patient need to be assessed.
  - Patients similar to the population in SPRINT with a Framingham risk > 15% with relatively few comorbidities may be considered to be treated to a target SBP < 120 mmHg.
- It is important to remember that lower targets will potentially increase the number of antihypertensive medications, drug interactions, risk of serious side effects, need for monitoring, and costs.
- Also, a SBP < 120 mmHg was a target in the trial; a sizeable portion of patients in the study **did not** reach this target.

Question 2a: What is the evidence for lower BP targets in patients with established CV disease?

- A 2018 Cochrane Review compared lower targets (< 135/85 mmHg) to standard targets (≤ 140 - 160/90 -100 mmHg) in patients with established CV disease. There were no differences in total mortality, total CV events, CV mortality or serious AE.

Question 2b: Is there evidence for the < 120 mmHg blood pressure target in patients with diabetes, history of previous stroke, or the very frail elderly?

- The results of SPRINT are not generalizable to all hypertensive patients with elevated CV risk.
  - Two recent Cochrane Reviews have evaluated lower BP targets in patients with diabetes or prior stroke. Results of the meta-analyses found that lower BP targets are not associated with better outcomes compared with standard BP targets (SBP < 140 mmHg).

- The strength of evidence for frail elderly is insufficient to draw any conclusions for treatment targets in this population.

Background:

Hypertension Canada (formerly the Canadian Hypertension Education Program) produces clinical practice guidelines for the diagnosis, risk assessment, prevention and treatment of hypertension in adults and children.[1]

- An update of the guidelines was published in 2018 along with a 2020 Highlights Booklet and presentation.
- The 2018 Hypertension Guidelines and the 2020 Hypertension Highlights from Hypertension Canada are available. https://guidelines.hypertension.ca/

The system used for grading recommendations in the Hypertension Canada Guidelines is shown in Table 1. The 2018 Hypertension Canada recommendations do not consistently cite the studies on which the grades of evidence are based.

Table 1: Hypertension Canada Grading Scheme for Recommendations[1]

Grading Scheme for Recommendations	
Grade A	Recommendations are based on randomized trials (or systematic reviews of trials) with high levels of internal validity and statistical precision, and for which the study results can be directly applied to patients because of similar clinical characteristics and the clinical relevance of the study outcomes.
Grade B	Recommendations are based on randomized trials, systematic reviews or pre-specified subgroup analyses of randomized trials that have lower precision, **or there is a need to extrapolate from studies because of differing populations or reporting of validated intermediate/surrogate outcomes rather than clinically important outcomes.**
Grade C	Recommendations are based on trials that have lower levels of internal validity and/or precision, or trials reporting non-validated surrogate outcomes, or results from non-randomized observational studies.
Grade D	Recommendations are based on expert opinion alone

- Categorization of hypertension for adults
  - Historically more emphasis has been placed on diastolic blood pressure (DBP) as a predictor of CV morbidity and mortality.
  - Observational studies have demonstrated associations between both higher systolic blood pressure (SBP) and DBP and increased CV disease risk.
  - Guidelines now focus on control of SBP and DBP.
- Four approaches are used to measure BP:
  - Automated office blood pressure (AOBP)
  - Non-automated (manual) office blood pressure monitoring (non-AOBP)
  - Home Blood Pressure Monitoring (HBPM)
  - Ambulatory Blood Pressure Monitoring (ABPM)

- The recommendations from Hypertension Canada for diagnosing hypertension are summarized in Table 2.

Table 2: **Guidelines for Diagnosing Hypertension**[1]

Visit 1	
Patients with features of a hypertensive urgency or emergency should be diagnosed as hypertensive. **Require immediate attention**	Grade D
If the visit 1 mean AOPB or non-AOBP SBP is ≥ 180 mmHg and/or the DBP is ≥ 110 mmHg then hypertension is diagnosed.	Grade D
If BP is high normal (**non-AOPB** SBP 130-139 mmHg and/or DBP 85-89 mmHg) then **annual follow-up** is recommended.	Grade C
If BP is high (non-AOBP ≥ 140/90 mmHg **OR** AOBP ≥ 135/85 mmHg), a history and physical examination should be performed. **Visit 2 should be scheduled within 1 month.** Note: the threshold for patients with diabetes is ≥ 130/80 mmHg (AOBP or non-AOBP)	Grade D
Subsequent visits	

• If clinically indicated, diagnostic tests to search for target organ damage and associated cardiovascular risk factors should be arranged within 2 visits.
• Visit 2 should be scheduled within 1 month
• Out of office measurements should be performed before visit 2.
  ◦ If mean daytime ABPM ≥ 135/85 mmHg or mean 24 hour ABPM ≥ 130/80 mmHg, hypertension is diagnosed.
  ◦ If mean of HBPM series is ≥ 135/85 mmHg, hypertension is diagnosed.
  ▪ Home BP series is two readings taken each morning and evening for 7 days. Discard the first day readings and average the last 6 days.
• If out of office measurements are not performed, patients can be diagnosed as hypertensive using serial office BP measurements (based on non-AOBP averaged across 3-5 visits). Hypertension is diagnosed if:
  ◦ Over 2 visits, the average SBP is ≥ 140 mmHg and/or DBP ≥ 90 mmHg **AND** there is macrovascular organ damage, diabetes, or CKD
  ◦ Over 3 visits, the average SBP is ≥ 160 mmHg and/or DBP ≥ 100 mmHg
  ◦ Over 4 to 5 visits, the average SBP is ≥ 140 mmHg and/or DBP ≥ 90 mmHg
• If AOBP ≤ 135/85 mmHg or non-AOBP < 140/90 mmHg **assess at yearly intervals**
	Grade D

Note: ≥ 2 readings should be taken during the same visit. If using an AOBP, the BP calculated and displayed by the device should be used. If using non-AOBP measurement, the first reading should be discarded and the subsequent readings averaged.	

- The rationale for repeating BP measurements is to rule out isolated clinic hypertension (i.e. "white coat" hypertension).
- The Hypertension Canada guidelines recommend that patients who are identified as having isolated clinic hypertension be followed up for future progression to hypertension.
  - There is suggestion it is an intermediate condition between normotension and sustained hypertension.[1]

- The evidence for the effect of isolated clinic hypertension on CV events from observational trials has found mixed results. Some trials found a slight increase in risk with isolated clinic hypertension and others found no increased risk.[2]
- Recent meta-analyses of these observational trials suggest that there may be a slight increase in CV morbidity and mortality associated with isolated clinic hypertension but it is substantially less than the risk associated with sustained hypertension.[3,4,5]

o Treating patients with isolated clinic hypertension with antihypertensives is not recommended. The effect of treating patients with isolated clinic hypertension has not been evaluated in well-designed trials.

Hypertension Canada Guidelines for follow up after diagnosis[1]

- Patients should be followed every 3-6 month or every 1-2 months for patients with higher BPs (Grade D).
- Patients receiving antihypertensives should be seen every 1-2 months until readings are below target on 2 consecutive visits or more often for symptomatic patients and those with severe hypertension, intolerance to antihypertensive drugs, or target organ damage (Grade D).
- Once target BP has been reached, patients should be seen every 3-6 months (Grade D).
- Standardized office BP measurements should be used for follow-up. AOBP is the preferred method of performing in office BP measurements (Grade C; **new guideline**).
- ABPM or HBPM is recommended for follow-up of patients with demonstrated "white coat" effect (Grade D; **new guideline**).

There may be variation between BP measurement techniques; therefore, it is important to ensure standardized measurement methods and techniques for both diagnosis and follow-up.

Table 3: Hypertension Canada Guideline Recommendations for Blood Pressure Thresholds for Initiation of Antihypertensive Therapy[1]

BP thresholds refer to non-AOBP measurements except in high risk of CVD patients where thresholds refer to AOBP measurements.

BP (mmHg)	Other Factors	Recommendation	Target BP (mmHg)	Grade of Recommendation
SBP ≥ 160 and/or DBP ≥ 100	Low risk (no target organ damage or CV disease risk factors)	Prescribe therapy	SBP < 140 and DBP <90	Grade A (SBP and DBP)
SBP ≥ 130 **(using AOBP)‡**	High risk of CV disease*	Patients with clinical indications should be treated with intensive management	SBP <120	Grade B (SBP)
SBP ≥ 130 and/ or DBP ≥ 80	Diabetes mellitus	Prescribe therapy	SBP < 130 and DBP < 80	Grade C for SBP Grade A for DBP
SBP ≥ 140 and/or DBP ≥ 90	All others	Prescribe therapy	SBP < 140 and DBP <90	Grade C for starting therapy and Grade A for target of SBP Grade A for DBP

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; CV, cardiovascular; AOBP, automated office blood pressure device

*Hypertension Canada defines high-risk patients (on the basis of **AOBP measurements**) as patients with clinical or subclinical cardiovascular disease **OR** chronic kidney disease (nondiabetic nephropathy, proteinuria < 1 g/d, estimated glomerular filtration rate of 20-59 mL/min/1.73 m^2) **OR** estimated 10-year global cardiovascular risk ≥15 % (Framingham Risk Score) **OR** age ≥75 years

‡ The Canadian Hypertension Guidelines recommend starting antihypertensive therapy at a SBP ≥ 130 mmHg in patients at high risk of cardiovascular disease. However, this threshold is not included in their diagnostic algorithm.

Hypertension Canada Guidelines on BP Measurement Techniques[1]

- BP should be measured after a patient sits comfortably and quietly (no talking and room should be quiet) for at least 5 minutes in a chair with back supported, both feet flat on the floor, and the unbent arm supported at heart level at mid-sternum.
- BP should be taken in both arms and if one arm has a consistently higher pressure, that arm should be used for BP measurement and interpretation.
- A cuff with an appropriate bladder size for the size of the arm should be used: bladder width should be close to 40% of the arm circumference and length should cover 80-100% of the arm circumference.
- The lower edge of the cuff should be 3 cm above the elbow crease.

- Details on measurement techniques are described in the 2020 Hypertension Canada Guidelines: https://guidelines.hypertension.ca/wp-content/uploads/2018/10/Hypertension-Guidelines-English-2018-WEB.pdf

For non-AOBP Measurements

- The first reading should be discarded and the following 2 measurements should be averaged and recorded as the patient's BP for that visit.

For AOBP Measurements

- The device should be set to take measurements at 1-2 minute intervals.
- The first measurement should be taken to verify cuff position and validity of the measurement.
- The patient should be left alone after the first measurement while the device automatically takes subsequent readings.
- The average BP as displayed on the device should be recorded, as well as the arm used and whether the patient was supine, sitting or standing.

Table 4: Examples of Target Organ Damage and Cardiovascular Risk Factors from Hypertension Canada 2018[1]

Examples of Target Organ Damage	Examples of Cardiovascular Risk Factors for Atherosclerosis
Stroke Ischemic stroke and transient ischemic attack Intracerebral hemorrhage Aneurysmal subarachnoid hemorrhage **Dementia** Vascular dementia Mixed vascular dementia and dementia of the Alzheimer's type **Hypertensive retinopathy** **Left ventricular dysfunction** Left ventricular hypertrophy **Coronary artery disease** Myocardial infarction Angina pectoris Congestive heart failure **Renal disease** Chronic kidney disease (GFR <60 mL/min/1.73 m^2) Albuminuria[a] **Peripheral artery disease** Intermittent claudication	**Non-modifiable** Age ≥ 55 years Male sex Family history of premature cardiovascular disease (age < 55 years in men, < 65 years in women) **Modifiable** Sedentary lifestyle Poor dietary habits Abdominal obesity Dysglycemia Smoking Dyslipidemia Stress Nonadherence

a. Hypertension Canada defines albuminuria as a persistent albumin to creatinine ratio of > 2 mg/mmol in men and > 2.8 mg/mmol in women. These thresholds correspond to a 24-hour urine collection for albumin of >30mg/day for both sexes.

- American and International Guidelines specific to the diagnosis and treatment of hypertension are also available.
  - 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: https://www-ahajournals-org.ezproxy.library.dal.ca/doi/full/10.1161/HYP.0000000000000065
  - 2018/ESC/ESH Guidelines for the Management of Arterial Hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Cardiology and the European Society of Hypertension: https://www.eshonline.org/

This section of the review will address two questions:

1) What blood pressure measurement techniques should be used to diagnose hypertension?
   a. What is the evidence for the diagnostic accuracy of different blood pressure measurements (ambulatory blood pressure, home blood pressure, and office blood pressure)?
   b. How do automated and non-automated office-based measurements compare for diagnosing hypertension?
   c. Is there evidence for improving the diagnostic accuracy of non-automated office-based blood pressure measurements?

2) What is the evidence to treat to a SBP < 120 mmHg in adults with high risk of cardiovascular disease?
   a. What is the evidence for lower BP targets in patients with established CV disease?
   b. Is there evidence for the < 120 mmHg blood pressure target in patients with diabetes, history of previous stroke, or the very frail elderly?

Blood Pressure Measurement

Office Blood Pressure Measurements

Non-automated (manual) office blood pressure monitoring (non-AOBP) - ausculatory method

- The manual ausculatory method (non-AOBP) involves a trained observer using a stethoscope to detect Korotkoff sounds, which are made by the turbulent flow of blood past the restricted area created by the inflated cuff.
  - Readings are made using a mercury or aneroid sphygmomanometer at the brachial artery.
    - Aneroid sphygmomanometers use a lever and bellows system (as opposed to a mercury column) to measure pressure and have been used as a mercury free alternative.
    - Hybrid sphygmomanometers utilize an electronic pressure gauge in place of the mercury column, but blood pressure is still determined using the ausculatory method.
- Non-AOPB measurements using a mercury sphygmomanometer were considered the gold standard for clinic based measurement for many years as it correlates well with simultaneous intra-arterial BP when performed correctly.[2]
- The disadvantages of diagnosing hypertension solely in the office setting include measurement errors, the limited number of measurements that can be made conveniently, and the confounding risk for isolated clinic hypertension.
  - Blood pressure is affected by various short-term factors, such as emotions, stress, pain, physical activity, and drugs (including caffeine and nicotine).
  - Isolated clinic hypertension in the medical setting and in the presence of medical personnel (known as "white coat" hypertension) is well-documented.
  - Epidemiologic data suggest that 15% to 30% of the population believed to have hypertension may have lower blood pressure outside of the office setting. [2]

The established threshold of 140/90 mmHg for a hypertension diagnosis is based on standardized non-AOPB measurements.

- Most clinical trials of hypertension treatment used the mean of at least 2 measurements taken while the patient was seated (some used the mean of the second and third measurements), allowed for at least 5 minutes between entry into the office and BP measurement, used an appropriately sized arm cuff, and placed the patient's arm at the level of the right atrium during measurement.[2]

Automated office blood pressure (AOBP) - oscillometric method

- Oscillometric sphygmomanometers use a pressure transducer to assess the oscillations of pressure in a cuff during gradual deflation. The point of maximum oscillation corresponds to the mean intra-arterial pressure.

- Systolic and diastolic measurements are calculated based on an empirically derived algorithm.
- These devices can be programmed to complete several measurements after a period of rest at appropriate time intervals without the presence of medical personnel.
- AOBP measurements with a validated device may avoid observer error and bias.

➢ **It can be difficult to accurately measure BP in patients with atrial fibrillation due to pulse irregularity.**

- **Hypertension Canada recommends performing multiple measurements to obtain consistent results.[1]**
- **Alternatively, the National Institute for Health and Care Excellence Hypertension guidelines (UK) recommend measuring BP manually using direct auscultation over the brachial artery if pulse irregularity is present.[6]**

Device Regulation, Validation, and Calibration of Office Based Monitors

Validation of devices requires independent assessment of accuracy of the device compared with a reference standard (mercury sphygmomanometer).

- This is especially important for AOBP devices, which use proprietary algorithms to calculate SBP and DBP.

The three most widely used protocols are the British Hypertension Society Protocol, the Association of the Advancement of Medical Instrumentation (AAMI) Standard, and the International Protocol of the European Society of Hypertension.

A list of devices of various types, results of validation testing, special populations included in validation testing, and recommendations can be found at http://www.dableducational.org/.

All sphygmomanometers require regular calibration and maintenance to maintain accuracy.

- Incorrect calibration has been associated with BP measurement errors in either direction with all types of sphygmomanometers.[7]
- One review recommends calibration at 3 year intervals for mercury sphygmomanometers, 6-month intervals for aneroid sphygmomanometers, and 12 month intervals for oscillometric devices.[8]

Out of Office Blood Pressure Measurements

Ambulatory Blood Pressure Monitoring - ABPM

➢ ABPM devices are small portable machines connected to a BP cuff worn by patients that record BP at regular intervals over 24 to 48 hours while patients go about their normal activities.

- Measurements are typically taken at 20-30 minute intervals. Results may be reported for 24 hours, daytime, and nighttime.
- Devices typically use oscillometric techniques which have replaced use of a microphone to measure Korotkoff sounds.

Home Blood Pressure Monitoring - HBPM

- HBPM devices are typically fully automated oscillometric devices that record pressure from the brachial artery.
  - Many HBPM devices are commercially available; some are validated according to standardized protocols.
  - Use of validated devices is recommended. Additional information on appropriate HBPM and devices can be found at the following link. https://www.ncbi.nlm.nih.gov/books/NBK91430/pdf/Bookshelf_NBK91430.pdf

Question 1: What blood pressure measurement techniques should be used to diagnose hypertension?

According to the 2018 Hypertension Canada Guidelines[1]

- AOBP measurement is the preferred in-office technique for diagnosing hypertension as compared to non-automated blood pressure measurements (non-AOBP) (Grade D).
- The use of both office blood pressure measurement and either ABPM or HBPM should be used for diagnosing hypertension (Grade C).

Question 1a: What is the evidence for the diagnostic accuracy of different blood pressure measurements (ambulatory blood pressure, home blood pressure, and office blood pressure)?

A 2014 Agency for Healthcare Research and Quality (AHRQ) systematic review evaluated the diagnostic accuracy of different BP measurement methods for diagnosing hypertension.[2]

- The review first established which BP measurement technique was the best predictor of CV events.
- ABPM was determined to be the reference standard based on the evidence reported in Table 5.

Table 5: Summary of AHRQ Results for Different BP Measurements and the Prediction of CV Events[2]

Method of Measurement	Evidence for Prediction of CV Events
Ambulatory Blood Pressure Monitoring	24 hours ABPM (9 cohort studies), nighttime ABPM (9 cohort studies), and daytime ABPM (10 cohort studies) were consistently and significantly associated with stroke and other CV outcomes, independent of office measurements and with greater predictive value than office based measurements (AOBP and non-AOBP), with hazard ratios ranging from 1.09 to 1.42.
Home Blood Pressure Monitoring*	5 cohort studies showed that elevated HBPM was significantly associated with increased risk for CV events, stroke, and all-cause mortality, independent of office blood pressure, with hazard ratios ranging from 1.17 to 1.39.
Office Blood Pressure Monitoring	Office based measurements (non-AOBP and AOBP) were found to be less accurate than ABPM and HBPM in predicting CV events (as described above).
*fewer studies have compared HBPM with office blood pressure measurement, the evidence is not as robust as it is for ABPM.	

- The AHRQ review also assessed which method of BP measurement should be used to confirm hypertension in patients who initially screen positive using office based measurements. Results are summarized in Table 6.

Table 6: Summary of AHRQ Results for Confirmation of Hypertension in Adults[2]

Method of Measurement	Evidence
Ambulatory Blood Pressure Monitoring	In 24 studies the proportion of participants with elevated office measurements (both AOBP and non-AOBP) and true hypertension (according to the ABPM reference standard) ranged from 35% to 93%.
Home Blood Pressure Monitoring*	In 7 studies the proportion of participants with elevated office measurements (both AOBP and non-AOBP) and true hypertension (according to HBPM as the reference standard) ranged from 45% to 84%.
Office Blood Pressure Monitoring	Office based measurements were less effective than ABPM and HBPM at identifying isolated clinic hypertension (as described above).
*fewer studies have compared HBPM with office blood pressure measurement, the evidence is not as robust as it is for ABPM.	

- The review concluded:
  - ABPM is the reference standard for confirming the diagnosis of hypertension. HBPM may also be a reasonable confirmatory method but has less evidence to support its use compared to ABPM.
  - Both ABPM and HBPM were more accurate than office based methods at identifying isolated clinic hypertension.
  - **Failure to confirm initial elevated office blood pressure measurements may result in misdiagnosis and overtreatment.**

Question 1b: How do AOBP and non-AOBP measurements compare for diagnosing hypertension?

- One particular method of office blood pressure measurement has not been consistently found to be more accurate than another in clinical trials; neither when compared directly with each other nor when compared with ABPM.
- The AHRQ review included 4 cohort studies directly comparing non-AOBP and AOBP. [2]
  - One study found similar sensitivity and positive predictive values when comparing non-AOBP vs. AOBP; however, it was determined the non-AOBP protocol used in this study does not apply to a typical clinic based system.
  - Three studies used more clinically applicable designs. While there were slight differences between the measurements, the diagnostic accuracy was considered similar. It was noted that the research protocols for non-AOBP measurements used multiple measures that were averaged.
- The AHRQ review also included 3 cohort studies which compared both non-AOBP and AOBP using ABPM as a reference for diagnosing hypertension. These 3 studies did not clearly favor non-AOBP or AOBP in terms of diagnosing hypertension. [2]
- Two recent meta-analyses have compared AOBP with other methods of BP measurements including ABPM and non-AOBP measurements. These meta-analyses pooled trials with different study designs (cross-sectional, prospective, retrospective and randomized) and had a high degree of heterogeneity. The majority of trials evaluated one particular AOBP device and very few of the trials were randomized.
  - These analyses concluded that AOBP was similar to daytime ABPM, with a mean difference in SBP in the range of -1.85 mmHg to -0.3 mmHg. [9,10]
    - **Note**: There was wide variation in the mean SBP across individual trials when comparing AOBP to daytime ABPM. For example, the individual trials in one meta-analysis had mean SBP differences ranging from -12 mmHg to + 9 mmHg between AOBP and daytime ABPM. [9]
  - In both meta-analyses the mean AOBP measurements were reported to be lower than non-AOBP measurement. One meta-analysis reported a mean difference in SBP of -10.48 mmHg when AOBP was compared to non-AOBP. The other meta-analysis reported a mean difference in SBP of -7.0 mmHg when AOBP was compared with

research non-AOBP (i.e. using standardized measurement techniques) and -13.4 mmHg when compared to clinic non-AOBP. [9,10]

- **Note**: There was wide variation in the mean SBP readings across individual trials when AOBP and non-AOBP measurements were compared. For example, the individual trials in one meta-analysis had mean SBP differences ranging from -0.5 mmHg to -20 mmHg between AOBP and non-AOBP. [9]

- A 2017 systematic review evaluated studies that assessed potential sources of inaccuracies with BP measurements. [7]
  - Device-related evaluations included comparisons of AOBP devices to non-AOBP devices and AOBP devices compared to ABPM.
    - Different models of AOBP devices compared to ABPM found a difference of mean SBPs ranging from -23 mmHg to +6 mmHg, and DBPs ranging from -3 mmHg to + 5.6 mmHg.
    - Different models of AOBP devices compared to non-AOBP measurements found a difference of mean SBPs ranging from -3.7 mmHg to 16.53 mmHg, and DBPs ranging from -3 mmHg to + 9.71 mmHg.
- Two studies have directly compared 2 different AOBP devices (both studies compared the same two devices).
  - The first study found no significant difference for SBP measurements but there were significant differences in DBP measurements (up to 5 mmHg) that varied depending on the interval setting of the AOBP devices.[11]
  - The second study found variations between the 2 different AOBP devices with a mean difference of 4 mmHg (± 7.4 mmHg) in SBP.[12]

Question 1c: Is there evidence for improving the diagnostic accuracy of non-AOBP measurements?

- Multiple BP measurements during a single clinic visit have better positive predictive value for hypertension than one measurement, when using non-AOPB measurements.
  - For example, a large observational identified 3,454 patients with stage 1 hypertension (based on the first non-AOBP measurement) and found that 35% were non-hypertensive when the second and third non-AOBP measurements were averaged.[13]
- Using standardized techniques (as per the Canadian Hypertension Guidelines) improves the accuracy of non-AOBP measurements and brings it more in line with ABPM.
  - An observational trial compared the accuracy of usual clinic BP measurements (non-AOBP) with standardized techniques using non-AOBP methods and ABPM (both daytime and 24 hours).[14]
    - Usual clinic BP measurements were higher than both standardized non-AOBP and ABPM (24 h and daytime).

Table 7: Blood Pressure Measurements with Different Methods[14]

Measurement	SBP mmHg (mean)	DBP mmHg (mean)
Usual Clinic (non-AOBP)	149.5	90.4
Standardized (non-AOBP)	138.7	85.5
Daytime ABPM	141.8	85.3
24 h ABPM	137.4	81.5

- Repeating non-AOBP measurements at subsequent office visits may help to identify patients with isolated clinic hypertension.
  - In 3 studies where initial elevated results using non-AOBP measurements were repeated at a second visit, 67% to 82% of the population had a diagnosis of hypertension confirmed.[2] The time interval for repeat visits ranged from 8 days to 1 month across the 3 studies.

What Evidence does Hypertension Canada use to establish the diagnostic thresholds with ABPM, HBPM and AOBP measurements?

Rationale provided in guidelines[1]: Both the ambulatory blood pressure thresholds (≥ 130/80 mmHg for 24 hour and ≥ 135/85 mmHg for daytime ABPM) and the home blood pressure threshold (≥ 135/85 mmHg) were established using results from **prognostic studies** examining CV mortality and morbidity.

For the AOBP threshold, the guidelines reference three studies (using 1 particular device) that report mean AOBP readings are comparable to daytime ambulatory BP readings; therefore, a mean AOBP of SBP ≥135 mmHg or DBP ≥85 mmHg is considered high.

Academic Detailing comment: It is important to remember there may be variations between different AOBP and HBPM devices for BP measurements. As a result, the diagnostic BP thresholds should be utilized as a guide.

Treating Patients at High Risk of Cardiovascular Disease

- The general goal of therapy in adults diagnosed with hypertension is to reach a SBP < 140 mmHg (Grade C) and a DBP target < 90 mmHg (Grade A).[1]
- Intensive management is promoted for patients with high risk of CV disease.
  - The Hypertension Canada guidelines define high risk patients on the basis of **AOBP** as people with clinical or subclinical CV disease **OR** CKD (nondiabetic nephropathy, proteinuria < 1 g/d, estimated glomerular filtration rate of 20-59 mL/min/1.73 m^2) **OR** estimated 10-year global CV risk ≥ 15 % (Framingham Risk Score) **OR** age ≥ 75 years.[1]
- In this high risk patient population the Canadian guidelines recommend initiating pharmacotherapy at a blood pressure threshold ≥ 130 mmHg on the basis of **AOBP** measurements and the BP targets in this high risk group is a SBP < 120 mmHg. (Grade B).[1]

Question 2: What is the evidence to treat to a target SBP < 120 mmHg in adults with high risk of cardiovascular disease?

- The definition of high risk patients used in the Hypertension Canada guidelines are the same as the patient population included in the **SPRINT** trial.[15]
- Details of the **SPRINT** trial:[15]
  - SPRINT was an open label RCT which evaluated intensive vs. standard blood pressure targets in high risk patients.
  - The inclusion criteria were:
    - Patients ≥ 50 years with
      - A SBP ranging from 130 to 180 mmHg (or 130-170 mmHg on up to 2 medications; 130-160 mmHg if on up to 3 medications; 130-150 mmHg if on up to 4 medications), **and**
      - an increased CV risk (e.g. ≥ 1 of: clinical or subclinical CV disease other than stroke; CKD with eGFR of 20 to 60 mL/min, Framingham risk ≥ 15%, or age greater than 75 years).
  - Notable exclusions were:
    - Patients with
      - A history of type-2 diabetes, stroke, proteinuric kidney disease, HF (recent EF < 35%
      - Recent CV disease symptoms requiring hospitalization (within last 3 months)
      - Residence in a nursing home
      - A standing SBP < 110 mmHg
  - SPRINT studied 9,361 patients
    - At baseline, ~28% had CKD; ~20% had CV disease (clinical or subclinical); ~20% were ≥ 75 years of age; and the average Framingham Risk Score over 10 years was ~20%.
  - The aim of the study was to evaluate a treatment strategy, not a specific drug regimen.

- Subjects were randomized to < 120 mmHg SBP vs. standard < 140 mmHg SBP targets.
- The mean baseline BP level at the beginning of the study were 140/78 mmHg in both treatment groups.
- The mean achieved SBP levels were 121.5 mmHg in the intensive treatment group and 134.6 mmHg in the standard treatment group.

- Antihypertensive use in the two treatment arms, both at baseline and during the trial, is summarized in Table 8.

Table 8: Antihypertensive Use in SPRINT[15]

	< 120 mmHg	**< 140 mmHg**
Baseline antihypertensive use	**>90% were using an antihypertensive at study entry (mean 1.8 in both treatment arms)**	
Mean # antihypertensives at last study observation	**2.7**	**1.8**
0	2.7%	11.3%
1	10.5%	31.1%
2	30.5%	33.3%
3	31.8%	17.2%
4+	24.3%	6.9%
ACEi or ARB	77% (37% ACE, 40% ARB)	55%
Diuretic	67%	43%
CCB	57%	35%
Beta-blocker	41%	31%
other	Up to 10%	Up to 6%

- **Note**: The study was stopped at a median follow up of 3.26 years due to an identified survival benefit in the intensive therapy treatment arm.
- The primary efficacy outcome was a composite of MI, other ACS, stroke, HF, or death due to CV cause.
  - The intensive treatment arm experienced lower rates of fatal and non-fatal CV events: 5.2% vs. 6.8%, NNT=63/3.3 years.
- Secondary outcomes included the individual components of the primary outcome and are reported in Table 9.

Table 9: Efficacy Results of SPRINT[15]

Efficacy Outcomes	SBP Target		ARR	HR (95% CI)	NNT for 3.3 years
	< 120	< 140			
Primary Outcome					
MI, other ACS, stroke, HF, or death from CV cause	**5.2%**	**6.8%**	**1.6%**	**0.75 (0.64 – 0.89)**	**63**
Secondary Endpoints					
MI	2.1%	2.5%	0.4%	0.83 (0.64-1.09)	NS
ACS	0.9%	0.9%	0%	1.00 (0.64-1.55)	NS
Stroke	1.3%	1.5%	0.2%	0.89 (0.63-1.25)	NS
HF	1.3%	2.1%	0.8%	0.62 (0.45-0.84)	125
Death from CV cause	0.8%	1.4%	0.6%	0.57 (0.38-0.85)	167
Death from any cause	3.3%	4.5%	1.2%	0.73 (0.60-0.90)	83
Primary outcome or death	7.1%	9.0%	1.9%	0.78 (0.67-0.90)	53

ARR, absolute risk reduction; NNT, number needed to treat; NS, not significant; HR, hazard ratio

- The intensive treatment arm experienced higher rates of serious AE related to the treatment; resulting in a NNH of 45 for 3.3 years.
  - Serious AE were defined as an event that was fatal or life threatening, resulted in significant or persistent disability, required or prolonged 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.
- Serious AE of hypotension, syncope, electrolyte abnormalities and acute renal failure all occurred significantly more frequently in the intensive treatment arm.

Table 10: Safety Results of SPRINT[15]

Adverse Events	SBP Target		ARI (ARR)	HR (p value)	NNH for 3.3 years
	< 120	< 140			
Serious Adverse Events (AE)					
Serious AE related to the intervention	**4.7%**	**2.5%**	**2.2%**	**1.88 (0.001)**	**45**
Total serious AE	38.3%	37.1%	1.2%	1.04 (0.25)	NS
Serious hypotension	2.4%	1.4%	1.0%	1.67 (0.001)	100
Serious syncope	2.3%	1.7%	0.6%	1.33 (0.05)	167
Serious acute renal failure	4.1%	2.5%	1.6%	1.66 (0.001)	63
Serious electrolyte abnormality	3.1%	2.3%	0.8%	1.35 (0.02)	125
Serious injurious falls	2.2%	2.3%	0.1%	0.95 (0.71)	NS
Adverse Lab Measures					
Hyponatremia (<130 mmol/L)	3.8%	2.1%	1.7%	1.76 (0.001)	59
Hypernatremia (>150 mmol/L)	0.1%	0%	0.1%	-	-
Hypokalemia (<3 mmol/L)	2.4%	1.6%	0.8%	1.50 (0.006)	125
Orthostatic hypotension					
With dizziness	1.3%	1.5%	(0.2%)	0.85 (0.35)	NS

ARI, absolute risk increase; NNH, number needed to harm; HR, hazard ratio

Points to Consider About SPRINT

- SPRINT included a select population with a mean Framingham risk of ~20% over 10 years with relatively few comorbidities.
  - SPRINT excluded patients living in nursing homes, patients with dementia, patients with certain co-morbidities common in the elderly, and patients with a standing SBP < 110 mmHg. The results of SPRINT may not be generalizable to hypertensive patients that were excluded from the trial.
  - A 2016 cross-sectional population based study found that approximately 8% of the general adult population and 17% of treated hypertensive adults in the United States meet the inclusion criteria for SPRINT. [16]
- The majority of patients in SPRINT were already receiving treatment with antihypertensives.
  - Patients were **not** newly diagnosed at study entry; patients in the standard treatment arm had therapies removed, if needed, in order to achieve targets at the start of the study.
  - Additionally, during the study patients had treatment removed in the standard treatment group if the SBP measured < 135 mmHg.
  - Patients unwilling or unable to adhere to multiple medications, or with a standing SBP < 110 mmHg, or with known secondary causes of hypertension were excluded from the trial.
- The trial was stopped early which impacts the evaluation of long term safety and efficacy.
  - Stopping the trial early for benefit adds risk of bias in favor of the lower BP target. This may exaggerate the benefits and underestimate the harms.
- An open label trial design was used. This was necessary in order to know which target group participants were in and make treatment adjustments. However, bias may have been introduced into SPRINT as a result of this design.
- The observed mean BP difference between the two groups was 15/7 mmHg. This is higher than would be expected with 1 antihypertensive, which was the average difference in the number of medications used in the two treatment arms (mean 2.8 in the intensive target arm vs. 1.8 in the standard target arm).
  - Several Cochrane Reviews have found the average SBP reduction produced with a single antihypertensive is in the range of 4 to 10 mmHg, depending on drug and dose.[17,18,19,20]
- In the controlled environment of a clinical trial more patients in the intensive treatment arm experienced serious AE related to the treatment.
  - It is expected that the rate of serious AE would be even higher in actual clinical practice.
- The BP measurements were obtained using an AOBP system where measurements were made after 5 minutes of quiet rest and most patients were left unattended.
  - Results may not apply if BP is measured by different methods or with different devices.

- A post-hoc analysis of the SPRINT trial reported that BP measurements varied somewhat across sites.[21] In 70% of study sites patients were left unattended at some point during BP measurement and in 30% of study sites patients were never unattended during BP measurements.[21]
  - Differences in BP measurements across study sites did not result in differences in outcomes.[21]

- The mean SBP in the intensive arm was 121 mmHg.
  - More than half the participants in the intensive treatment arm had BP measurements above target suggesting that achieving the < 120 mmHg target may be difficult for many patients.
- The study design of SPRINT does not determine if there is an intermediate SBP where a protective effect is seen. For example other BP targets, such as < 130 mmHg, may offer similar benefits as seen in SPRINT.
  - There are several ongoing trials which explore the protective effects of different BP targets. For example the Optimal Blood Pressure and Cholesterol Targets for Preventing Recurrent Stroke in Hypertensive (ESH-CHL-SHOT) trial will evaluate targets < 145-135 mmHg, < 135-125 mmHg and < 125 mmHg.
- Questions SPRINT does not answer:
  - Does the lower target apply to all patients with a high risk of CV disease?
  - Does the lower target apply to patients with an intermediate CV risk?
  - Will the benefit continue in the long term?
  - What are the risks in the long term?
  - Does choice of antihypertensive matter?
  - Does a SBP target somewhere between < 120 mmHg and < 140 mmHg have similar benefit (i.e. <1 30 mmHg)?
  - Should antihypertensive therapy be started in untreated high risk patients with a SBP ≥ 130 mmHg as recommended in the Hypertension Canada Guidelines?

Question 2a: What is the evidence for lower BP targets in patients with established CV disease?

- People with a history of CV disease are considered a high risk population. However, relatively few trials have assessed the optimal blood pressure targets exclusively in patients with established CV disease, rather this population usually represents a portion of the overall study population.
  - For example, in the SPRINT trial 16.7% of the study population had clinical CV disease.
    - The breakdown of the types of CV disease were not provided in the SPRINT analysis; a history of stroke was an exclusion criteria.
- Therefore, at present the optimal BP target for reducing morbidity and mortality in people with hypertension and a history of CV disease has not been clearly established.

- A 2018 Cochrane Review (Saiz et al.) assessed if a lower BP targets should be recommended in patients with established CV disease (MI, angina, stroke, or peripheral vascular occlusive disease). [22]
  - The review assessed if lower BP targets (≤ 135/85 mmHg) are associated with better outcomes compared to standard BP targets (≤ 140 - 160/90 -100 mmHg).
    - The review included 6 open label RCTs (N=9,484 subjects) including SPRINT patients with established CV disease. Four studies compared SBP targets, one compared DBP targets, and one compared mean BP targets.
    - BP targets at 1 year were achieved by 66% in the lower target group and 74% in the standard target group. At 1 year, the mean SBP was 9.5 mmHg lower and the mean DBP was 4.93 mmHg lower in the lower target group vs. the standard target group.
    - Patients were treated with commonly used antihypertensive medications. The average number of antihypertensives in the standard BP group was 1.9 and 2.4 in the lower BP target group.
  - The primary outcomes were:
    - Total mortality
    - Total AE
    - Total CV events including MI, stroke, sudden death, hospitalization or death from HF and other significant vascular events such as ruptured aneurysms.
    - CV mortality
  - There were no differences in total mortality, CV morality, total CV events, or serious AE.

Table 11: Results of Lower vs. Standard Targets in Patients with Hypertension and a History of CV Disease[22]

Outcome	Event Rate		ARR (ARI)	RRR (RRI)	NNT for 3.7 years		Quality of evidence (GRADE)
	Lower target	Standard target			NNT	95% CI	
Total mortality	7.10%	6.80%	(0.3%)	(4.4%)	NS	-	Moderate
CV mortality	3%	3.2%	0.2%	4%	NS	-	Moderate
Total CV events	10.7%	12.3%	1.6%	13%	NS	-	Low
Serious AE	18.6%	18.9%	0.3%	1.6%	NS	-	Low

- ARR, absolute risk reduction; ARI, absolute risk increase; RRR, relative risk reduction; RRI, relative risk increase; NNT, number needed to treat
- Inclusion criteria: participants ≥ 18 years with hypertension or receiving treatment for hypertension with a positive CV history of MI, stroke (not including TIA), chronic peripheral vascular occlusive disease or angina pectoris.
- Mean age was 57 – 71 years, all studies included more men than women, ethnicity varied across trials
- The mean follow up duration was 3.7 years (1 – 4.7 years)

- The conclusion of the review was that there is insufficient evidence to support lower BP targets in patients with established CV disease.

Question 2b: Is there evidence for the < 120 mmHg blood pressure target in patients with diabetes, history of a previous stroke, or the very frail elderly?

An evaluation of evidence from meta-analyses of RCTs that address these specific clinical groups are reported below.

1. Patients with Diabetes Mellitus

A 2013 Cochrane Review (Arguedas et al.) evaluated if lower BP targets (any target < 130/85 mmHg) are associated with a reduction in mortality and morbidity compared with standard targets in people with diabetes.[23]

- Five open label RCTs including 7,362 patients with a mean follow up of 4.5 years were included in the review.
  - One trial (ACCORD) compared outcomes associated with a lower SBP target of < 120 mmHg to a standard SBP target of < 140 mmHg in 4,734 patients with type II diabetes.
  - The four remaining trials (N=2,580) compared outcomes associated with a lower DBP target to a standard DBP target in patients with type II diabetes.
- In the ACCORD trial, the lower target group achieved a mean BP of 119.3/64.4 mmHg which was significantly lower than the mean achieved BP of 133.5/70.5 mmHg in the standard target treatment arm.
  - There were no differences between treatment groups for the primary outcome of total mortality, CV mortality, non-CV mortality, MI, HF, or ESRD.
  - For the secondary outcome of stroke there was an ARR of 1.1% in favor of the lower treatment arm (NNT = 91 for 4.7 years) [RR 0.58; 95% CI 0.39 to 0.88, p=0.009].
  - The lower target treatment arm received more antihypertensive medications in order to achieve the lower BP.
  - There was a significant increase in the number of serious AE attributed to BP medications resulting in an ARI of 2% (NNT = 50 for 4.7 years) [RR 2.58; 95% CI 1.70 to 3.91, p<0.0001].
- In the four DBP target studies, participants in the lower DBP arm had a significantly lower mean BP compared to participants in the standard arm (128/76 mmHg vs. 135/83 mmHg, p < 0.0001).
  - There was a trend towards reduction in total mortality in the group assigned to the lower DBP target (RR 0.73, 95% CI 0.53 to 1.01, p=0.05).
  - There was no difference in CV mortality, non-CV mortality, stroke, MI or HF. ESRD and total serious adverse events were not reported in any of the trials.
- The review concluded that "evidence from randomized trials does not support blood pressure targets lower than the standard targets in people with elevated BP and diabetes".

2. Patients with Prior Stroke

A 2018 Cochrane Review (Zonneveld et al.) investigated if BP lowering drugs (started at least 48 hours after a stroke or TIA) were effective for the prevention of recurrent stroke or major vascular events.[24]

- The review included 11 RCTs (N=38,742) of adult patients with an ischemic stroke, hemorrhagic stroke or TIA. Three of the studies (N=3,632) compared intensive BP lowering to standard BP lowering.
  - Study duration ranged from 12 months to 44 months. The median time from event to inclusion in the study ranged from 62 days to 4.5 months.
  - There were different BP targets in the individual trials; < 130 mmHg vs. 130-140 mmHg in one trial; < 130 mmHg or a reduction of 10 mmHg if SBP was between 125 mmHg and 140 mmHg at randomization vs. 140 mmHg in one trial; < 125 mmHg vs 140 mmHg in one trial.
    - There were no differences between treatment arms for recurrent stroke (any type) or major vascular events (composite of non-fatal stroke, non-fatal MI, or death from vascular cause) when intensive vs. standard BP lowering targets were compared.
    - There were no differences between treatment arms for other outcome comparisons including time to recurrent stroke, ischemic stroke, hemorrhagic stroke, MI, vascular death, or all cause death.
- The review concluded that the optimal BP target in this patient population is unknown since there were no differences in outcomes between lower targets compared to standard targets.

3. Very Frail Elderly Patients

A 2017 systematic review and meta-analysis (Weiss et al.) evaluated the benefits and harms of intensive BP treatment in adults aged 60 years and older.[25] This review included an evaluation of the evidence for frail elderly patients.[25]

- It was identified that most studies in elderly patients explicitly exclude patients with dementia and/or diminished functional status. **Post-hoc subgroup analyses** from 2 RCTs (SPRINT and HYVET) were identified that considered patients with frailty.
  - This SPRINT analysis was a small subgroup of the total SPRINT population, was not pre-specified, and was possibly underpowered.
    - 8.7% of the SPRINT population were deemed frail. The intensive arm of this group achieved a mean SBP of 124.3 mmHg (95% CI 123.5-125 mmHg) compared to 135 (95% CI 134.2-135.8 mmHg) in the standard arm.[26] There was no statistically significant difference in the primary outcome between the target arms in the subgroup of frail elderly patients; HR 0.68 (95% CI 0.45-1.01)(p=0.06).[26]
    - **Note**: SPRINT excluded patients living in nursing homes, patients with dementia, patients with certain co-morbidities common in the elderly, and patients with a

standing SBP < 110 mmHg. This exclusion criteria means that a substantial subset of frail patients were not included in the trial.

- The Hypertension in the Very Elderly Trial (HYVET) was a double blind, placebo controlled study of antihypertensives in people with hypertension aged 80 years and over. This study compared the treatment with antihypertensives to placebo in individuals ≥ 80 years of age. This was not a BP target study.
  - A post-hoc secondary analysis established a frailty index for all available HYVET participants and evaluated the effects of antihypertensives on frail elderly people over 22-23 months.[27]
  - Both frailer and fitter older adults appeared to gain from the treatment of hypertension for fatal and non-fatal stroke and CV events, but not total mortality.[27]
  - **Note:** A large amount of data was missing for this comparison (N=3,845 in full trial vs. N=2,656 in secondary assessment) so must be interpreted with caution.
  - This analysis evaluated the effects of treatment with antihypertensives but did not evaluate different treatment targets.

- Weiss et al. determined there is insufficient evidence to draw any conclusions for treatment targets in frail elderly patients.[25]

What about in patients with intermediate cardiovascular risk?
Details of the HOPE-3 BP Study[28]

- The Heart Outcomes Prevention Evaluation trial, a 2x2 factorial double-blind RCT, evaluated the impact of BP lowering, lipid lowering or the combination of the two in reducing major CV events in patients with intermediate CV risk (defined as a 1% annual risk of a CV event).
  - Results of the BP lowering and lipid lowering were reported separately.
  - The results of the BP study are summarized here.
- N= 12,705; median duration 5.6 years; double blind study, multinational
- Included patients were:
  - Women ≥ 65 years and men ≥ 55 years with 1 or more CV risk factors OR women 60-64 with ≥ 2 risk factors (listed below):
    - Waist/hip ratio ≥ 0.85 (women) or ≥ 0.90 (men)
    - Smoker or recent ex-smoker (last 5 years)
    - HDL-C < 1.3 mmol/L (women) or < 1.0 mmol/L (men)
    - Dysglycemia (e.g. uncomplicated diet controlled diabetes)
    - Early renal dysfunction (eGFR < 60, Cr > 1.4mg/dL, microalbuminuria)
    - Family history of early CHD (M < 55y, F < 65y)

- At baseline
  - Demographics: mean age 66 years, female sex 46%, racially and ethnically diverse
  - CV risk factors: Elevated waist:hip 87%, recent/current smoking 28%, low HDL 38%; 38% reported history of hypertension with 21% taking antihypertensives (other than ARBs, ACE-I or thiazides).
  - Mean BP 138.1/81.9 mmHg (both treatment arms)
- Following a run-in phase where all patients received active drug to ensure adherence and tolerability patients were randomized to receive
  - Candesartan 16mg/hydrochlorothiazide 12.5mg daily (N=6,356) OR placebo (N=6,349)
  - Drug doses were fixed and not titrated to specific targets throughout the trial
  - Participants also received individualized structured lifestyle advice
- Achieved BP was
  - Treatment group: 128.2/76.3 mmHg (mean)
  - Placebo group: 133.9/79.1 mmHg (mean)
- Co-primary Outcomes:
  - Composite of CV death, MI, stroke
  - Above outcome, plus resuscitated cardiac arrest, HF, revascularization
- Results
  - There were no statistically significant differences between the two groups for either primary outcome.
  - There was no statistically significant benefit for any secondary outcomes (i.e. individual components of co-primary outcomes, HF, revascularization, angina with objective evidence of ischemia, hospitalization for CV causes, new diagnosis of diabetes, or all-cause mortality).
- Adverse Events
  - Discontinuation rates: 24.4% vs. 25.2% (p=NS)
  - Symptomatic hypotension, lightheadedness and dizziness: 3.4% vs. 2.1% ($p<0.001$); however, there were no significant differences in syncope.
  - Renal dysfunction: 0.5% vs. 0.3% (p=0.13)
- Conclusion
  - In patients with intermediate CV risk and a baseline BP close to 140/80 mmHg, treating with a combination of antihypertensives to a mean BP of less than 130/80 mmHg does not have an impact on any clinical outcomes (all-cause mortality, CV mortality, fatal or non-fatal MI, fatal or non-fatal stroke HF, revascularization, angina with evidence of ischemia, etc.).

Antihypertensive Drug Therapy Tidbit: Thiazide-Type vs. Thiazide-Like Diuretics

Recently, a stronger distinction has been made between thiazide or thiazide-type (TT) diuretics and thiazide-like (TL) diuretics.[1]

Thiazides or Thiazide-Type (TT) Diuretics	Thiazide-Like (TL) Diuretics
shorter-acting	longer-acting
hydrochlorothiazide	chlorthalidone and indapamide

Since 2017 Hypertension Canada has given preference to the longer-acting TL diuretics for adults *without compelling indications* with diastolic hypertension +/- systolic hypertension.[1,2]

Hypertension Canada's 2018 guidelines for choice of therapy for adults with hypertension *without compelling indications* with diastolic hypertension with or without systolic hypertension:[2]

Initial therapy should be with either monotherapy or single pill combination.
Recommended monotherapy choices are:
a. A **thiazide/thiazide-like diuretic** (Grade A) with **longer-acting diuretics preferred** (Grade B);
b. A *B*-blocker (in patients younger than 60 years; Grade B);
c. An ACE inhibitor (in nonblack patients; Grade B);
d. An ARB (Grade B); or
e. A long-acting calcium channel blocker (CCB) (Grade B).

Should thiazide-like diuretics be preferred?

Summary Statements:

- No RCT has directly compared TT and TL diuretics for CV outcomes and currently available evidence has several important limitations.
- As for safety, a 2014 Cochrane Review found chlorthalidone had a greater reduction in serum potassium than hydrochlorothiazide or indapamide.
  - Monitor electrolytes, especially in the first 2 weeks after starting TT or TL diuretics and after dose changes.
- The observational evidence investigating the possible association between hydrochlorothiazide use and increased risk of non-melanoma skin cancer (NMSC) has several significant limitations.
- Hydrochlorothiazide is **not** the only antihypertensive agent associated with photosensitivity reactions.
  - Well-designed studies are needed to investigate hydrochlorothiazide, other diuretics, and other antihypertensive drugs and possible associations with NMSC.
- Patients should be educated on sun safety and be advised to regularly check their skin for new or changing marks or growths, especially patients taking medications associated with photosensitivity, such as hydrochlorothiazide.
- The Veterans Affairs Cooperative Study #597 Diuretic Comparison Project to be published in 2023, may provide more guidance on diuretic preference.

TT vs TL Diuretics for Cardiovascular Outcomes

- No RCT has directly compared TT vs TL diuretics for CV outcomes.
- The biggest meta-analysis on the topic included 21 trials, with >480,000 patient-years of data and was referenced by Hypertension Canada guidelines.[1,3]
  - The meta-analysis authors suggest, "in contrast to TT diuretics, treatment with TL diuretics also resulted in a significant reduction of coronary events and all-cause mortality".[3]
  - Meta-analysis results:

	TT vs. placebo RR (95% CI)	**TL vs. placebo** RR (95% CI)
Cardiovascular Events	**0.67 (0.56-0.81)**	**0.67 (0.60-0.75)**
Coronary Events	0.81 (0.63-1.05)	**0.76 (0.61-0.96)**
Cerebrovascular Events	**0.52 (0.38-0.69)**	**0.68 (0.57-0.80)**
Heart Failure	**0.36 (0.16-0.84)**	**0.47 (0.36-0.61)**
Mortality	0.86 (0.75-1.00)	**0.84 (0.74-0.96)**

Very similar point estimates and 95% CI between groups for all outcomes

  - **Is there really a difference?** It is uncertain. Limitations to this meta-analysis include:
    - Patients in TL trials were older (mean age 68 vs. 60 years).
    - All TL trials used low-doses, whereas most of the TT trials used high-doses. (This is an important difference. A 2018 Cochrane Review evaluated high-doses of TT and TL diuretics vs. placebo and low-doses of TT and TL diuretics vs. placebo. They found that low-doses reduced the risk of mortality and coronary heart disease, and high-doses did not.) [4]
    - TT trials used a mix of drugs, several which are not available in Canada.
    - No TT vs. TL statistical analysis was completed
- A 2013 Canadian retrospective cohort study of 29,873 patients ≥66 years of age followed for up to 5 years found no difference in CV outcomes (death or hospitalization for MI, stroke and HF) between patients who were newly treated with chlorthalidone vs. hydrochlorothiazide.[5]
  - Study limitations include: Observational design, short follow-up, and sample size may have been too small to detect a difference.
- **Bottom Line:** No RCT has directly compared TT and TL diuretics for CV outcomes. Currently available evidence has several important limitations.

TT vs TL Diuretics and Risk of Hypokalemia or Hyponatremia

- TT and TL diuretics can cause electrolyte abnormalities, but is one worse than the other?
- A 2017 meta-analysis found no statistically significant difference in the incidence of hypokalemia or hyponatremia between TT and TL diuretics.[6]
  - Other studies which have compared individual agents have varying results.[5,7,8,9]

- A 2014 Cochrane Review found a greater reduction in serum potassium with chlorthalidone than hydrochlorothiazide or indapamide.[7] Another meta-analysis found no difference between hydrochlorothiazide and indapamide.[8]
- The 2013 Canadian cohort study found an increased incidence of hospitalization with hypokalemia (HR $_{adjusted}$ = 3.06; 95% CI, 2.04-4.58) or hyponatremia (HR $_{adjusted}$ = 1.68; 95% CI, 1.24–2.28) in those using chlorthalidone vs. hydrochlorothiazide.[5]
- Differences in potency across the class and use of higher doses in the past make determining differences in the risk of hypokalemia and hyponatremia difficult.[6,9] Some researchers have tried to account for these barriers in their research.[9]
- **Bottom-line:** MONITOR electrolytes, especially in the first 2 weeks after starting TT or TL diuretics and after dose changes.[10]

Hydrochlorothiazide and Risk of Non-Melanoma Skin Cancer

- Exposure to drugs that increase skin sensitivity to light is an important risk factor for non-melanoma skin cancer (NMSC).[11]
  - Hydrochlorothiazide has long been known to increase skin sensitivity to light.[11]
  - Chlorthalidone, indapamide and other antihypertensives including some ACEi, CCBs and *B*-blockers are also associated with photosensitivity.[12]
- Health Canada conducted a review on the association between hydrochlorothiazide and risk of NMSC. They concluded that prolonged use (≥ 3 years) of hydrochlorothiazide may increase risk of NMSC.[11]
- Health Canada suggests patients taking hydrochlorothiazide should…
  - Be informed of the potential risk of NMSC.[11]
  - Be advised to regularly check their skin for new or changing marks or growths, and report anything suspicious to their healthcare professional.[11]
  - Limit exposure to sunlight, avoid using tanning equipment, and use adequate sun protection (e.g., SPF 30 or higher, clothing, and a hat) to minimize risk.[11]
  - Alternatives may be considered for those at particularly high risk.[11]
    - Health Canada does not provide guidance on alternative drug selection.
- Limitations to the available evidence:

  - Only observational studies exist.[12,13]
  - Lack of data and adjustment for NMSC risk factors (e.g., sun exposure, skin color, and family history of skin cancer).[13]
  - High heterogeneity between studies, and likely publication bias.[13]
  - There is limited evidence assessing risk associated with other diuretics.[13]
    - A Canadian report concluded that "switching from hydrochlorothiazide to other diuretics, such as chlorthalidone is not supported by either pharmacological or epidemiological data." [12]

- **Bottom Line:** Well-designed studies are needed to understand associations between NMSC and hydrochlorothiazide, other diuretics, and other antihypertensives. Patients should be educated on sun safety and be advised to regularly check their skin for new/changing marks or growths.

Cost Comparison: hydrochlorothiazide < chlorthalidone < indapamide (see Appendix 1)

Combos Available: Few single pill combinations contain TL diuretics (see Appendix 1)

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HYPERTENSIVE DISORDERS OF PREGNANCY

Summary Statements:

- Hypertensive disorders of pregnancy (HDP) occur in about 7% of pregnancies in Canada and 10% of pregnancies worldwide.
- HDP encompass a range of conditions: chronic hypertension (detected prior to pregnancy or at <20 weeks gestation), gestational hypertension (detected at ≥20 weeks gestation), preeclampsia and other hypertensive effects, which can cause fetal, newborn, and maternal complications.
- Hypertension in pregnancy is defined as a systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg (average of at least 2 measurements taken at least 15 minutes apart).
- Hypertension can be further classified as severe or non-severe hypertension.
    - Non-severe hypertension:
        - Blood pressure (BP) between 140/90 mmHg and <160/110 mmHg.
    - Severe hypertension:
        - SBP of ≥160 mmHg or a DBP of ≥110 mmHg.
            - This threshold has been established based on its association with increased risk of maternal stroke.
- BP measurement devices that have been validated for use in pregnancy and preeclampsia should be used to measure BP in pregnant women.
- The SOGC have most recently published guidelines on the diagnosis, evaluation and management of HDP in 2014, and Hypertension Canada in partnership with the SOGC published their first guideline for the management of hypertension in pregnancy in 2018.
- The Reproductive Care Program of Nova Scotia is currently updating the Nova Scotia Prenatal Record, and the Nova Scotia Prenatal Record Companion Document.
- Unfortunately, many Nova Scotians do not have a family doctor. Pregnant women without a family doctor can call their local Prenatal Clinic to make an appointment. A list of available clinics across Nova Scotia is available here: http://www.nshealth.ca/service-details/Prenatal%20Clinics.

Question 1: Which antihypertensive medications should be avoided in pregnancy?

- Consideration should be given to the risk of teratogenicity when prescribing antihypertensive medications to women of child-bearing age, since 50% of pregnancies are not planned.

- ACEi, ARBs, direct renin inhibitors, atenolol, and spironolactone should be avoided in pregnancy.

Question 2: What is the role of ASA in preventing preeclampsia?

- A 2018 meta-analysis by Roberge et al. found a significant reduction in the risk of preterm preeclampsia in high risk patients who started ASA therapy compared to placebo at ≤16 weeks gestation and at a daily dose of ≥100 mg.
    - There was no significant difference between ASA and placebo groups when ASA was started at >16 weeks gestation or at a daily dose of <100 mg.
- The largest trial assessing ASA at a daily dose of ≥100 mg initiated at ≤16 weeks gestation was the ASPRE trial. ASPRE found that ASA 150 mg once daily at night started at 11-14 weeks gestation and continued until 36 weeks gestation reduced the risk of preterm preeclampsia compared to placebo in women at high risk (NNT = 38, 95% CI 23-101).
- The Reproductive Care Program of Nova Scotia Recommends:
  In pregnant women at high risk for developing pre-eclampsia (see Table 10), initiating ASA 150 mg (or in its absence, 2 x 81 mg tablets = 162 mg) once daily at bedtime reduces the risk of preeclampsia.
    - ASA should be:
        - initiated between 11-16 weeks gestation (ideally between 11-14 weeks), and
        - continued until 36 weeks gestation.

Question 3: What is the role of calcium supplementation in preventing preeclampsia?

- A 2018 Cochrane Review identified that supplementation with ≥1 g/day of elemental calcium in pregnant women with low dietary calcium intake reduces the risk of preeclampsia.
- The Reproductive Care Program of Nova Scotia Recommends: Calcium supplementation with ≥ 1 g of elemental calcium/day in those with low calcium intake to prevent preeclampsia.

Question 4: How should antihypertensive agents be managed in HDP?

The management of some of the HDP are outside of the scope of this review, the focus of this section is treatment of <u>non-severe hypertension in pregnancy without comorbid conditions.</u>

Question 4a: What is the evidence for treating non-severe hypertension in pregnancy without comorbidities?

Question 4b: Is one drug or class of drug better than another for treating non-severe hypertension in pregnancy without comorbid conditions?

- A 2018 Cochrane Review found that use of antihypertensive drug therapy in women with mild to moderate hypertension in pregnancy, without co-morbidities (e.g., diabetes or renal disease), significantly reduced the risk of severe hypertension compared to no antihypertensive drug therapy (NNT = 10, 95% CI 8-13).
    - *B*-blockers or calcium channel blockers were more effective than methyldopa in avoiding an episode of severe hypertension.
        - RR = 0.70 (95% CI, 0.56-0.88)
- According to local clinical reviewer opinion, the preferred first line antihypertensive agents in this patient population are oral labetalol or nifedipine XL.

Question 4c: What is the evidence for the 2018 Hypertension Canada treatment target of a "DBP of 85 mmHg for pregnant women receiving antihypertensive therapy with chronic hypertension or gestational hypertension"?

- The SOGC 2014 guidelines recommend that antihypertensive drug therapy may be used to keep SBP at 130–155 mmHg and DBP at 80–105 mmHg (I-B; Low/Weak).
- According to Hypertension Canada 2018 guidelines, a DBP of 85 mmHg should be targeted for pregnant women receiving antihypertensive therapy with chronic hypertension or gestational hypertension (Grade B). A similar target could be considered for pregnant women with preeclampsia (Grade D).
- This difference in BP treatment targets is based on results of the CHIPS trial, a recent RCT:
    - The CHIPS trial compared less-tight control [target DBP = 100 mmHg (100-104 mmHg)] vs. tight control [target DBP = 85 mmHg (81-85 mmHg)] of hypertension in pregnant women with non-severe nonproteinuric pre-existing hypertension or gestational hypertension.
    - **Academic Detailing Note:**
        - **CHIPS compared the upper end vs the lower end of the SOGC target DBP range of 80-105 mmHg**.
    - According to the trial protocol, CHIPS investigators hypothesized that less tight control may improve uteroplacental perfusion, fetal growth, and through these fetal/neonatal well-being.
    - They actually found no significant difference in the risk of the composite outcome of pregnancy loss or high-level neonatal care for more than 48 hours (the primary outcome) between less-tight and tight control groups.
    - However, there was a significantly higher risk of developing severe hypertension in the less-tight control group (target DBP = 100 mmHg) compared to the tight control group (target DBP = 85 mmHg) (NNH = 8, 95% CI 5-14).

- Study may have been underpowered and we must interpret results with caution.

- The CHIPS trial provides some reassurance that treating non-severe hypertension in pregnancy in patients without comorbid conditions to the lower end of the current SOGC target DBP range, may be safer than previously thought, and is associated with a lower risk of developing severe hypertension. However, caution must be exercised to ensure DBP does not fall to <80 mmHg as this may limit uteroplacental perfusion.

Question 5: According to guidelines and local clinical reviewers, which women at risk, or who have developed a HDP should obstetrics be consulted?

- According to the Reproductive Care Program of Nova Scotia, consultation with an obstetrician should be considered:
  - For women with a history of previous preeclampsia or other strong clinical markers of increased risk, especially multifetal pregnancy, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease (antiphospholipid syndrome, systemic lupus erythematosus). Women with multiple other risk factors for preeclampsia should also be considered for consultation. See Table 10 and Appendix 3.
  - For any pregnant woman **diagnosed with a HDP.**

Question 6: How should antihypertensive agents be managed postpartum?

- The time of peak BP postpartum is at 3 to 6 days after delivery, and BP should be monitored during this time.
- There is very limited evidence to guide the management of HDP postpartum. Authors of a recent systematic review of 39 studies (N = 2901) were unable to recommend a particular BP threshold, agent, or model of care.
  - There is very little evidence to guide the management of antihypertensive drugs in the weeks after delivery.
- All medications should be assessed for safety in breastfeeding (see lactation drug information resources in Table 8).
- The SOGC 2014 guidelines suggest nifedipine XL, labetalol, methyldopa, captopril, and enalapril to be generally acceptable for use in breastfeeding.
  - Although it is considered safe during breastfeeding, **methyldopa may increase risk of postpartum depression.** The National Institute for Health and Care Excellence (NICE) recommends to consider switching to an alternative therapy within 2 days of delivery.

Background:

- Hypertensive disorders of pregnancy (HDP) occur in about 7% of pregnancies in Canada and 10% of pregnancies worldwide.[1,2]
  - 1% having pre-existing hypertension [3]
  - 5-6% having gestational hypertension [3]
  - 1-2% having preeclampsia [3]
- Rates of HDP are expected to rise due to an increase in the proportion of older, obese, and medically complex patients in the obstetric population.[3]
- HDP can cause fetal, newborn and maternal complications.
  - Fetal and newborn complications include: fetal growth restriction, preterm delivery, and fetal and neonatal morbidity and mortality.[1]
  - Maternal complications include: pulmonary edema, kidney injury, and stroke.[2]
  - Even after the pregnancy, HDP can increase the woman's risk of later developing hypertension, type 2 diabetes, obesity, CKD, CV disease, and cardiac death; with the risk of CV disease increasing with increasing severity of HDP.[1]
- Guidelines:
  - The Society of Obstetricians and Gynaecologists of Canada (SOGC) most recently updated their guideline on the diagnosis, evaluation and management of HDP in 2014.[3]
  - In 2018, Hypertension Canada in partnership with the SOGC, published their first guideline for the management of hypertension in pregnancy.[1]
    - The systems for rating evidence and the strength of recommendations from the SOGC and Hypertension Canada Guidelines are available in Appendix 2.
  - American and international groups have also recently published guidelines on the topic.[4,5,6]
- **The Reproductive Care Program of Nova Scotia is currently updating the Nova Scotia Prenatal Record**, and the Nova Scotia Prenatal Record Companion Document.[7] The update is anticipated to be published in 2020.
  - The Companion Document is a detailed guide and reference for prenatal care providers using the Nova Scotia Prenatal Record. It includes instructions on assembly of the prenatal record, a glossary of terms related to pregnancy and prenatal care, details on completing each section of the record, guidelines for antenatal screening, and related resources. The Prenatal Record and Companion Document are available online at: http://rcp.nshealth.ca/ .
- Unfortunately, many Nova Scotians do not have a family doctor. Pregnant women without a family doctor can call their local Prenatal Clinic to make an appointment. A list of available clinics across Nova Scotia is available here: http://www.nshealth.ca/service-details/Prenatal%20Clinics.

Classification of HDP:

- Hypertension in pregnancy is defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg (average of at least 2 measurements taken at least 15 minutes apart).[1]
- HDP encompass a range of conditions: chronic (pre-existing or pre-pregnancy) hypertension, gestational hypertension, preeclampsia and other hypertensive effects.[3]

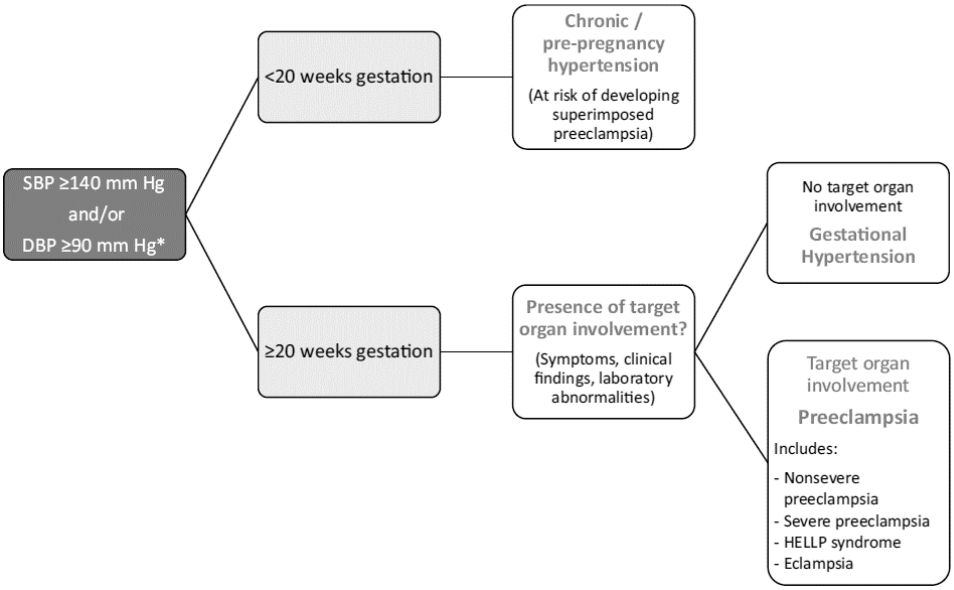

*Figure 1. Simplified Classification of Hypertensive Disorders of Pregnancy. Reprinted from Canadian Journal of Cardiology 34 (2018), Butalia S et al for Hypertension Canada, "Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy" 526-531. Copyright 2018 with permission from Elsevier. DBP, diastolic blood pressure; HELLP, hemolysis elevated liver enzymes and low platelets; SBP, systolic blood pressure. *Rule out white coat hypertension and transient hypertension.*

- Hypertension can be further classified as **severe** or **non-severe hypertension**.
    - Non-severe hypertension:
        - Blood pressure (BP) between 140/90 mmHg and < 160/110 mmHg ^.[1,3]
    - Severe hypertension:
        - SBP of ≥ 160 mmHg or a DBP of ≥ 110 mmHg ^.[1,3]

^ Based on the average of ***at least*** two measurements, taken at least 15 minutes apart, using the same arm.[1,3]

- A **BP of ≥ 160/110 mmHg is associated with an increased risk of maternal stroke**; therefore, it is used as the threshold for severe hypertension.[1]

Table 1. Classification of the HDP, According to the SOGC 2014 Guideline:[3]

Pre-existing (chronic) hypertension	This is defined as hypertension that was present either pre-pregnancy or that develops at < 20^0 weeks gestation.
• With comorbid condition(s)	Comorbid conditions (e.g., pre-gestational type 1 or 2 diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened CV risk.
• With evidence of preeclampsia	This is also known as 'superimposed preeclampsia' and is defined by the development of one or more of the following at ≥ 20 weeks: • Resistant hypertension *(see Table 4)* • New or worsening proteinuria • One/more adverse condition(s) *(see Table 2)* • One/more severe complication(s) *(see Table 2)* Severe preeclampsia is defined as preeclampsia with one or more severe complication(s).
Gestational hypertension	This is defined as hypertension that develops for the first time at ≥20^0 weeks gestation.
• With comorbid condition(s)	Comorbid conditions (e.g., pregestational type 1 or 2 diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened cardiovascular risk.
• With evidence of preeclampsia	Evidence of preeclampsia may appear many weeks after the onset of gestational hypertension. Preeclampsia is defined by gestational hypertension and one or more of the following: • New proteinuria • One/more adverse condition(s) *(see Table 2)* • One/more severe complication(s) *(see Table 2)* Severe preeclampsia is defined as preeclampsia with one or more severe complication(s).
Preeclampsia	Preeclampsia may arise de novo. It is defined by gestational hypertension and one or more of the following: • New proteinuria • One/more adverse condition(s) *(see Table 2)* • One/more severe complication(s) *(see Table 2)* Severe preeclampsia is defined as preeclampsia with one or more severe complication(s).
Other hypertensive effects	
Transient hypertensive effect	Elevated BP may be due to environmental stimuli or the pain of labour, for example.
White coat hypertensive effect	BP that is elevated in the office (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) but is consistently normal outside of the office (<135/85 mmHg) by ABPM or HBPM.
Masked hypertensive effect	BP that is consistently normal in the office (SBP < 140 mmHg or DBP < 90 mmHg) but is elevated outside of the office (≥ 135/85 mmHg) by ABPM or repeated HBPM.
ABPM, ambulatory BP monitoring; BP, blood pressure; CV, cardiovascular; DBP, diastolic blood pressure; HBPM, home BP monitoring; SBP, systolic blood pressure.	

- Preeclampsia is a consequence of a mismatch between utero-placental supply and fetal demands, which leads to an exaggerated inflammatory response with maternal and fetal manifestations.[3]
  - The most common maternal manifestations are hypertension and proteinuria.[3]

- Eclampsia is the convulsive manifestation of HDP and is a severe manifestation of the disease. It is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causes.[5]

Table 2. Adverse Conditions and Severe Complications of Preeclampsia, According to the SOGC 2014 Guideline:[3]

Organ System Affected	Adverse Conditions (that increase the risk of severe complications)	Severe Complications (that warrant delivery)
CNS	• Headache/visual symptoms	• Eclampsia • PRES • Cortical blindness or retinal detachment • Glasgow coma scale < 13 • Stroke, TIA, or RIND
Cardiorespiratory	• Chest pain/dyspnea • Oxygen saturation < 97%	• Uncontrolled severe hypertension (over a period of 12hr despite use of three antihypertensive agents), • Oxygen saturation < 90%, need for ≥ 50% oxygen for > 1hr, intubation (other than for Caesarean section), pulmonary edema • Positive inotropic support • Myocardial ischaemia or infarction
Haematological	• Elevated WBC count • Elevated INR or aPTT • Low platelet count	• Platelet count < $50x10^9$/L • Transfusion of any blood product
Renal	• Elevated serum creatinine • Elevated serum uric acid	• Acute kidney injury (creatinine > 150 µM with no prior renal disease) • New indication for dialysis
Hepatic	• Nausea or vomiting • RUQ or epigastric pain • Elevated serum AST, ALT, LDH, or bilirubin • Low plasma albumin	• Hepatic dysfunction (INR > 2 in absence of DIC or warfarin) • Hepatic haematoma or rupture
Feto-placental	• Non-reassuring FHR • IUGR • Oligohydramnios • Absent or reversed end-diastolic flow by Doppler velocimetry	• Abruption with evidence of maternal or fetal compromise • Reverse ductus venosus A wave • Stillbirth

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CNS, central nervous system; DIC, disseminated intravascular coagulation; FHR, fetal heart rate; INR, international normalized ratio; IUGR, intrauterine growth restriction; LDH, lactate dehydrogenase; PRES, posterior reversible leukoencephalopathy syndrome; RIND, reversible ischaemic neurological deficit <48hr; RUQ, right upper quadrant; TIA, transient ischaemic attack; WBC, white blood cell.

Measurement of Blood Pressure in Pregnancy:

- Accurate measurement of BP during pregnancy is important.
  - Inaccurate BP measurement can result in under or overestimation of BP. This could lead to inappropriate treatment decisions, and increase the risk of complications.[8]

- BP measurement in pregnancy should be done using non-pregnancy standardized techniques.[3] See the "Hypertension Canada Guidelines on BP Measurement Techniques" section on Page 20 of this document.

Table 3. SOGC 2014 Guideline Recommendations for Measurement of BP:[3]

Recommendation	Grade
BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP machine that has been validated for use in preeclampsia.	II-2A; Low/Strong
Automated BP machines that have not been validated for use in preeclampsia may under- or over- estimate BP in those women and comparison of readings using mercury sphygmomanometry or a calibrated aneroid device is recommended.	II-2A; Low/Strong
In the office setting, when BP elevation is non-severe and preeclampsia is not suspected, either ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) is useful to confirm persistently elevated BP. • Comment: HBPM is done by the woman using an automated device, with duplicate measurements taken at least twice daily over several days. When HBPM values are normal but office values elevated, ABPM or repeated HBPM are recommended. There is insufficient data in pregnancy to guide choice between HBPM and ABPM.	II-2C; Very low/Weak
When HBPM is used, maternity care providers should ensure that patients have adequate training in measuring their BP and interpreting the readings taken.	III-C; Very low/Strong
The accuracy of all BP measurement devices used in hospitals or offices should be checked regularly against a calibrated device.	II-3C; Very low/Strong
The accuracy of all automated devices used for HBPM should be checked regularly against a calibrated device.	III-C; Very low/Strong

- The physiologic changes that occur in pregnancy may affect the accuracy of automated (oscillometric) BP monitoring devices.[9]
  - For example, decreased arterial vascular compliance and increased interstitial edema in preeclampsia may affect detection of the oscillation pattern by the BP cuff, which can result in underestimation of BP.[9]
- BP measurement devices that have been validated for use in pregnancy and preeclampsia should be used to measure BP in pregnant women.[3,9]
- Lists of approved devices for office and HBPM use, and information regarding machines validated in pregnancy and preeclampsia are available at: http://www.dableducational.org/sphygmomanometers.html and http://www.bhsoc.org/bp-monitors/bp-monitors/.[3]

Diagnosis of Hypertension in Pregnancy:

Table 4. SOGC 2014 Guideline Recommendations for Diagnosis of Hypertension:[3]

Recommendation	Grade
The diagnosis of hypertension should be based on office or in-hospital BP measurements.	II-B; Low/Strong
Hypertension in pregnancy should be defined as an office (or hospital) SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.	II-2B; Low/Weak for SBP and Low/Strong for DBP
'Resistant' hypertension should be defined as the need for three antihypertensive medications for BP control at ≥ 20 weeks gestation.	III-C; Low/Weak
A 'transient' hypertensive effect should be defined as office SBP ≥ 140 mmHg or a DBP ≥ 90 mmHg which is not confirmed after rest, or on repeat measurement on the same or on subsequent visits. • Comments: To exclude transient BP elevations repeat (office or community) BP measurement is recommended. ○ Non-severely elevated BP should be confirmed by repeat measurement, at least 15 min apart at that visit. BP should be measured three times; the first value is disregarded, and the average of the second and third taken as the BP value for the visit. Up to 70% of women with an office BP of ≥ 140/90 mmHg have normal BP on subsequent measurements on the same visit, or by ABPM or HBPM. The timing of reassessment should consider that elevated office BP may reflect a situational BP rise, 'white coat' effect, or early preeclampsia.	II-2B; Very low/Weak
A 'white coat' hypertensive effect refers to BP that is elevated in the office (i.e., SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) but ABPM or HBPM SBP is < 135 mmHg and DBP is < 85 mmHg.	II-2B; Very low/Strong
A 'masked' hypertensive effect refers to BP that is normal in the office (i.e., SBP < 140 mmHg and DBP < 90 mmHg) but elevated by ABPM or HBPM (i.e., SBP ≥ 135 mmHg or DBP ≥ 85 mmHg).	II-2B; Very low/Weak
Severe hypertension should be defined, in any setting, as a SBP of ≥ 160 mmHg or a DBP of ≥ 110 mmHg based on the average of at least two measurements, taken at least 15 minutes apart, using the same arm.	II-2B; Low/Strong

Measurement of Proteinuria in Pregnancy:

- All pregnant women should be assessed for proteinuria, to detect renal disease and screen for preeclampsia.[3]

Table 5. SOCG 2014 Guideline Recommendations on Measurement of Proteinuria:[3]

Recommendation	Grade
All pregnant women should be assessed for proteinuria. • Comment: All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease, and at ≥ 20 weeks to screen for preeclampsia in those at increased risk.	II-2B; Low/Weak
Urinary dipstick testing (by visual or automated testing) may be used for screening for proteinuria when the suspicion of preeclampsia is low.	II-2B; Low/Weak
Significant proteinuria should be defined as ≥ 0.3 g/d in a complete 24-hour urine collection or ≥ 30 mg/mmol urinary creatinine in a spot (random) urine sample.	II-2B; Moderate/Strong
Significant proteinuria should be suspected when urinary dipstick proteinuria is ≥ 1+.	II-2A; Moderate/Strong
More definitive testing for proteinuria (by urinary protein:creatinine ratio or 24 hour urine collection) is encouraged when there is a suspicion of preeclampsia, including: ≥ 1+ dipstick proteinuria, in the setting of hypertension with rising BP, or when BP is normal but women have symptoms or signs suggestive of preeclampsia.	II-2A; Moderate/Strong
Proteinuria testing does not need to be repeated once the significant proteinuria of preeclampsia has been confirmed.	II-2A; Moderate/Strong
There is insufficient information to make a recommendation about the accuracy of the urinary albumin:creatinine ratio.	II-2L; Low/Strong

This section of the review will address 6 questions:

1) Which antihypertensive medications should be avoided in pregnancy?
2) What is the role of ASA in preventing preeclampsia?
3) What is the role of calcium supplementation in preventing preeclampsia?
4) How should antihypertensive agents be managed in HDP?
    a. What is the evidence for treating non-severe hypertension in pregnancy without comorbidities?
    b. Is one drug or class of drug better than another for treating non-severe hypertension in pregnancy without comorbid conditions?
    c. What is the evidence for the 2018 Hypertension Canada treatment target of a DBP of 85 mmHg for pregnant women receiving antihypertensive therapy with chronic hypertension or gestational hypertension?
5) According to guidelines and local clinical reviewers, which women at risk, or who have developed a HDP should obstetrics be consulted?
6) How should antihypertensive agents be managed postpartum?

Question 1: Which antihypertensive medications should be avoided in pregnancy?

Table 6. SOGC 2014 Guideline Recommendations on Aspects of Care Specific to Women with Pre-existing Hypertension:[3]

Recommendation	Grade
Pre-conceptual counselling for women with pre-existing hypertension is recommended.	III-C; Very low/Weak
The following antihypertensive drugs are acceptable for use in the first trimester of pregnancy: methyldopa, labetalol, and nifedipine.	all II-2B; all Low/Weak
ACE inhibitors and ARBs should be discontinued when planning pregnancy or as soon as pregnancy is diagnosed.	II-2D; Low/Weak
Atenolol should be discontinued when pregnancy is diagnosed.	I-D; Low/Weak
Planned changes in antihypertensive agent(s) for care in pregnancy should be made while the woman is planning pregnancy if the woman has uncomplicated preexisting hypertension, or, if in the presence of comorbid conditions, she is likely to conceive easily (within 12 months).	III-L; Very low/Weak

- As 50% of pregnancies are not planned, consideration should be given to the risk of teratogenicity when prescribing antihypertensive medications to women of child-bearing age.[2,3]
- Woman who plan to become pregnant should have all medications assessed for safety in pregnancy as part of pre-conception planning.

Table 7. Common Antihypertensive Medications to Avoid in Pregnancy:

Angiotensin Converting Enzyme inhibitors (ACEi), Angiotensin II Receptor Blockers (ARBs) and Direct Renin Inhibitors
First Trimester Exposure

• Studies have found conflicting results on the safety of ACEi/ARB exposure in the first trimester.
• In 2006, Cooper et al. published one of the first large studies assessing the risk of teratogenicity associated with first trimester ACEi exposure.[10]
  ○ They found that infants with first trimester exposure to an ACEi had an increased risk of major congenital malformations, mainly to fetal CV and central nervous systems.
  ○ This study was limited by several confounders including not adjusting for obesity or diet controlled type 2 diabetes.
• Motherisk completed a meta-analysis in 2011 on the relationship between first trimester exposure to ACEi or ARBs and major congenital malformations.[11]
  ○ 5 studies were included in the meta-analysis (N = 1,094,071 infants), including the Cooper et al. study.
  ▪ 786 infants were exposed to ACEi or ARBs
  ▪ 1,813 infants were exposed to other antihypertensive drugs

ACEi or ARB exposure vs. healthy control	Other antihypertensive exposure vs. healthy controls	ACEi or ARB vs. other antihypertensive exposure
RR = 1.78 (95% CI, 1.07-2.94)	RR = 1.45 (95% CI, 1.15-1.83)	RR = 1.41 (95% CI, 0.66-3.04)

- A sensitivity analysis was completed to assess the impact of individual study effect size on the meta-analysis results.
  - When Cooper et al. (the study with the largest effect size) was removed, there was no longer a significant difference between ACEi or ARB exposure vs. healthy controls.
    - RR = 1.44 (95% CI, 0.78-2.67)
- Authors concluded, "Results suggest that first trimester exposure to ACEi and ARBs is not associated with an elevated risk of major malformations compared with other antihypertensives. First trimester exposure to antihypertensives in general, rather than to ACEi and ARBs, may be associated with an elevated risk of major malformations. A possible explanation may be related to specific characteristics of this population, which are known to be related to congenital malformations, such as diabetes mellitus. Specific use of ACEi/ARBs during the 1st trimester does not appear to further elevate the risk of major congenital malformations. High quality studies are needed to corroborate these results."
- Limitations to this meta-analysis include that all studies were observational, study design varied between trials, and authors were unable to obtain data from several trials.

- Similarly, three recently published small cohort studies, also suggest first trimester exposure to ACEi or ARBs may not increase the risk of major malformations or low birth weight compared to other antihypertensives.[12,13,14] Hypertension itself may increase the risk of major birth defects.[12]

SOGC 2014 Guideline Comments:[3]

- ACEi and ARBs should be discontinued when planning pregnancy or as soon as pregnancy is diagnosed.
- Although no equivalent agent for renoprotection is available for use in pregnancy, much of ACEi/ARB-related renoprotection is provided by lowering BP, achievable by alternatives.
- When replacing an ACEi or ARB, how long it will take to conceive should be considered.
- If an ACEi is discontinued pre-pregnancy in a woman with renal disease, yet conception does not occur after 12 months and proteinuria is rising despite excellent BP control, it may be prudent to reinstate ACE inhibition, perform monthly pregnancy tests, and proceed with investigations of subfertility. A multidisciplinary approach towards comorbidities and/or CV risk factors is recommended.

Second and Third Trimester Exposure

- Some fetotoxic effects associated with second and third trimester exposure to ACEi are:[3,15,16]

Renal impairment	Neonatal hypotension	Hypoplastic lungs
Oligohydramnios	Patent ductus arteriosus	Anuria
Hypocalvaria	Limb deformities	Death

Fetotoxic effects are common! One study found half of newborns exposed had complications.[15]

- Data regarding the risk of fetal harm from ARB or direct renin inhibitor exposure is less robust than that for ACEi. They seem to have similar fetotoxic effects and should be avoided. **ACEi, ARB, and direct renin inhibitor use is contraindicated in pregnancy.[17]**

Atenolol

- Has been associated with fetal intrauterine growth restriction (IUGR), particularly with use in early pregnancy.[3,18]

• A retrospective cohort study of 312 pregnancies complicated by HDP, compared women on no antihypertensive treatment, atenolol monotherapy, other monotherapies, or multiple drug combinations.[18]   ○ Infant weight and length were significantly lower in the atenolol group vs. the non-atenolol monotherapy or the no treatment group. • The SOGC recommend that atenolol should be discontinued when pregnancy is diagnosed (I-D; Low/Weak).[3]
Spironolactone
• Generally avoid use in pregnancy due to anti-androgenic effects, which may cause undervirilization of male infants.[17,19] • Limited evidence from case reports and animal studies are available.[19]
Prazosin
• May be associated with increased stillbirths.[2,3]
Oral Hydralazine
• Oral hydralazine monotherapy is not recommended by the SOGC due to maternal side effects (e.g., tachycardia and dizziness).[2,3]

Academic Detailing Comment:

- As per the SOGC 2014 guidelines, ACEi and ARBs should be discontinued when planning pregnancy or as soon as pregnancy is diagnosed.[3]
  - Women who have had accidental exposure to these agents in the first trimester may be reassured by observational evidence suggesting first trimester ACEi or ARB exposure may not have a higher risk of congenital malformations than other antihypertensives.

Thoughts on Thiazides:

- Thiazide use in pregnancy is controversial. Diuretics can theoretically cause impaired fetal growth due to the reduction of plasma volume, cardiac output, and uteroplacental perfusion.[17,20] Other fetal or newborn risks of thiazides include hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia and death from maternal complications. They may also effect smooth muscle and inhibit labor.[23]
- In 2009, Motherisk published a review on diuretic use in pregnancy.[20]
  - Several studies, including a meta-analysis of 9 RCTs (N = 7000) did not find an increased risk of fetal growth restriction, birth defects, neonatal thrombocytopenia, jaundice, and maternal pancreatitis.[20]
- The SOCG state that thiazide diuretics can be used in pregnancy, based on results of a 2007 Cochrane Review.[3,21] However, thiazide diuretics **are not considered first line options**.[3]
- Hypertension Canada lists thiazide diuretics as **second-line** oral antihypertensive medications used in pregnancy **(Grade D)**.[1]
- Local clinical reviewer opinion as well as several drug information resources recommend that **thiazides be avoided in settings in which uteroplacental perfusion is already reduced (e.g., preeclampsia or IUGR) and in gestational hypertension** due to the maternal

hypovolemia characteristic of the disease. There are usually safer alternatives to use in pregnant women. [17,23,40]

Medication Safety in Pregnancy and Lactation Resources:

- It is important to check the safety of any drug used during pregnancy (and lactation). Drug safety information in pregnancy and lactation can be found using the following resources:

Table 8. Pregnancy and Lactation Drug Information Resources:

Books	Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in Pregnancy and Lactation: a reference guide to fetal and neonatal risk. Philadelphia (PA): Lippincott Williams & Wilkins; 2017.
	• Available in print, e-book, and app formats
	  ○ E-book available online via Dalhousie, IWK and NSHA Libraries
	Hale TW, Rowe HE. Medications and Mothers Milk. New York (NY): Springer Publishing Company; 2017.
	• Available in print, e-book, and online version
	  ○ E-book available online via IWK and NSHA Libraries
	  ○ Online version available via IWK Library
	Schaefer C, Peters P, Miller RK. Drugs During Pregnancy and Lactation: Treatment Options and Risk Assessment. London: Elsevier Science & Technology; 2015.
	• Available in print and as an e-book
	  ○ E-book available online via IWK and NSHA Libraries

MotherToBaby	MotherToBaby is an American based service of the non-profit Organization of Teratology Information Specialists, which provides evidence-based information to mothers, healthcare professionals, and the general public about medications and other exposures during pregnancy and while breastfeeding. <u>Pregnancy and Lactation Drug Information Content:</u> • Fact Sheets: Answer frequently asked questions about exposures during pregnancy and breastfeeding. Fact Sheets can be downloaded for free. • Literature for Your Office: Brochures, posters, and flyers. • Note: Patient specific teratogen counseling services from Mother to Baby are not available to Canadian residents at this time.
	<u>Availability:</u> • https://mothertobaby.org/ • **Free**
Micromedex	<u>Pregnancy and Lactation Drug Information Content:</u> • Pregnancy & Lactation section in monographs

	• Reproductive Risk Databases: REPROTEXT, REPROTOX, Shepard's Catalog of Teratogenic Agents, Teratogen Information System (TETRIS)
	Availability: • https://www.micromedexsolutions.com/micromedex2/librarian/ • Apps available • **Subscription required** (available through Dalhousie, IWK and NSHA Libraries)
Pubmed	Availability: • https://www.ncbi.nlm.nih.gov/pubmed/ • **Free database use**, links to articles may require institution subscriptions (e.g., Dalhousie, IWK or NSHA libraries)
Regional Drug Information Service (RDIS)	The RDIS provides drug information support to health-care providers in Nova Scotia. This is not a consumer service. The service is supported by Pharmacists at the Halifax Infirmary site of the NSHA located in Halifax, Nova Scotia.
	Availability: • Monday to Friday (excluding holidays) 8 AM to 4 PM • Provincial Line: 1-902-473-4211 • Community pharmacists are subject to a fee for service
Toxicology Data Network (TOXNET)	Pregnancy and Lactation Drug Information Content: • Developmental and Reproductive Toxicology Database (DART) • Drugs and Lactation Database (LactMed)
	Availability: • https://toxnet.nlm.nih.gov/ • App available • **Free** (links to articles may require institution subscriptions)
Note: The Motherisk Program at the Hospital for Sick Children in Toronto was a teratogen information service. Unfortunately, on April 16th 2019 the Motherisk Helplines were closed.	

Question 2: What is the role of ASA in preventing preeclampsia?

Table 9. SOGC 2014 Guideline Recommendations on ASA to Prevent Preeclampsia and its Complications:[3]

Recommendations	Grade
Low dose ASA **is not** recommended to prevent preeclampsia in women at **low risk** • Comment: Low dose ASA does not decrease preeclampsia incidence in low risk nulliparous women (RR 0.93, 95% CI 0.81–1.08), although first trimester aspirin initiation is untested in RCTs.	1-E; Moderate/Weak
Low dose ASA **is** recommended to prevent preeclampsia in women at **increased risk** ASA should be: taken in a low dose (75–162 mg/day), administered at bedtime, initiated after diagnosis of pregnancy but before 16 weeks gestation and considered for continuation until delivery*	1-A; High/Strong III-B; Very low/Strong I-B; Moderate/Strong I-B; Low/Weak I-C; Very low/Weak

* Since these guidelines were published, newer evidence suggests to continue ASA until 36 weeks gestation. See discussion on the ASPRE trial and the Reproductive Care Program of Nova Scotia's recommendations on ASA later in the document.

Who is at high risk for developing preeclampsia?

- The SOGC have a risk stratification scheme (see Appendix 3).
- The Reproductive Care Program of Nova Scotia suggests that patients at high risk of developing preeclampsia are those with **one or more "high risk" factors**. Patients with a combination of **at least two "moderate risk" factors may also be identified at high risk** for developing preeclampsia.[40]

Table 10. Preeclampsia Risk Factors, from the Reproductive Care Program of Nova Scotia

High Risk Factors	Moderate Risk Factors
History of preeclampsia especially with an adverse outcome	Nulliparity
Multifetal gestation	Obesity (BMI > 30)
Chronic hypertension	Family history of preeclampsia in mother or sister
Type 1 or 2 diabetes mellitus	Age ≥ 40 years
	African Canadian
Renal disease	Low socioeconomic status
Autoimmune disease (antiphospholipid syndrome, systemic lupus erythematosus)	History of maternal low birth weight or small for gestational age, previous adverse pregnancy outcome, greater than 10 year pregnancy interval

- The American College of Obstetricians and Gynecologists list very similar risk factors to those in Table 10. They note that the "moderate-risk factors vary in their association with increased risk of preeclampsia", and that "a combination of multiple moderate-risk factors may be used by clinicians to identify women at high risk of preeclampsia."[5]

How does ASA prevent preeclampsia?

- The exact mechanism of action of ASA to prevent preeclampsia is uncertain. It may prevent preeclampsia by reducing inflammation and regulating platelet thromboxane and vascular wall prostacyclin synthesis.[22,23] The benefits of low dose ASA may be related to the transformation of the uterine spiral arteries which occurs by 16 weeks gestation.[3]

The Evidence:

- The 2014 SOGC guidelines acknowledge that who should receive ASA, when, and at what dose is unclear.[3]
  - A 2018 meta-analysis by Roberge et al. and the recent ASPRE trial attempted to answer some of these questions.[24,25]

Summary of the Roberge et al. Meta-Analysis: [24]

- This meta-analysis was designed to determine the effect of ASA on preventing preterm and term preeclampsia, and the impact of gestational age at onset of therapy and dose.
- Included 16 RCTs (N = 18,907)
  - Trials compared any dose of ASA vs. placebo/no treatment
  - Trials varied in regards to gestational age at onset of ASA or placebo
    - One small trial (n = 84) started ASA at 8-10 weeks of gestation, 4 trials started ASA as early as 11 weeks, and 11 trials enrolled participants at week 12 of gestation or later.
  - Patients were at moderate-high risk
- Primary outcome and results:
  - Preterm preeclampsia with delivery at < 37 weeks of gestation
    - RR = 0.62 (95% CI, 0.45-0.87)
- Secondary outcome and results:
  - Term preeclampsia with delivery at ≥ 37 weeks of gestation
    - RR = 0.92 (95% CI, 0.70-1.21)
- These results suggest that ASA reduces the risk of preterm preeclampsia, but not term preeclampsia. Authors propose this may be because:
  - The pathophysiology of the two conditions may be different, or
  - The risk of pre-term and term preeclampsia are actually both decreased by ASA, but the effect is to increase the gestational age at delivery with preeclampsia, so that cases of

term preeclampsia that are prevented by ASA are "replaced" by new cases of term preeclampsia which would have otherwise been preterm preeclampsia if ASA had not been taken.

- Subgroup analysis:
  - Assessed the effect of gestational age at onset of therapy and dose of ASA.
  - The number of trials and participants varied across the combinations of gestational age at onset of therapy and dose:
    - Onset of ASA was at ≤16 weeks gestation in 13 trials (n=5858)
      - With daily dose of ASA < 100 mg in 7 trials (n=3599)
      - With daily dose of ASA ≥ 100 mg in 6 trials (n=2259 – most were at high risk)
    - Onset of ASA was at >16 weeks gestation in 4 trials (n=8810)
      - With daily dose of ASA < 100 mg in 3 trials (n=8256)
      - With daily dose of ASA ≥ 100 mg in 1 trial (n=554)
  - Subgroup analysis results:

Table 11. Effect of ASA vs. Placebo on Preterm Preeclampsia Depending on Gestational Age at Onset of Therapy and Daily Dose (reported as relative risk (RR)):

Daily Dose of ASA	Gestational age at onset of therapy	
	≤16 weeks gestation	>16 weeks gestation
< 100 mg	RR = 0.59 (95% CI, 0.29-1.19)	RR = 1.00 (95% CI, 0.80-1.25)
≥ 100 mg	**RR = 0.33 (95% CI, 0.19-0.57)**	RR = 0.88 (95% CI, 0.54-1.43)

- Conclusion:
  - ASA significantly reduced the risk of preterm preeclampsia compared to placebo. However, in the subgroup analysis this difference was only observed in the subgroup of patients with onset of ASA therapy at ≤16 weeks gestation and at a daily dose of ≥100 mg.
- Limitations of the meta-analysis:
  - Of the 46 trials identified, only 16 were included in the meta-analysis due to data not being available.
    - Publication bias
  - Safety outcomes were not reported within this publication, results were reported separately.
  - Small sample size for the onset of ASA at >16 weeks gestation and ≥ 100 mg dose group.
- Strengths of the meta-analysis:
  - Included several recent RCTs, including the ASPRE trial.
  - Trials in the subgroup of ASA onset at ≤ 16 weeks gestation and daily dose ≥ 100 mg were homogeneous.

Summary of the ASPRE Trial: [25]

- The ASPRE trial by Rolnik et al. compared the use of ASA 150 mg vs. placebo to reduce the risk of preterm preeclampsia in women at high risk. It is the largest trial assessing ASA at a daily dose of ≥ 100 mg initiated at ≤ 16 weeks gestation.
- Multicenter, double-blind, randomized, placebo-controlled trial
  - 26,941 women were screened, but only 2641 met eligibility criteria, and of those 1776 enrolled.
    - **Participants were at high risk for preterm preeclampsia**.
- Intervention and comparator:
  - ASA 150 mg or placebo once daily at night starting at 11-14 weeks gestation and continued until 36 weeks gestation (or the onset of labour if before 36 weeks).
- Inclusion criteria:
  - Age ≥ 18 years, singleton pregnancy, live fetus at time that scanning was performed at 11-13 weeks of gestation, and high risk for preterm preeclampsia (according to the risk calculator tool).
    - A risk calculator using a combination of maternal factors with biophysicial and bio-chemical measurements obtained at 11-13 weeks gestation was used to calculate risk. This tool is available online at: https://fetalmedicine.org/research/assess/preeclampsia/first-trimester.
- Exclusion criteria limited the participants to a low bleed risk population.
  - For example, they excluded patients taking aspirin regularly within 28 days before screening, patients with bleeding disorders such as von Willebrand's disease, peptic ulceration, or long term NSAID use.
- Primary outcome and results:
  - Preterm Preeclampsia: Delivery with preeclampsia at < 37 weeks of gestation.
    - 13/798 (1.6%) in ASA group
    - 35/822 (4.3%) in placebo group
      - adjusted odds ratio (OR) = 0.38 (95% CI, 0.20-0.74)
- Secondary outcomes and results:
  - Adverse outcomes of pregnancy at < 34 weeks, < 37 weeks, and ≥ 37 weeks of gestation (including term preeclampsia)
  - Stillbirth or neonatal death
  - Neonatal death or complications
  - Neonatal therapy
  - Poor fetal growth

- There was no significant difference between ASA and placebo in the incidence of any of the secondary outcomes. However, the trial was not adequately powered to assess these outcomes.

- Adverse Events (AE)
  - There were no significant differences in rates of serious AE, any AE, or by type of AE (including vaginal bleeding, anemia, nausea/vomiting, abdominal or pelvic pain, and dyspepsia or heartburn) between ASA and placebo.

Table 12. Summary of the ASPRE Trial Results:

Outcome	Event Rate		ARR (ARI)	RRR (RRI)	NNT from 11-14 weeks to 36 weeks gestation	
	ASA	Placebo			NNT or NNH	95% CI
Preterm preeclampsia (Primary outcome)	**1.6%**	**4.3%**	**2.63%**	**61.7%**	**NNT = 38**	**23-101**
Adverse outcomes at:						
<34 weeks gestation	4.01%	6.45%	2.44%	37.81%	NS*	-
<37 weeks gestation	9.9%	14.11%	4.21%	29.85%	NS*	-
≥37 weeks gestation	22.31%	20.8%	(1.5%)	(7.22%)	NS	-
Stillbirth or neonatal death	1%	1.7%	0.7%	41.1%	NS	-
Neonatal death or complications	4.0%	5.8%	1.83%	31.3%	NS	-
≥ 1 Adverse event	25.9%	25.5%	(0.39%)	(1.5%)	NS	-

ARR, RRR and NNTs calculated using the Dalhousie Clinical Significance Calculator.
Neonatal death or complications was a composite of: miscarriage, stillbirth or neonatal death, intraventricular hemorrhage, neonatal sepsis, neonatal anemia, respiratory distress syndrome, and necrotizing enterocolitis.
ARI, absolute risk increase; ARR, absolute risk reduction; NNH, number needed to harm; NNT, number needed to treat; NS, not significant; RRI, relative risk increase; RRR, relative risk reduction
*No significant difference reported in the trial, however a significant difference was calculated using the Dalhousie Clinical Significance Calculator

- Conclusion:
  - ASA 150 mg once daily at night started at 11-14 weeks gestation and continued until 36 weeks gestation reduced the risk of preterm preeclampsia compared to placebo in women at high risk (NNT = 38, 95% CI 23-101).

- Limitations:
  - The risk calculator tool used in the trial is not widely used locally.
  - The study was not powered to adequately assess the secondary outcomes.

Why does the SOGC recommend to take ASA at <u>bedtime</u>?

- This recommendation is based on the results of 2 trials, one of which is the ASpirina en EMbarazo (Aspirin in Pregnancy) (ASEM) Trial.[26]
  - Randomized, double-blind, placebo-controlled trial

- Patients randomized to receive placebo or ASA, and to one of three treatment times (upon awakening, 8 hours after awakening, or bedtime).
- Results:
  - BP was decreased compared to placebo in the ASA 8 hours after awakening group and to a greater extent in the ASA bedtime group, but there was no difference when ASA was administered at awakening.
  - Rates of serious adverse outcomes (preeclampsia, preterm delivery, IUGR, and gestational hypertension) were lower in the 8 hours after awakening and bedtime ASA groups compared to placebo and upon awakening ASA groups.

- The variation of results between morning and bedtime administration groups may be due to circadian rhythms in thromboxane and prostacyclin production, circulating platelets, platelet aggregation, clotting, and ASAs inhibition of angiotensin II. There is also a faster rate of ASA clearance from the body when administered in the morning versus the evening.[26]

Is low dose ASA safe in pregnancy?

- Low dose ASA safety in the *first trimester*:
  - Limited evidence
  - A 2002 meta-analysis of 8 studies did not find an increase in the overall risk of congenital malformations; however, ASA exposure during the first trimester was associated with an increased risk of gastroschisis. Unfortunately, the dose of ASA was not specified in most studies. [27]
  - A 2005 case-control study found no increased risk of neural-tube defects, exomphalos/gastroschisis, or cleft lip/palate associated with ASA exposure in weeks 5-12 of pregnancy.[28]
- Low dose ASA safety in the *second and third trimesters*:
  - Most evidence for the use of ASA for preventing preeclampsia is in women beginning therapy in the second trimester.[24]
  - There were no significant differences in AE between ASA and placebo in the ASPRE trial.[25]
  - Another 2018 meta-analysis from Roberge et al. evaluated the effect of low dose ASA on the risk of placental abruption and antepartum hemorrhage.[29] They found:
    - No statistically significant difference in the risk of placental abruption or antepartum hemorrhage between ASA < 100 mg daily vs. placebo, regardless of whether treatment was started at ≤ 16 or > 16 weeks gestation.
    - For the comparison of ASA ≥ 100 mg daily vs. placebo, there was also no statistically significant difference in the risk of placental abruption or antepartum hemorrhage, regardless of whether treatment was started at ≤16 or >16 weeks gestation. ***There were however differences in trends between these two subgroups.***

- The RR trended towards benefit (less placental abruption or antepartum hemorrhage with ASA ≥100 mg vs. placebo) in the onset of ASA at ≤16 weeks gestation subgroup (RR = 0.62; 95% CI, 0.31-1.26)
- The RR trended towards harm (more placental abruption or antepartum hemorrhage with ASA ≥ 100 mg vs. placebo) in the onset of ASA at >16 weeks gestation subgroup (RR = 2.08; 95% CI, 0.86-5.06).
- With the **trend** of lower risk in one of these subgroups and higher risk in the other, the **difference in risk** of placental abruption or antepartum hemorrhage **between these two subgroups** was statistically significant (p = 0.04).

- It is important to note that although the trials were divided based on ASA initiation at greater or less than 16 weeks gestation, there was variation in timing of therapy between trials.

- Two ASA for the prevention of preeclampsia trials evaluated malformation and developmental impairment at 18 months of age. There were no significant differences in these outcomes between patients treated with ASA or placebo/no treatment. [30,31]

- Evidence Summary from: Briggs GG, Freeman RK, Towers CV, Forinash AB. Drugs in Pregnancy and Lactation: a reference guide to fetal and neonatal risk. Philadelphia (PA): Lippincott Williams & Wilkins; 2017.
  - Low dose ASA (e.g., 40-150 mg/day) is "compatible" with pregnancy
  - Aspirin induced fetal and neonatal toxicity has not been observed after the chronic use of low dose aspirin for the prevention of gestational hypertension, preeclampsia, and eclampsia.
  - Toxicities associated with full dose ASA near term such as hemorrhage, premature closure of the ductus arteriosus, pulmonary hypertension, or prolonged labour were not observed with low dose ASA.
- The SOGC states that low dose ASA neither increases nor decreases miscarriage risk, and there is no evidence of teratogenicity or other short- or long-term adverse pediatric effects.[3]
- Prior to starting ASA, patients should be assessed for bleeding risk. Patients at high risk of bleeding (e.g., those with bleeding disorders or peptic ulceration) were excluded from the ASPRE trial.[25]

Summary:

- The SOGC 2014 guidelines recommend the off-label use of low dose ASA to prevent preeclampsia in patients at increased risk, but acknowledge that it remains unclear as to in who, when and at what dose ASA should be started.[3] Recently published evidence partially answers these questions.[24,25]

- All comparisons across dose regimes have been from meta-analyses. No trials have directly compared initiating low dose ASA at ≤16 vs. >16 weeks gestation or compared varying doses of ASA.
- The most recent meta-analysis, which included the ASPRE trial, found that ASA started at or prior to 16 weeks gestation at a daily dose ≥100 mg reduced the risk of preterm preeclampsia compared to placebo in women at high risk.[24]

The Reproductive Care Program of Nova Scotia Recommends:

In pregnant women at high risk for developing pre-eclampsia (see Table 10), initiating ASA 150 mg (or in its absence, 2 x 81 mg tablets = 162 mg) once daily at bedtime reduces the risk of preeclampsia.[40, 47]

- ASA should be:
  - initiated between 11-16 weeks gestation (ideally between 11-14 weeks), and
  - continued until 36 weeks gestation.

Question 3: What is the role of calcium supplementation in preventing preeclampsia?

Table 13. SOGC 2014 Guideline Recommendations on Calcium Supplementation to Prevent Preeclampsia and its Complications:[3]

Recommendation	Grade
Calcium supplementation (of at least 1 g/day, orally) is recommended for women with low dietary intake of calcium (< 600 mg/day), for preventing preeclampsia and its complications. • Comments: The benefits of calcium are probably restricted to women with low calcium intake (< 600 mg/day). An alternative to supplementation may be 3–4 dairy servings/day (250–300 mg calcium/serving).	I-A; High/Strong

How does calcium prevent preeclampsia?

- One proposed explanation is that calcium supplementation lowers resistance in the uterine and umbilical arteries which can improve uteroplacental blood flow.[32]

Is there evidence for calcium supplementation to prevent preeclampsia?

A 2018 Cochrane Review by Hofmeyr et al. assessed the use of calcium supplementation during pregnancy to prevent HDP. [32]

- Trials could include pregnant women of **any risk** category. Trials with women diagnosed with a HDP at enrollment were excluded.
- The meta-analysis included 27 RCTs (N = 18,064)
  - High dose calcium supplementation (≥ 1 g elemental calcium/day) vs. placebo
    - 14 trials (n = 15,730)
    - Most trials used doses of 1.5 to 2 g elemental calcium/day
  - Low dose calcium supplementation (< 1 g elemental calcium/day) vs. placebo/no treatment
    - 12 trials (n = 2334)
  - High dose vs. low dose calcium supplementation
    - 1 trial (n = 262)
    - 2 g vs. 500 mg calcium/day
- In most of the trials included, supplementation was started around 20 weeks of pregnancy.

- Primary Outcomes:
  - Women
    - High blood pressure (with or without proteinuria)
    - Preeclampsia
  - Child
    - Preterm birth
    - Admission to NICU
    - Stillbirth or death before discharge from hospital
- Subgroup Analysis:
  - Women at low / average risk vs. high risk of HDP
  - Women with low vs. adequate baseline dietary calcium intake
    - Most women enrolled in the low baseline dietary calcium studies had a mean baseline calcium intake of ~600mg/day or less

Table 14. Summary of Hofmeyr GJ et al. Cochrane Review, High Dose Calcium Supplementation vs. Placebo Results:

Outcome	Event Rate		Risk Ratio (95% CI)
	High Dose (≥1 g/day) Calcium Supplementation	Placebo	
High Blood Pressure +/- Proteinuria	16.3%	19%	0.65 (0.53-0.81)
Low-risk women	16.3%	18.7%	0.71 (0.57-0.89)
High-risk women	16%	38%	0.47 (0.22-0.97)
Adequate calcium diet	21.8%	24.4%	0.90 (0.81-0.99)
Low calcium diet	13.5%	16.3%	0.44 (0.28-0.70)
Pre-eclampsia	4.8%	6.5%	0.45 (0.31-0.65)
Low-risk women	4.9%	6%	0.59 (0.41-0.83)
High-risk women	3.2%	17.6%	0.22 (0.12-0.42)
Adequate calcium diet	6.7%	7.8%	0.62 (0.32-1.20)
Low calcium diet	3.9%	5.7%	0.36 (0.20-0.65)
Preterm Birth	9.5%	10.4%	0.76 (0.60-0.97)
Low-risk women	9.7%	10.4%	0.84 (0.67-1.05)
High-risk women	4.4%	10.7%	0.45 (0.24-0.83)
Adequate calcium diet	10.6%	10.8%	0.59 (0.26-1.33)
Low calcium diet	8.9%	10.2%	0.81 (0.64-1.02)
Maternal death or serious morbidity	-	-	-
Adequate calcium diet	-	-	-
Low calcium diet	3.4%	4.3%	0.80 (0.66-0.98)
HELLP Syndrome	0.2%	0.1%	2.67 (1.05-6.82)

HELLP, hemolysis elevated liver enzymes and low platelets

Table 15. Summary of Hofmeyr GJ et al. Cochrane Review, High Dose vs. Low Dose Calcium Supplementation Results:

Outcome	Event Rate		ARR (ARI)	RRR (RRI)	NNT from 20 weeks gestation	
	High Dose (≥1 g/day) Calcium Supplementation	Low Dose (<1 g/day) Calcium Supplementation			NNT	95% CI
Preeclampsia	5.7%	13.7%	7.98%	58.4%	13	7-105
Preterm birth	2.4%	7.9%	5.47%	69.2%	NS	-

ARR, RRR and NNTs calculated using the Dalhousie Clinical Significance Calculator.
ARI, absolute risk increase; ARR, absolute risk reduction; NNT, number needed to treat; NS, not significant; RRI, relative risk increase; RRR, relative risk reduction.

- Conclusions:
  - Supplementation with ≥ 1 g/day of elemental calcium in women with low dietary calcium intake reduces the risk of preeclampsia.
    - The greatest reduction in risk of preeclampsia occurred in the high risk group.
  - Supplementation with ≥ 1 g/day of elemental calcium also reduces the risk of:
    - Developing hypertension
    - Maternal death or serious morbidity in women with low dietary calcium
    - Preterm birth in women of high risk
  - Although there was an increased risk of HELLP syndrome, the event rates were quite low.
    - The SOGC accepts that the benefits of calcium supplementation more than offset the possible increase in HELLP.[3]
- Limitations of the meta-analysis:
  - The evidence for the effect of high dose calcium supplementation on preeclampsia and preterm birth is of low quality.
  - Low dose calcium RCTs included those with quasi-random designs.
  - Potential for publication bias
  - Only one study compared high vs. low dose calcium supplementation.

The Reproductive Care Program of Nova Scotia Recommends:

Calcium supplementation with ≥ 1 g of elemental calcium/day in those with low calcium intake to prevent preeclampsia.[40]

Therapeutic Tip:

- For optimal absorption, calcium salts (except calcium citrate) should be taken with food, and doses of elemental calcium > 500 mg/day should be administered in divided doses.[33]
  - The administration time of calcium supplements or calcium rich foods should be spaced apart from some medications or supplements (e.g., iron or levothyroxine) due to

impairment in absorption of one or both components.[33] Encourage patients to speak to their pharmacist regarding appropriate timing of calcium supplementation or dietary calcium consumption.

- FYI: Most prenatal multivitamins only contain a limited amount of calcium. For example, the recommended daily dose of Materna® Prenatal Multivitamin only contains 250 mg of elemental calcium.[34]

Question 4: How should antihypertensive agents be managed in HDP?

The focus of this section will be on the treatment of non-severe hypertension in pregnancy ***without*** **comorbid conditions.**

Non-severe hypertension (BP 140-159/90-109 mmHg) in pregnancy *without* comorbid conditions:

Table 16. SOGC 2014 Guideline Recommendations on Antihypertensive Therapy for Non-severe Hypertension without Comorbid Conditions:[3]

Recommendation	Grade
Antihypertensive drug therapy may be used to keep SBP at 130–155 mmHg and DBP at 80–105 mmHg.	I-B; Low/Weak
The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference.	III-C; Very low/Weak
Initial therapy in pregnancy can be with one of a variety of antihypertensive agents available in Canada: methyldopa labetalol other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol), and calcium channel blockers (nifedipine)	 I-A; High/Strong I-A; High/Strong I-B; Moderate/Strong I-A; High/Strong
ACE inhibitors and ARBs should not be used during pregnancy	II-2E; Moderate/Strong
Atenolol and prazosin are not recommended prior to delivery	I-D; Moderate/Weak

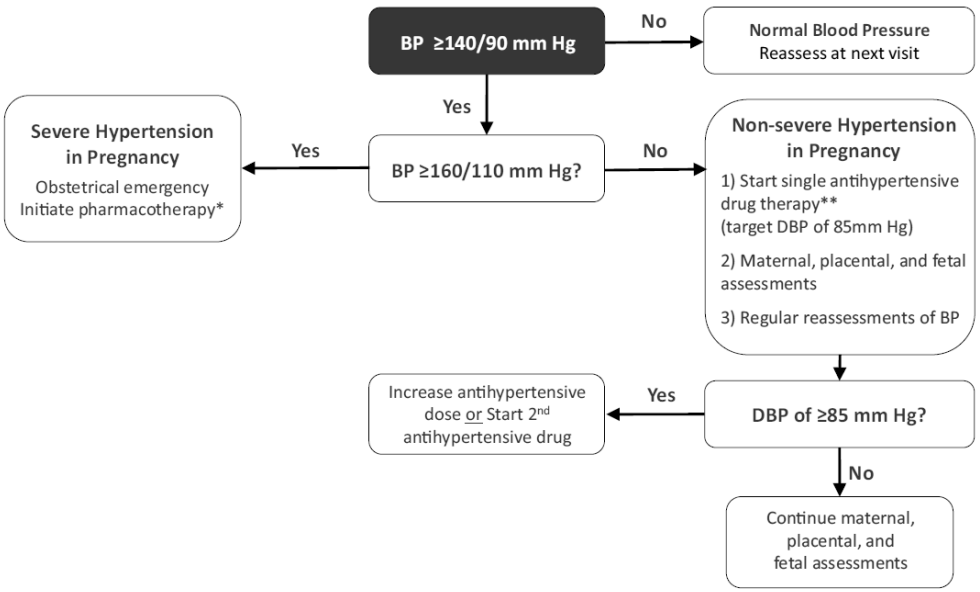

*Figure 2. Management of Hypertension in Pregnancy. Reprinted from Canadian Journal of Cardiology 34 (2018), Butalia S et al for Hypertension Canada, "Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy" 526-531. Copyright 2018 with permission from Elsevier.*See SOGC 2014 guidelines, ** see Table 17 for initial antihypertensive therapy recommendations.*

Table 17. Hypertension Canada 2018 Guideline Recommendations for the Management of Non-severe Hypertension in Pregnancy:[1]

Recommendation	Grade
Antihypertensive therapy is recommended for average SBP measurements of ≥140 mmHg or DBP measurements of ≥90 mmHg in pregnant women with chronic hypertension, gestational hypertension, or preeclampsia.	Grade C
Initial antihypertensive therapy should be monotherapy from the following first-line drugs: oral labetalol, oral methyldopa, long-acting oral nifedipine, or other oral *B*-blockers (acebutolol, metoprolol, pindolol, and propranolol).	Grade C
Other antihypertensive drugs can be considered as second-line drugs including: clonidine, hydralazine, and thiazide diuretics.	Grade D
ACE inhibitors and ARBs should not be used in pregnant women	Grade C Grade D
A DBP of 85 mmHg should be targeted for pregnant women receiving antihypertensive therapy with chronic hypertension or gestational hypertension. A similar target could be considered for pregnant women with preeclampsia.	Grade B Grade D
Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy. Add-on drugs should be from a different drug class chosen from first-line or second-line options.	Grade C Grade D

Therapeutic Tips:

- BP usually falls in early pregnancy (nadir ≈ 20 weeks) before rising towards pre-pregnancy levels by term. A patient's antihypertensive regime should be reassessed regularly, and some patients with pre-pregnancy hypertension may not need to continue antihypertensive medications from early pregnancy.[3]
- In pregnancy, successful treatment of hypertension occurs in >70% of women who are primarily treated with only one drug. Whereas for hypertension outside of pregnancy, the corresponding success rate is only 30% to 50%.[2]

There has been debate over how to best manage non-severe hypertension in pregnancy due to concerns that treatment would decrease uteroplacental perfusion, which could lead to adverse fetal outcomes.[2] A 2018 Cochrane Review and the CHIPS trial have addressed the following questions:[35,36]

Question 4a: What is the evidence for treating non-severe hypertension in pregnancy without comorbidities?

Question 4b: Is one drug or class of drug better than another for treating non-severe hypertension in pregnancy without comorbid conditions?

The 2018 Cochrane Review by Abalos et al. evaluated the possible benefits, risks and side-effects of antihypertensive drug treatments for women with mild to moderate hypertension during pregnancy.[35]

- It included 58 RCTs (N = 5909)
  - Antihypertensive drug vs. no antihypertensive drug/placebo
    - 31 trials (n = 3485)
  - Antihypertensive drug vs. another antihypertensive drug
    - 29 trials (n = 2774)
- Study population:
  - Mild-moderate hypertension in pregnancy (SBP of 140-169 mmHg and/or DBP of 90-109 mmHg)
  - Eight studies recruited women during the first and second trimester, 20 recruited women during the second and third trimester of pregnancy, and 21 recruited only during the third trimester. Gestational age at trial entry was not reported in nine studies.
  - **Many trials excluded patients with diabetes or renal disease**
- Primary outcomes:
  - Severe hypertension (SBP ≥ 170 mmHg, or DBP ≥ 110 mmHg)
  - Proteinuria/pre-eclampsia
  - Total reported fetal or neonatal death
  - Small-for-gestational age
  - Preterm birth
- Results:
  - Antihypertensive drug vs. no antihypertensive drug/placebo
    - Severe hypertension
      - RR = 0.49 (95% CI, 0.40-0.60); moderate-certainty evidence
    - The statistically significant reduction in severe hypertension was maintained across all hypertension subtypes (hypertension alone, hypertension + proteinuria, chronic hypertension, unclassified/mixed).
    - There were no significant differences in the risk of proteinuria/pre-eclampsia, total reported fetal or neonatal death, small-for-gestational age, preterm birth, maternal side-effects, admission to neonatal or intensive care nursery, neonatal hypoglycemia, or neonatal bradycardia.

- Antihypertensive drug vs. another antihypertensive drug
  - *B*-blockers or calcium channel blockers (CCB) are more effective than methyldopa in avoiding an episode of severe hypertension.
    - RR = 0.70 (95% CI, 0.56-0.88)

Table 18. Summary of Abalos et al. Cochrane Review Results:

Outcome	Event Rate		ARR (ARI)	RRR (RRI)	NNT during pregnancy	
	Any Antihypertensive drug	No Antihypertensive Drug/Placebo			NNT	95% CI
Severe hypertension	**9.4%**	**19.8%**	**10.45%**	**52.8%**	**10**	**8-13**
Proteinuria/ preeclampsia	17%	18.5%	1.54%	8.3%	NS	-
Total reported fetal or neonatal death	2.7%	4.1%	1.4%	34.2%	NS*	-
Small-for-gestational age	15.2%	15.2%	0%	0%	NS	-
Preterm birth	25.5%	27.7%	2.27%	8.2%	NS	-
	***B*-Blocker or CCB**	**Methyldopa**				
Severe hypertension	**19.3%**	**29%**	**9.65%**	**33.3%**	**10**	**6-33**

ARR, RRR and NNTs calculated using the Dalhousie Clinical Significance Calculator.
ARI, absolute risk increase; ARR, absolute risk reduction; NNT, number needed to treat; NS, not significant; RRI, relative risk increase; RRR, relative risk reduction.
RR reported in the meta-analysis may differ slightly from those calculated using event rates in the Dalhousie Clinical Significance Calculator
*No significant difference reported in the meta-analysis, however a significant difference was calculated using the Dalhousie Clinical Significance Calculator

- Conclusion:
  - In women with mild to moderate hypertension in pregnancy, without co-morbidities (i.e. diabetes, or renal disease), use of antihypertensive drug therapy significantly reduced the risk of severe hypertension compared to no antihypertensive drug therapy (NNT = 10, 95% CI 8-13).
  - There was no significant difference between antihypertensive drug therapy and no antihypertensive drug therapy groups in the risk of fetal or neonatal death, small-for-gestational age, or preterm birth.
- Limitations of the meta-analysis:
  - All of the included trials were small – largest was 314 patients.
  - Overall, the quality of studies included in this review were moderate to poor.

Local Clinical Reviewer Opinion:

- The preferred first line antihypertensive agents in this patient population are oral labetalol or nifedipine XL.[40,41]

Question 4c: What is the evidence for the 2018 Hypertension Canada treatment target of a DBP of 85 mmHg for pregnant women receiving antihypertensive therapy with chronic hypertension or gestational hypertension?

The Control of Hypertension in Pregnancy Study (CHIPS) compared the effect of less-tight vs. tight control of nonproteinuric non-severe hypertension in pregnancy, on perinatal and maternal outcomes.[36]

According to the trial protocol, CHIPS investigators hypothesized that less-tight control may improve uteroplacental perfusion, fetal growth, and through these fetal/neonatal well-being. They wanted to determine if less tight control vs. tight control of non-severe hypertension would decrease fetal/neonatal risk without increasing maternal risk.

- CHIPS was an open label, multicenter (111 sites, including the IWK!), international RCT
  - N = 987
    - Women were a mean age of 34 years, mostly non-smokers, 1/3 were nulliparous, were enrolled at a mean of 23-24 weeks gestation, most had preexisting hypertension, and more than half were on antihypertensives at enrollment.
- The trial compared:
  - Less-tight control [target DBP = 100 mmHg (100-104 mmHg)] vs. tight control [target DBP = 85 mmHg (81-85 mmHg)] until delivery
    - Labetolol was recommended as the drug of choice in the study protocol.
    - In the tight control group, antihypertensive medication was decreased in dose or discontinued if DBP fell to ≤ 80 mmHg due to safety concerns around limiting uteroplacental perfusion.
  - **Academic Detailing Note:**
    - **CHIPS compared the upper end vs the lower end of the SOGC target DBP range of 80-105 mmHg.**
- Inclusion criteria:
  - Pregnant women with non-severe, non-proteinuric preexisting hypertension or gestational hypertension with:
    - DBP of 90-105 mmHg if they were not receiving antihypertensive therapy, or 85-105 mmHg if they were receiving antihypertensives, and
    - A live singleton fetus at 14^0 to 33^6 weeks gestation.
- Exclusion criteria:
  - SBP ≥ 160 mmHg
  - **Proteinuria**
  - ACEi use at 14^0 weeks gestation or later
  - Contraindication to either trial group because of **a preexisting condition (e.g., pregestational diabetes or renal disease)**
  - Needed to be delivered for maternal or fetal reasons

- Multiple gestation
- Fetus with a major anomaly or chromosomal abnormality
- Plans to terminate the pregnancy

- BP measurement:
  - The CHIPS trial used mercury, aneroid, or automated blood pressure monitoring devices to monitor participants' BP.
  - BP was measured 3 times by a health professional at each visit, and the average of the 2nd and 3rd DBP was recorded as the DBP for that visit.
- Primary outcome:
  - Composite of pregnancy loss or high-level neonatal care (greater-than-normal newborn care) for more than 48 hours until 28 days of life or until discharge home, whichever was later.
- Secondary outcome:
  - Serious maternal complications occurring up to 6 weeks post-partum or until hospital discharge, whichever was later.
- Other outcomes:
  - Components of the primary and secondary outcomes
  - Fetal growth
  - Newborn complications
  - Severe hypertension (≥ 160/110 mmHg) in the mother

- Results:

Table 19. Summary of the CHIPS Trial Results, Target DBP 100 mmHg vs. 85 mmHg:

Outcome	Event Rate		ARR (ARI)	RRR (RRI)	NNT or NNH	95% CI
	Target DBP = 100 mmHg	Target DBP = 85 mmHg				
Primary Outcome*	31.4%	30.7%	(0.7%)	(2.3%)	NS	-
Small-for-gestational-age newborn:						
Birth weight <10th percentile	16.1%	19.7%	3.58%	18.2%	NS	-
Birth weight <3rd percentile	4.7%	5.3%	0.64%	12.1%	NS	-
At least one serious neonatal complication**	8.3%	8.4%	0.02%	0.2%	NS	-
Serious Maternal complications***	3.7%	2.0%	(1.6%)	(78.2%)	NS	-
Placental abruption	2.2%	2.3%	0.02%	1.0%	NS	-
Severe Hypertension	**40.6%**	**27.5%**	**(13.11%)**	**(47.7%)**	**NNH = 8**	**5-14**
Preeclampsia	48.9%	45.7%	(3.19%)	(7.0%)	NS	-

ARR, RRR and NNTs calculated using the Dalhousie Clinical Significance Calculator.
ARI, absolute risk increase; ARR, absolute risk reduction; NNH, number needed to harm; NNT, number needed to treat; NS, not significant; RRI, relative risk increase; RRR, relative risk reduction.
*Composite of pregnancy loss (miscarriage, ectopic pregnancy, pregnancy termination, stillbirth, or neonatal death) or high-level neonatal care (greater-than-normal newborn care) for more than 48 hours until 28 days of life or until discharge home, whichever was later.
** Severe respiratory distress, sepsis in the first 48 hours of life, bronchopulmonary dysplasia, severe retinopathy of prematurity, central nervous system complications, and necrotizing enterocolitis.
*** Uncontrolled hypertension, transient ischemic attack or stroke, pulmonary edema, renal failure, and transfusion.

- Conclusion of main results:
  - There was no significant difference in the risk of the composite outcome of pregnancy loss or high-level neonatal care for more than 48 hours (the primary outcome) between less-tight and tight control groups.
  - Less-tight control (target DBP = 100 mmHg) of non-severe nonproteinuric pre-existing hypertension or gestational hypertension was associated with a significantly higher risk of developing severe hypertension compared to tight control (target DBP = 85 mmHg) (NNH = 8, 95% CI 5-14).
- Other results:
  - Duration:
    - The median duration of study participation before delivery was 12.1 weeks and 11.4 weeks for the less-tight control and the tight control groups respectively.

- BP control:
  - From randomization to delivery, BP was higher in the less-tight control group vs. the tight control group.
    - Mean SBP 138.8 ± 0.5 mmHg vs. 133.1 ± 0.5 mmHg, p <0.001
    - Mean DBP 89.9 ± 0.3 mmHg vs. 85.3 ± 0.3 mmHg, p <0.001
      - Note: This is only a 5 mmHg difference in mean DBP between groups.
- Medication use:
  - Labetalol was the most commonly used antihypertensive (used by ~2/3 of women)
  - Antihypertensive medication was taken after randomization by fewer women in the less-tight control group than in the tight-control group:
    - Before delivery (73.4% vs. 92.6%, p <0.001)
    - After delivery (65.5% vs. 78.3%, p <0.001)
  - Most patients in both groups were only on 1 antihypertensive agent.

- Limitations:
  - The CHIPS trial may have been underpowered to find a difference in the primary outcome.
    - Need to interpret results, including significant differences in secondary outcomes such as severe hypertension, with caution.

- Several post-hoc analyses of the CHIPS trial have been published:

1) The CHIPS Randomized Controlled Trial (Control of Hypertension in Pregnancy Study): Is Severe Hypertension Just an Elevated Blood Pressure?[37]
   - Severe hypertension was associated with increased risk of pregnancy loss or need for high-level neonatal care > 48h, preeclampsia, low birth weight, and preterm delivery.
2) Control of Hypertension In Pregnancy Study randomized controlled trial - are the results dependent on the choice of labetalol or methyldopa?[38]
   - The outcome results for less-tight vs. tight control groups did not depend on the choice of labetalol or methyldopa.
3) The Cost Implications of Less Tight Versus Tight Control of Hypertension in Pregnancy (CHIPS) trial.[39]
   - Analysis of differences in mean costs for less-tight vs. tight control.
     - For all 3 provinces assessed (ON, BC, AB) the cost of services and wards was higher in the less-tight control group, but the difference was not statistically significant.

Implications to Practice:

- The difference in BP treatment targets between the 2014 SOGC guidelines (SBP 130-155 mmHg and DBP 80-105 mmHg) and the 2018 Hypertension Canada guidelines (DBP of 85 mmHg) reflects the results of the CHIPS trial which was published in 2015.[36]
- Not all guideline groups have changed BP treatment target recommendations based on the results of the CHIPS trial. The American College of Obstetricians and Gynecologists is awaiting the results of the Chronic Hypertension and Pregnancy (CHAP) Project before reassessing their recommendations.[2,4,42]
- The CHIPS trial provides some reassurance that treating non-severe hypertension in pregnancy in patients without comorbid conditions to the lower end of the current SOGC target DBP range may be safer than previously thought, and is associated with a lower risk of developing severe hypertension. However, caution must be exercised to ensure DBP does not fall to < 80 mmHg as this may limit uteroplacental perfusion.

Timing of Delivery:

- The presence of hypertension impacts the timing of delivery.[3]
- The SOGC have made the following recommendations for those with gestational or pre-existing hypertension:

Table 20. SOGC 2014 Guideline Recommendations for Timing of Delivery in Women with Gestational or Pre-existing Hypertension:[3]

Recommendation	Grade
Women with gestational hypertension:	
For women with gestational hypertension (without preeclampsia) at ≥ 37^0 weeks gestation, delivery within days should be discussed.	I-B; Low/Weak
For women with gestational hypertension (without preeclampsia) at < 37^0 weeks gestation, there is insufficient evidence to make a recommendation about the benefits or risks of expectant management.	III-L; Very low/Weak
Women with pre-existing hypertension:	
For women with uncomplicated pre-existing hypertension who are otherwise well at ≥ 37^0 weeks gestation, delivery should be considered at 38^0–39^6 weeks gestation.	II-1B; Low/Weak

Non-severe hypertension (BP 140-159/90-109 mmHg) in pregnancy ***with*** **comorbid conditions**:

- The management of non-severe hypertension in pregnant women *with* comorbid conditions is outside of the scope of this review.
- The management of hypertension in this patient population should be done so in consultation with an obstetrician.[40,41]

Severe hypertension (SBP ≥ 160 mmHg or DBP ≥ 110 mmHg) in pregnancy:

Table 21. SOGC 2014 Guideline Recommendations on Place of Care:[3]

Recommendation	Grade
In-patient care should be provided for women with severe hypertension or severe preeclampsia.	II-2B; Low/Strong

Table 22. Hypertension Canada 2018 Guideline Recommendations on the Management of Severe Hypertension in Pregnancy:[1]

Recommendation	Grade
Women with severe hypertension with SBP ≥ 160 mmHg or DBP ≥ 110 mmHg in pregnancy require urgent antihypertensive therapy because it is considered an obstetrical emergency.	Grade D

- The management of severe hypertension is outside of the scope of this review.
- In Nova Scotia, patients within the Halifax Regional Municipality should be sent to the IWK Health Centre, and those in other areas of the province sent to the nearest emergency room for assessment and treatment.

Preeclampsia:

- The management of preeclampsia is outside of the scope of this review.
- The management of preeclampsia must be done so in consultation with an obstetrician (by telephone if necessary).[3,40]

Question 5: According to guidelines and local clinical reviewers, which women at risk, or who have developed a HDP should obstetrics be consulted?

For women at risk:

Table 23. SOGC 2014 Guideline Recommendations on Predicting Preeclampsia:[3]

Recommendation	Grade
Women should be screened for clinical risk markers of preeclampsia from early pregnancy.	II-2 C; Low/Strong
Consultation with an obstetrician or an obstetric internist, by telephone if necessary, should be considered for women with a history of previous preeclampsia or another strong clinical marker of increased preeclampsia risk, particularly multiple pregnancy, antiphospholipid antibody syndrome, significant proteinuria at booking (at the first antenatal visit, usually early in pregnancy), or a pre-existing condition of hypertension, diabetes mellitus, or renal disease. ➢ Comment: Women can be offered subspecialty referral, and must receive more frequent assessments, if they have one strong risk factor, or two or more minor risk factors (See Appendix 3, Risk Markers for Preeclampsia).	II-2 B; Very low/ Strong

The Reproductive Care Program of Nova Scotia Recommends:

- Consultation with an obstetrician should be considered for women with:
  - A history of previous preeclampsia, or
  - Other strong clinical markers of increased risk, especially multifetal pregnancy, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease (antiphospholipid syndrome, systemic lupus erythematosus), or
  - Multiple other risk factors for preeclampsia. [40]
    (See Table 10, Preeclampsia Risk Factors, from the Reproductive Care Program of Nova Scotia and Appendix 3.)

For women diagnosed with HDP:

The Reproductive Care Program of Nova Scotia Recommends:

- Consultation with an obstetrician should be considered for any pregnant woman diagnosed with HDP, by telephone if necessary.[40]
- Women with HDP will also require increased fetal surveillance:
  - For indications and frequency of fetal surveillance, including for those with stable and unstable cardiac disease or gestational hypertension, please see the Reproductive Care Program of Nova Scotia's Nova Scotia Prenatal Record Companion Document at: http://rcp.nshealth.ca/publications/nova-scotia-prenatal-record-companion-document.

Question 6: How should antihypertensive agents be managed postpartum?

- HDP can persist or arise de novo in the postpartum period.[3,43]
- The time of peak BP postpartum is at 3 to 6 days after delivery.[3]
- About 1/3 of eclampsia occurs postpartum, with nearly half of those occurring at >48 hours after delivery.[43]
- Gestational hypertension typically resolves by 6 weeks postpartum and the hypertension of severe preeclampsia usually within 3-6 months.[3]
- There is very limited evidence to guide the management of HDP postpartum. Authors of a recent systematic review of 39 studies (N = 2901) were unable to recommend a particular BP threshold, agent, or model of care.[43]
  - Most studies assessed the acute control of severe hypertension or short-term BP control in women remaining in hospital postpartum.
  - There is very little evidence to guide the outpatient management of antihypertensive drugs in the weeks after delivery.
- Patients with postpartum hypertension should be managed by a practitioner comfortable with managing the condition.[40]
- Follow-up may need to continue beyond 6 weeks postpartum.[40]

In 2014 the SOGC made the following recommendations regarding postpartum treatment of HDP:

Table 24. SOGC 2014 Guideline Recommendations on Postpartum Treatment of HDP:[3]

Recommendation	Grade
Care in the 6 weeks postpartum	
BP should be measured during the time of peak postpartum BP, at days three to six after delivery.	III-B; Low/Strong
Women with postpartum hypertension should be evaluated for pre-eclampsia (either arising de novo or worsening from the antenatal period).	II-2 B; Low/Weak
Consideration should be given to continuing antihypertensive therapy postpartum, particularly in women with antenatal preeclampsia and those who delivered preterm.	II-2I; Low/Weak
Severe postpartum hypertension must be treated with antihypertensive therapy, to keep SBP <160 mmHg and DBP <110 mmHg.	I-A; Moderate/Strong
In women without co-morbidities, antihypertensive therapy should be considered to treat non-severe postpartum hypertension to keep BP <140/90 mmHg.	III-I; Very low/Weak

Women with co-morbidities other than pre-gestational diabetes mellitus should be treated to keep BP < 140/90 mmHg.	III-C; Very low/Weak
Women with pre-gestational diabetes mellitus should be treated to keep BP < 130/80 mmHg.	III-C; Very low/Weak
Antihypertensive agents generally acceptable for use in breastfeeding include the following: nifedipine XL, labetalol, methyldopa (see note below), captopril, and enalapril.	III-B; Moderate/Weak
There should be confirmation that end-organ dysfunction of preeclampsia has resolved.	III-C; Very low/Strong
NSAIDs should not be given postpartum if hypertension is difficult to control, there is evidence of kidney injury (oliguria and/or an elevated creatinine) or platelets are < $50x10^9$/L.	III-C; Low/Weak
Postpartum thromboprophylaxis should be considered in women with preeclampsia, particularly in the presence of other risk factors.	II-2B; Low/Weak
Care beyond 6 weeks postpartum	
Women with a history of severe preeclampsia (particularly those who presented or delivered before 34 weeks' gestation) should be screened for pre-existing hypertension and underlying renal disease.	II-2B; Low/Weak
Referral for internal medicine or nephrology consultation (by telephone if necessary) should be considered for women with: (i) postpartum hypertension that is difficult to control, or (ii) women who had preeclampsia and have at 3–6 months postpartum either ongoing proteinuria, decreased eGFR (< 60 ml/min), or another indication of renal disease (such as abnormal urinary sediment).	III-A; Low/Weak
Women who are overweight should be encouraged to attain a healthy body mass index to decrease risk in: future pregnancy and for long-term health.	 II-2A; Mod/Strong I-A; Low-mod/Strong
Women with pre-existing hypertension or persistent postpartum hypertension should undergo the following investigations (if not done previously) at least 6 weeks postpartum: urinalysis; serum sodium, potassium and creatinine; fasting glucose; fasting lipid profile; and standard 12-lead electrocardiography.	III-I; Low/Weak
Women who are normotensive but who have had a HDP, may benefit from assessment of traditional cardiovascular risk markers.	II-2B; Low-moderate/Weak
All women who have had a HDP should pursue a healthy diet and lifestyle.	I-B; Low/Weak

Antihypertensive Agents in Breastfeeding:

- All medications should be assessed for safety in breastfeeding.
- Many antihypertensive medications are acceptable to use in breastfeeding women.[2] There is no clear best choice of agent, and will depend on patient factors.[3]
  - Resources for lactation drug information include: Hale's Medications and Mother's Milk, LactMed, MotherToBaby, and Briggs' Drugs in Pregnancy and Lactation (see Table 8).
- Although the SOGC consider methyldopa to be "generally acceptable" for use in breastfeeding, **methyldopa may increase risk of postpartum depression**.[3,44,46] The National Institute for Health and Care Excellence (NICE) recommends to consider switching to an alternative therapy within 2 days of delivery.[44,45]
- The SOGC recommend that caution may be exercised in preterm and low birth weight infants due to immature drug clearance and/or increased susceptibility to drug effects.[3]

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HYPERTENSION IN CHILDREN

Summary Statements:

- The prevalence of hypertension in children is increasing.
- Secondary hypertension is more common in children than adults.
  - Children who develop hypertension should have a focused history and physical examination and investigations for secondary causes.
    - Common causes of secondary hypertension in children are renal, renovascular, endocrine, or cardiac disorders.
- In obese children and adolescents, primary hypertension is more common than secondary hypertension.
- Hypertension Canada recommends that BP should be measured regularly in children 3 years of age and older by a health care professional using standardized pediatric techniques.
- Unlike adults, a child's or adolescent's blood pressure is NOT compared to a single diagnostic threshold, instead, BP percentiles are used.
  - BP readings should be compared with norms for age, sex, and height.
    - Normative BP tables are available.
- Family physicians should be familiar with the criteria for diagnosis of hypertension in children and adolescents (See Question 3).
- Most children and adolescents with hypertension should be managed by an expert in pediatric hypertension (See Question 4).

Background:

- The prevalence of hypertension in children is increasing, partly due to increasing rates of childhood obesity.[1,2]
  - About 2% of Canadian children and adolescents have hypertension.[1]
- Results of a 2012-2015 Canadian Health Measures Survey by Stats Canada found overweight or obese children and youth had a significantly higher average blood pressure (BP) than normal weight children.[3]
- Besides obesity, children with other chronic conditions, including sleep-disordered breathing, CKD, and preterm birth also have higher rates of hypertension.[4]
- Other risk factors for hypertension include a family history of hypertension and male sex.[5]
- Secondary hypertension is more common in children than adults.
  - Children who develop hypertension should have a focused history and physical examination and investigations for secondary causes.[1,2]
    - Common causes of secondary hypertension in children are renal, renovascular, endocrine, or cardiac disorders.[2]
- In obese children and adolescents, primary hypertension is more common than secondary hypertension.[2]
- Guidelines:
  - Hypertension Canada published their inaugural guidelines for BP measurement, diagnosis, and assessment of risk of pediatric hypertension in 2016, in response to primary care practitioners request for guidance.[2]
    - These guidelines were updated in 2017 and 2018, and also include guidance on the prevention and treatment of hypertension in children.[1,6]
    - The next update is planned for 2020.[1]
  - The system for grading the strength of recommendations from the Hypertension Canada Guidelines is available in Appendix 2.
    - **Most** of the guideline recommendations are based on expert opinion (Grade D).
      - **Unfortunately, this area of practice has extremely limited evidence available to guide decision making.**
  - The American Academy of Pediatrics have most recently published guidelines on the topic in 2017.[4]

This section of the review will address 4 questions:

1) Which children and adolescents should have their BP monitored?
2) How should BP be measured in children and adolescents?
3) How is hypertension diagnosed in children and adolescents?
4) In what practice setting should children and adolescents with hypertension be managed?

Question 1: Which children and adolescents should have their BP monitored?

- The role of screening for hypertension in children and adolescents has not been well studied.

Table 1. Hypertension Canada 2018 Guideline Recommendations on Accurate Measurement of BP in Children (guideline 1):[1]

Recommendation	Grade
BP should be measured regularly in children 3 years of age and older by a health care professional using standardized pediatric techniques.	Grade D

- The above recommendation from Hypertension Canada is based on expert opinion alone.
  - **"**Regularly" is not defined.
- The American Academy of Pediatrics provide more detailed recommendations in regards to **frequency** of BP monitoring in children ≥3 years of age **depending on risk**.[4]
  - BP should be measured annually in children and adolescents ≥ 3 years of age.[4]
  - BP should be checked in all children and adolescents ≥ 3 years of age at every health care encounter if they have obesity, are taking medications known to increase BP, have renal disease, a history of aortic arch obstruction or coarctation, or diabetes.[4]
- The American Academy of Pediatrics also recommend that children < 3 years of age with increased risk of developing hypertension should have their BP measured.[4]
  - See Table 2 for conditions with increased risk of developing hypertension.
    - Note: Many of these patients would be followed by a pediatric subspeciality team.
- The Canadian Paediatric Society endorse the Rourke Baby Record and the Greig Health Record, which are evidence-based health promotion guides for clinicians caring for children and adolescents.[7]
  - The 2017 Nova Scotia Rourke Baby Record (for infants and children ages 0-5 years) recommends checking BP if *at risk* (see Table 2) starting at 2-3 years of age.[8]
  - The 2016 Greig Health Record (for children ages 6-17 years) recommends checking BP at preventive care visits every 1 to 2 years.[7]

Table 2. Some Conditions Associated with Elevated BP, for Which BP Should be Monitored:[4,9]

History of prematurity, very low birth weight, or other neonatal complications requiring intensive care
Congenital heart disease (repaired or unrepaired)
Recurrent urinary tract infections, hematuria, or proteinuria
Known renal disease or urologic malformations
Family history of congenital renal disease
Solid-organ transplant
Malignancy or bone marrow transplant
Treatment with drugs known to raise BP (see Table 3)
Other systemic illnesses associated with hypertension (e.g., neurofibromatosis, tuberous sclerosis, sickle cell disease)
Evidence of elevated intracranial pressure
Obesity
Hypertension symptoms or other concerns

Table 3. Common Medications Associated with Elevated BP:[4]

OTC	Prescription	Illicit
Decongestants NSAIDS Caffeine Some alternative therapies, herbal and nutritional supplements	Stimulants for ADHD Hormonal contraception Steroids Tricyclic antidepressants	Amphetamines Cocaine

ADHD, Attention Deficit/Hyperactivity Disorder; NSAIDS, Non-steroidal Anti-inflammatory Drugs; OTC, Over The Counter

Is BP being monitored in children and adolescents?

- Rates of BP screening in children and adolescents varies greatly across the world.[10]
  - America = 66% to 97% [10]
  - United Kingdom and Australia = 9% to 22% [10]
  - A survey of 197 Dutch pediatricians, residents and final-year medical students, found 71% of participants only measured BP during ambulatory visits for children with a diagnosis or suspected diagnosis associated with abnormal BP, or with risk factors for hypertension.[11]
- A 2016 Canadian retrospective cohort study determined rates of hypertension screening in children and adolescents. They also assessed the proportion of patients who received timely follow-up after an initial abnormal BP reading.[5]
  - Data from 79 Toronto primary care providers were used.
    - Patient encounters from age 3 to 18 years were recorded.

- Results:
  - Of the 9667 children and adolescents identified, 62% had at least 1 BP measurement recorded between the ages of 3 and 18 years.
  - The most common rate of BP recording was every 1 to 2 years.
  - Obesity or family history of hypertension was not associated with an increased rate of BP recording.
  - There was a higher rate of BP screening in female patients and those with an older age at first encounter.
    - Perhaps due to initiation of oral contraceptives.
  - 8% of the cohort had at least 1 elevated BP.
    - Only 5% of those had at least 1 further BP recorded within 6 months.
- Authors' Conclusions:
  - Initial screening was common, but when an abnormal BP was recorded, timely follow-up was infrequent.
  - Known risk factors of hypertension (e.g., family history of hypertension or obesity) were not associated with more frequent BP recording.

Why should we be monitoring BP in children and adolescents?

- Unlike adult hypertension, there is no evidence assessing the effects of treating childhood hypertension on "hard" clinical outcomes such as MI, stroke, or CV death later in life; instead, we rely mostly on surrogate outcome data in this population.
- Data from observational studies demonstrate both short and long term adverse effects of elevated BP in children and adolescents.
  - Elevated BP in childhood:
    - Tracks into adulthood.[2,12,13]
    - Is associated with target organ damage, including left ventricular hypertrophy (LVH), increased carotid intimal-medial thickness (an early marker of atherosclerosis), cognitive deficits, and renal damage in pediatric patients.[13]
    - Is associated with an increased risk of hypertension and metabolic syndrome at ≥ 30 years of age.[13]
- There is limited evidence on the benefits of treating hypertension in this population.
  - A 2014 Cochrane Review on pharmacological interventions for hypertension in children did not find any RCTs reporting clinical outcomes, only BP reduction.[14]
  - However, a randomized trial investigating BP targets in children with CKD (n = 84), and a retrospective cohort study of 22 children with primary or secondary hypertension, found treatment of hypertension reduced LVH.[15,16]

Why aren't children and adolescents being routinely screened for hypertension?

- Several reasons have been suggested, including:[10,13,17]
  - Complications are rare, especially compared to adults
  - Lack of "hard" clinical outcome data
  - Complexity of measuring BP
    - Requires availability of various BP cuff sizes
    - Child must cooperate and remain calm
  - Complexity of interpreting the BP reading
    - Requires access and familiarity of normative BP tables
  - Remuneration

Local Clinical Reviewer Opinion

- It can be difficult for family physicians to adopt recommendations to monitor BP regularly in all patients ≥ 3 years of age.[17]
- Children and adolescents often go years without visits to their family doctor, and are often only seen when acutely ill, which is not an opportune time to assess a patient for hypertension.[17]
- BP monitoring should be considered annually if children or adolescents with no risk factors are visiting the office, and at every visit if they have risk factors for developing hypertension.[17]

Question 2: How should BP be measured in children and adolescents?

Table 4. Hypertension Canada 2018 Guideline Recommendations on Accurate Measurement of BP in Children (Guideline 1-3):[1]

Recommendation	Grade
BP should be measured regularly in children 3 years of age and older by a health care professional using standardized pediatric techniques	Grade D
BP may be measured with a mercury sphygmomanometer, aneroid sphygmomanometer, or oscillometric device. Abnormal oscillometric values should be confirmed with auscultation.	Grade D Grade C
BP varies with age, sex, and height in children and, therefore, BP values should be compared with norms for age, sex, and height.	Grade D

What is standardized pediatric technique?

Table 5. Standardized Approach for BP Measurement in Children, from the Hypertension Canada 2018 Guidelines:[1]

1. Children who will undergo BP measurement should avoid stimulant medications before evaluation. At the time of evaluation, the child should be seated in a quiet room for 5 minutes with back supported before the measurement of blood pressure
2. The right arm is the preferred location for BP measurement for comparison with normative data because of the possibility of coarctation of the aorta, which might result in an erroneously low BP measurement being obtained in the left arm
3. A cuff size with a bladder width that is at least 40% of the arm circumference and the cuff bladder length should cover 80%-100% of the circumference of the arm. The arm should be bare and supported with the BP cuff at heart level. To obtain accurate measurements in children a range of pediatric and adult cuff sizes should be available
4. The pressure should be increased rapidly to 30 mm Hg above the level at which the radial pulse is extinguished
5. The stethoscope should be placed below the bottom edge of the cuff and above the antecubital fossa. The bell or diaphragm of the stethoscope should be held gently and steadily over the brachial artery
6. The control valve should be opened so that the rate of deflation of the cuff is approximately 2 mm Hg per heartbeat
7. The systolic level—the first appearance of a clear tapping sound (phase I Korotkoff)—and the diastolic level (the point at which the sounds disappear; phase V Korotkoff)—should be recorded. In some children, Korotkoff sounds can be heard to 0 mm Hg. If Korotkoff sounds persist as the level approaches 0 mm Hg, then the point of muffling of the sound is used (phase IV Korotkoff) to indicate the diastolic pressure
8. The BP should be recorded to the closest 2 mm Hg using the manometer (or 1 mm Hg using electronic devices)

BP, blood pressure.

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- A wide range of pediatric cuff sizes should be available in family physician's offices.
  - To pick the proper cuff size see step 3 of the standardized approach for BP measurement in children (Table 5).
- The following video from the American Academy of Pediatrics illustrates how to properly measure BP in a child: https://www.youtube.com/watch?v=JLzkNBpqwi0&feature=youtu.be.
- Documentation:
  - BP measurements should be recorded in the patients' medical record.
  - The state of the child (e.g., resting, crying) should also be recorded.

Can oscillometric devices be used in children?

- Oscillometric devices are attractive options as they require little training and have low inter-observer variability, however there are limitations to using them in this population:[18]
  - Most oscillometric devices are designed for adults.[2,19]
  - They use proprietary algorithms used to estimate BP, and few have been validated in children.[18,19]
  - Device inflation and deflation speeds, motion artifact, and the need for lower deflation thresholds in children are major sources of error.[19]
  - The child may not tolerate the device well due to high initial cuff inflation pressure and longer time to complete the reading.[2]
    - These limitations can make it difficult to obtain an accurate resting BP with an oscillometric device, **which may overestimate BP in children**.[10,18]
- There is limited evidence comparing auscultatory and oscillometric BP measurement techniques in young patients.[2]
- According to Hypertension Canada, it is reasonable to use auscultatory technique or oscillometric devices in this population.[2]
  - Abnormal readings from oscillometric devices should be confirmed with auscultatory technique.[2]
- Oscillometric devices should be calibrated regularly and validated for use in the pediatric population.
  - For a list of validated devices check: http://www.dableducational.org/sphygmomanometers.html

How do we interpret a child's BP?

- Unlike adults, a child's or adolescent's blood pressure is NOT compared to a single diagnostic threshold, instead, BP percentiles are used.[1]
- The BP reading should be compared with norms for age, sex, and height.[1]

- Normative BP tables use height percentiles as defined by the **CDC growth charts** (not WHO growth charts).[1]
  - CDC growth charts are available online at: https://www.cdc.gov/growthcharts/clinical_charts.htm

➢ Several normative BP tables are available:

- The normative BP tables referenced by the Hypertension Canada guidelines and recommended by a local clinical reviewer are "Blood Pressure Levels for Boys by Age and Height Percentile" and "Blood Pressure Levels for Girls by Age and Height Percentile" from the National Heart, Lung, and Blood Institute's 2004 Fourth Report.[2,17,20,21]
  - These tables are based on BP data from ~65,000 children.[10]
  - Used auscultation methods to obtain BP.[1]
  - To use, with the appropriate sex table, locate the child's age on the left side of the table and follow the age row horizontally across the table to the intersection of the line for the height percentile as shown in the vertical column. Here the 50th, 90th, 95th, and 99th percentiles are defined for systolic blood pressure (SBP) and diastolic blood pressure (DBP).[1]
  - Available online at: https://www.nhlbi.nih.gov/files/docs/guidelines/child_tbl.pdf and in Appendix 4.

➢ Some simplified BP charts have also been developed.[22]

- Banker et al. created a simplified BP chart **screening tool** using CDC growth chart and the Fourth Report BP table data.[22]
  - Available online at: https://med.uth.edu/pediatrics/nephrology-hypertension/nephrology-research/ and in Appendix 5.
  - This tool requires only gender and **absolute** height to screen BP, no height percentiles needed.
  - Color coded areas identify blood pressure category.
  - 100% sensitivity, 94.7% systolic specificity, and 99.3% diastolic specificity for hypertension.
    - False positive rate <6%
  - Should be used for screening only, not for diagnosis.

Guideline Watch:

➢ The American Academy of Pediatrics have changed their definition of stage 1 and stage 2 hypertension, and have updated the normative BP tables in their 2017 Clinical Practice Guidelines.

- They have changed the BP dataset the tables are based on by removing data from children who were overweight or obese.[4]

- Hypertension Canada has not yet made these changes.

Local Clinical Reviewer Opinion

- All physicians who care for children and adolescents should have access to, and be familiar with, normative BP tables to interpret BP in this patient population.[17]

Question 3: How is hypertension diagnosed in children and adolescents?

- Hypertension in children and adolescents is underdiagnosed.[23]
  - Family physicians should be familiar with the criteria for diagnosis of hypertension in this patient population.

Table 6. Hypertension Canada 2018 Guideline Recommendations on Criteria for Diagnosis of Hypertension in Children:[1]

Recommendation	Grade
Using office BP measurements, children can be diagnosed as hypertensive if SBP or DBP is ≥95th percentile for age, sex, and height, measured on at least 3 separate occasions.	Grade C
If the BP is ≥95th percentile, BP should be staged. Stage 1 is defined by BP between the 95th percentile and 99th percentile plus 5 mmHg. Stage 2 is defined by BP >99th percentile plus 5 mmHg.	Grade D
i. If BP is stage 1, BP measurements should be repeated on 2 more occasions within 1 month; if hypertension is confirmed, evaluation (*as described in section IV. Routine Laboratory Tests for the Investigation of Children With Hypertension in the 2018 Hypertension Canada guidelines[1])* and/or appropriate referral should be initiated within 1 month, or both.	Grade D
ii. If BP is stage 2, prompt referral should be made for evaluation and therapy.	Grade C
All children with suspected or confirmed hypertension should undergo a hypertension-focused history and physical evaluation (see Table 7).	Grade C

- The definition of hypertension in children is based on being at the extreme end of the normal distribution of BP.[2]
- Due to a high rate of false-positive high BP readings at a single visit, multiple visits are required to confirm the diagnosis of hypertension.[10]
- Hypertension Canada do not make any recommendations on how many BP readings to take at each office visit.[1]
  - The American Academy of Pediatrics recommend **if the initial BP is elevated** (≥90th percentile), providers should perform 2 additional oscillometric or auscultatory BP measurements at the same visit and average them.
    - If using auscultation, this averaged measurement is used to determine the child's BP category (i.e., normal, stage 1, or stage 2 hypertension).
    - If the averaged oscillometric reading is ≥ 90th percentile, 2 auscultatory measurements should be taken and averaged to define the BP category.[4]
- Staging BP is important. Stage 2 hypertension requires prompt evaluation by a specialist as:

- Symptoms are more common.[2]
- There is increased prevalence of target organ damage.[2]
- Hypertensive emergencies are more frequent.[2]

Table 7. History and Physical Examination of Children:[1]

1. Medical history

Symptoms
- Of hypertension
- Of an underlying disorder*

Past medical history
- For underlying cause of hypertension,* including neonatal history
- Identify other cardiovascular risk factors including inactivity, smoking, and dietary factors
- Family history

2. Patient physical examination
- Height, weight, and body mass index
- Vital signs including upper and lower limb blood pressures
- Evaluation for signs of end organ damage
- Fundi, cardiovascular, and neurologic systems
- Evaluation for underlying cause of hypertension*

* Systems to review include renal, cardiovascular, endocrine, and neurologic, as well as medications/drugs and sleep disorders.

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What about white coat hypertension?

- Up to 50% of children who are evaluated for elevated office BP have white coat hypertension.[4]
- Ambulatory blood pressure monitoring (ABPM) is useful to classify hypertension into the following categories:

Table 8. Hypertension Canada's Suggested Schema to Classify BP in Children:[1]

Classification	Office BP	Mean ambulatory SBP or DBP during wake or sleep period, or both	SBP or DBP load, %
White coat hypertension	≥ 95th percentile	< 95th percentile	< 25
Masked hypertension	< 95th percentile	≥ 95th percentile	≥ 25
Ambulatory hypertension	≥ 95th percentile	≥ 95th percentile	25-50
Severe ambulatory hypertension	≥ 95th percentile	≥ 95th percentile	> 50

BP, blood pressure; DBP, diastolic BP; SBP, systolic BP.

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Note: Load is defined as the percentage of valid ambulatory BP measurements above a set threshold value (e.g., 95th percentile) for age, sex, and height.[4]

- Guidelines on the use of ambulatory BP measurement in children can be found in the Hypertension Canada 2018 guidelines.[1]

Local Clinical Reviewer Opinion

- ABPM should be conducted and interpreted by an expert in pediatric hypertension using an ABPM device validated in children.[17]
  - This is in agreement with Hypertension Canada guideline recommendations. [1,2]

Question 4: In what practice setting should children and adolescents with hypertension be managed?

Health Behavior Management:

- Family physicians, allied-health team members, and other health care practitioners can promote healthy behaviors to children (and their families) with hypertension or those at risk.[6]
- Modifying BMI, diet, and physical activity can improve markers of CV health.[6]
- A RCT of 44 obese children, randomized participants to either 60 minutes of physical activity 3 times a week for 3 months, or to no change in physical activity status.[24]
  - Results:
    - After 3 months, BP was reduced in the physical activity arm. The mean difference in clinic SBP and DBP between arms was 7 mmHg, which was statistically significant.
  - After the initial 3 months, all participants were invited to participate in an exercise program for a further 3 months.
    - After 6 months of increased physical activity, the initial exercise arm had a significant reduction in carotid intima-media thickness and arterial stiffness compared to the control arm.
  - Authors' Conclusion:
    - "Participation in physical activity programs should be encouraged in young obese children to reduce systemic BP and prevent the premature development of atherosclerosis."
- Combining dietary improvements and physical activity can reduce SBP and DBP significantly more than either intervention alone.[6]
- Patients and their families should be educated and encouraged to eat healthy and participate in safe physical activity to help prevent and treat hypertension.
- A full discussion of health behavior management is outside of the scope of this review.

Pharmacological Management:

- Recommendations for pharmacological management were added to the Hypertension Canada guidelines in 2017.[6]
  - Note: If interested to read further on this topic please see the 2017 version of the guidelines, as the 2018 guidelines only provide a brief summary.[1,6]
- **Hypertension Canada strongly recommends that the guidelines for pharmacologic treatment of pediatric hypertension by primary care practitioners should apply only to children ≥12 years of age.[6]**

- Hypertension Canada provides recommendations for initial therapy for children ≥12 years of age with primary hypertension for practitioners who are comfortable in prescribing antihypertensive medications to children and adolescents.[6]
  - They also acknowledge that referral to an expert in pediatric hypertension for BP management is **always an acceptable alternative**.[6]
- **Hypertension Canada recommends that young children and those suspected of having a secondary cause of hypertension should be referred to and managed by experts in pediatric hypertension.[6]**
  - Young children are more likely to have a secondary cause of hypertension, and targeting therapy to the cause should be directed by an expert in pediatric hypertension.[6]

Table 9. Summary of Recommended Practitioner Type to Manage Children with Hypertension:[1,6,17]

Patient Population:	Management By:
Children <12 years of age	Expert in pediatric hypertension*
Children or adolescents (at any age) with/suspected secondary cause of hypertension	Expert in pediatric hypertension*
Children or adolescents (at any age) with stage 2 hypertension	Expert in pediatric hypertension*
Children or adolescents ≥12 years of age with stage 1 hypertension **without** a suspected secondary cause of hypertension	Expert in pediatric hypertension* **OR** a practitioner who is comfortable in prescribing antihypertensive medications to children and adolescents (**BUT** If BP goals are not achieved with standard-dose monotherapy for ≥6 months, patients should be referred to an expert in pediatric hypertension)
* Pediatric Nephrologist or General Pediatrician (practitioner type may depend on available health care resources)	

- The decision to start drug therapy depends on several factors, including:[6]
  - Symptoms
  - Level of BP elevation
  - Target organ damage
  - Response to nonpharmacological interventions
  - Comorbid conditions (e.g., diabetes, CKD, or HF)
- **The evaluation of hypertension after initial diagnosis, and the pharmacological management of hypertension in children and adolescents is outside of the scope of this review.**

Local Clinical Reviewer Opinion:

- Although children and adolescents can be diagnosed as hypertensive if SBP or DBP is ≥95th percentile for age, sex, and height, measured on at **least 3 separate occasions**, it is

reasonable to refer the patient to pediatric nephrology or general pediatric services (practitioner type may depend on resources available in your region) **after 2 occasions**.[17]

When is urgent care required?

- Hypertension is relatively common (2%) in the pediatric population.[1]
  - First-episode hypertensive emergencies in children are rare, occurring in only 2 per 10,000 emergency department visits.[25]
- Clinical judgement must be used to determine the severity of hypertension and the potential for life-threatening end-organ damage.[25]
  - This determines the timing and intensity of management.[25]
- The American Academy of Pediatrics recommend that patients should be referred to an emergency department when:[4]
  - BP reading is at the stage 2 hypertension level and the patient is **symptomatic**, or
  - BP is >30 mmHg above the 95th percentile (or >180/120 mmHg in an adolescent).
- **Symptoms of hypertension** may include:
  - Irritability, fatigue, dizziness, changes in mental status, headache, seizure, visual disturbances, other focal neurologic complaints, CV complaints suggestive of HF (such as chest pain, palpitations, cough, edema, or shortness of breath), abdominal pain, and vomiting.[6,25]
- The BP reading itself may be less important than whether end-organ **symptoms and/or damage are present** and associated with an **acute change** in BP.[25]
  - In other words, a child with an acute increase in BP may have a hypertensive emergency even though their BP is only moderately elevated.[25]

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Appendix 1: Antihypertensive Drug Tables

Single Entity Oral Antihypertensive Agents Also Available in Single Pill Combinations:

Drug *(Brand)*	Available Strengths	Dose Initial [Usual Maintenance]	Nova Scotia Pharmacare Status	Cost/Month $ (Maintenance)
Angiotensin Converting Enzyme Inhibitors (ACEi)*				
Cilazapril (*Inhibace,* generic)	1, 2.5, 5 mg	2.5 mg once daily [2.5-5 mg once daily]	FB	7.49-12.89
Enalapril (*Vasotec*, generic)	2.5, 5, 10, 20 mg	5 mg once daily [10-40 mg daily in 1 single or 2 divided doses]	FB	8.33-20.12
Lisinopril (*Zestril, Prinivil,* generic)	5, 10, 20 mg	10 mg once daily [10-40 mg once daily]	FB	5.40-13.00
Perindopril (*Coversyl*, generic)	2, 4, 8 mg	4 mg once daily [4-8 mg once daily]	FB	6.13-8.49
Quinapril (*Accupril,* generic)	5, 10, 20, 40 mg	10 mg once daily [10-20 mg once daily]	FB	6.96
Ramipril (*Altace*, generic)	1.25, 2.5, 5, 10, 15 mg	2.5 mg once daily [2.5-10 mg once daily]	FB	2.45-3.10
Trandolapril (*Mavik*, generic)	0.5, 1, 2, 4 mg	1 mg once daily [1-2 mg once daily]	FB	5.29-6.08
Angiotensin II Receptor Blockers (ARB)*				
Azilsartan *(Edarbi)*	40, 80 mg	20 mg once daily [40-80 mg once daily]	NB	40.41
Candesartan (*Atacand*, generic)	4, 8, 16, 32 mg	8 mg once daily [8-32 mg once daily]	FB NB: 4 mg	6.84
Eprosartan *(Teveten)*	400, 600 mg	600 mg once daily [600 mg once daily]	FB	37.58
Irbesartan *(Avapro,* generic)	75, 150, 300 mg	75 mg once daily [150-300 mg once daily]	FB	6.84
Losartan (*Cozaar*, generic)	25, 50, 100 mg	25 mg once daily [50-100 mg once daily]	FB	9.44
Olmesartan (*Olmetec*, generic)	20, 40 mg	20 mg once daily [20-40 mg once daily]	FB	9.06
Telmisartan (*Micardis*, generic)	40, 80 mg	40 mg once daily [40-80 mg once daily]	FB	6.48
Valsartan (*Diovan*, generic)	40, 80, 160, 320 mg	80 mg once daily [80-320 mg once daily]	FB	6.29-6.48
Beta-Blockers*				
Atenolol (*Tenormin*, generic)	25, 50, 100 mg	50 mg once daily [50-100 mg once daily]	FB	3.32-5.46
Pindolol (*Visken*, generic)	5, 10, 15 mg	5 mg BID [10 mg BID-15 mg TID] Note: Doses over 30 mg/day should be given in three divided doses	FB	15.00-80.05
Calcium Channel Blockers*				
Amlodipine (*Norvasc*, generic)	2.5, 5, 10 mg	5 mg once daily [5-10 mg once daily]	FB	4.03-5.98
Verapamil (*Isoptin*, generic)	**IR:** 80, 120 mg **SR:** 120, 180, 240 mg	**IR:** 80 mg TID [80-160 mg TID] **SR:** 180-240 mg daily [180 mg daily to 240 mg BID]	FB NB: SR 120 mg	IR: 24.62-49.23 SR: 15.50-20.70
Direct Renin Inhibitors‡				
Aliskiren *(Rasilez)*	150, 300 mg	150 mg once daily [150-300 mg once daily]	NB	42.17
Thiazide Diuretics*				
Hydrochlorothiazide (generic)	12.5, 25, 50 mg	12.5 mg once daily [12.5-25 mg once daily]	FB	0.47-0.97
Thiazide-Like Diuretics*				
Chlorthalidone (generic)	50 mg	12.5 mg once daily [12.5-25 mg once daily]	FB	1.08-2.16
Indapamide (*Lozide*, generic)	1.25, 2.5 mg	1.25 mg once daily [1.25-2.5 mg once daily]	FB	2.24-3.55
Other Diuretics				
Amiloride (generic)*	5 mg	5 mg once daily [5-10 mg/day]	FB	18.86
Spironolactone *(Aldactone,* generic)‡	25, 100 mg	25-100 mg/day [25-100 mg/day]	FB	3.92-8.97

FB = Full Benefit, NB = Not a Benefit, IR: Immediate Release, SR: Sustained Release. Doses are for hypertensive patients without additional risk factors. Dose adjustments may be required in the elderly, in individuals with renal or hepatic impairment, or for those with other additional risk factors.
* Dosing information accessed from Canadian Pharmacists Association Monographs, July 11, 2019, available in RxTx. https://www.e-therapeutics.ca
‡ Dosing information accessed from Micromedex, July 11, 2019. https://www.micromedexsolutions.com/micromedex2/librarian/
$ Pricing obtained from McKesson Canada on June 24th, 2019. No fees or markups have been included.
For additional prescribing information, see product monographs.

Currently Available Single Pill Combinations:

ACEi Containing Single Pill Combinations (SPCs)				
Drugs *(Brand)*	**Available Strengths**	**Initial Dose* [Usual Maintenance Dose Range]‡**	**Nova Scotia Pharmacare Status**	**Cost/Month $**
Calcium Channel Blocker Combinations				
Perindopril + Amlodipine (*Viacoram*, generic)	3.5/2.5 mg 7/5 mg 14/10 mg	3.5/2.5 mg once daily [7/5 mg once daily]	NB	24.23-29.33
Trandolapril + Verapamil (*Tarka*)	2/240 mg 4/240 mg	Fixed combination is not for initial therapy [2/240 mg - 4/240 mg once daily]	NB	57.61-63.93
Thiazide Diuretic Combinations				
Cilazapril + Hydrochlorothiazide (*Inhibace Plus,* generic)	5/12.5 mg	Fixed combination is not for initial therapy [5/12.5 mg once daily]	FB	12.51
Enalapril + Hydrochlorothiazide (*Vaseretic,* generic)	5/12.5 mg 10/25 mg	Fixed combination is not for initial therapy [5/12.5 mg - 10/25 mg once daily]	NB	27.26-38.21
Lisinopril + Hydrochlorothiazide (*Zestoretic,* generic)	10/12.5 mg 20/12.5 mg 20/25 mg	Fixed combination is not for initial therapy [10/12.5 mg - 20/25 mg once daily]	FB	6.43-7.73
Quinapril + Hydrochlorothiazide (*Accuretic ,* generic)	10/12.5 mg 20/12.5 mg 20/25 mg	Fixed combination is not for initial therapy [10/12.5 mg - 20/25 mg once daily]	FB	13.81-14.36
Ramipril + Hydrochlorothiazide (*Altace HCT,* generic)	2.5/12.5 mg 5/12.5 mg 5/25 mg 10/12.5 mg 10/25 mg	Fixed combination is not for initial therapy [2.5/12.5 mg - 10/25 mg once daily]	FB	3.95-6.03
Thiazide-Like Diuretic Combinations				
Perindopril + Indapamide (*Coversyl Plus (LD, HD),* generic)	2/0.625 mg 4/1.25 mg 8/2.5 mg	*Coversyl Plus* & *Coversyl Plus HD* not for initial therapy [2/0.625 mg - 8/2.5 mg once daily]	FB NB: 2/0.625 mg	15.34-21.56

ARB Containing SPCs				
Drugs *(Brand)*	**Available Strengths**	**Initial Dose* [Usual Maintenance Dose Range]‡**	**Nova Scotia Pharmacare Status**	**Cost/Month $**
Calcium Channel Blocker Combinations				
Telmisartan + Amlodipine *(Twynsta)*	40/5 mg 40/10 mg 80/5 mg 80/10 mg	Fixed combination is not for initial therapy [40/5 mg - 80/10 mg once daily]	FB	23.75
Thiazide Diuretic Combinations				
Candesartan + Hydrochlorothiazide (*Atacand Plus,* generic)	16/12.5 mg 32/12.5 mg 32/25 mg	Fixed combination is not for initial therapy [16/12.5 mg once daily]	FB	6.47-9.14
Eprosartan + Hydrochlorothiazide *(Teveten Plus)*	600/12.5 mg	Fixed combination is not for initial therapy [600/12.5 mg once daily]	FB	37.58
Irbesartan + Hydrochlorothiazide (*Avalide,* generic)	150/12.5 mg 300/12.5 mg 300/25 mg	Fixed combination is not for initial therapy except for severe hypertension [150/12.5 mg - 300/12.5 mg once daily]	FB	6.55-6.84
Losartan + Hydrochlorothiazide (*Hyzaar,* generic)	50/12.5 mg 100/12.5 mg 100/25 mg	Fixed combination is not for initial therapy except for severe hypertension [50/12.5 mg - 100/25 mg once daily]	FB	9.25-9.44

Olmesartan + Hydrochlorothiazide (*Olmetec Plus*, generic)	20/12.5 mg 40/12.5 mg 40/25 mg	Fixed combination is not for initial therapy [20/12.5 mg - 40/25 mg once daily]	FB	18.11
Telmisartan + Hydrochlorothiazide (*Micardis Plus,* generic)	80/12.5 mg 80/25 mg	Fixed combination is not for initial therapy [80/12.5 mg - 80/25 mg once daily]	FB	6.29
Valsartan + Hydrochlorothiazide (*Diovan HCT,* generic)	80/12.5 mg 160/12.5 mg 160/25 mg 320/12.5 mg 320/25 mg	Fixed combination is not for initial therapy [80/12.5 mg - 160/25 mg once daily]	FB	6.64-6.72
Thiazide-Like Diuretic Combinations				
Azilsartan + Chlorthalidone (*Edarbyclor)*	40/12.5 mg 40/25 mg	May be used as initial therapy in patients with severe essential hypertension [40/12.5 mg - 40/25 mg once daily]	NB	40.18

Beta-Blocker Containing SPCs

Drugs *(Brand)*	Available Strengths	Initial Dose* [Usual Maintenance Dose Range]‡	Nova Scotia Pharmacare Status	Cost/Month $
Thiazide Diuretic Combinations				
Pindolol + Hydrochlorothiazide (*Viskazide)*	10/25 mg 10/50 mg	Fixed combination is not for initial therapy [10/25 mg once daily]	FB	35.83
Thiazide-Like Diuretic Combinations				
Atenolol + Chlorthalidone (*Tenoretic,* generic)	50/25 mg 100/25 mg	Fixed combination is not for initial therapy [50/25 mg - 100/25 mg once daily]	FB	9.59-15.71

Direct Renin Inhibitor Containing SPCs

Drugs *(Brand)*	Available Strengths	Initial Dose* [Usual Maintenance Dose Range]‡	Nova Scotia Pharmacare Status	Cost/Month $
Aliskiren + Hydrochlorothiazide *(Rasilez HCT)*	150/12.5 mg 150/25 mg 300/12.5 mg 300/25 mg	Fixed combination is not for initial therapy [150/12.5 mg – 300/25 mg once daily]	NB	42.60

Diuretic Only SPCs

Drugs *(Brand)*	Available Strengths	Initial Dose‡ [Usual Maintenance Dose Range]‡	Nova Scotia Pharmacare Status	Cost/Month $
Hydrochlorothiazide + Amiloride (generic)	50/5 mg	[25/2.5 mg once daily]	FB	3.88-7.76
Hydrochlorothiazide + Spironolactone (*Aldactazide,* generic)	25/25 mg 50/50 mg	12.5/12.5 mg once daily [25/25 mg once daily]	FB	7.84-16.59
Hydrochlorothiazide + Triamterene (generic)	25/50 mg	12.5/25 mg once daily [25/50 mg once daily]	FB	3.65

FB = Full Benefit, NB = Not a Benefit, SPC = Single Pill Combinations. Doses are for adult hypertensive patients without additional risk factors. Dose adjustments may be required in the elderly, in individuals with renal or hepatic impairment, or for those with other additional risk factors.

* Dosing information accessed from drug product monographs available from the Health Canada Drug Product Database, July 11, 2019. https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

‡ Dosing information accessed from Canadian Pharmacists Association (CPhA) Compendium of Therapeutic Choices (CTC) Hypertension Drug Tables, July 11, 2019, available in RxTx. https://www.e-therapeutics.ca

Note: As reflected in dosing listed above, most Health Canada approved drug product monographs for SPCs do not currently recommend fixed combination for initial therapy. This differs from Hypertension Canada 2018 guidelines which suggest that initial therapy for adults with diastolic hypertension +/- systolic hypertension without compelling indications should be with either monotherapy or a SPC (Hypertension Canada recommended initial SPC choices are: ACEi or ARB + CCB, or ACEi or ARB + diuretic).

$ Pricing obtained from McKesson Canada: June 24th, 2019. No fees or markups have been included.

For additional prescribing information, see product monographs.

Appendix 2: Systems for Rating Evidence and the Strength of Recommendations from SOGC and Hypertension Canada Guidelines

SOGC Key to Evidence Statements and Grading of Recommendations:[3]

Quality of evidence assessment	Classification of recommendations
I: Evidence obtained from at least one properly randomized controlled trial (RCT) **II-1:** Evidence from well-designed controlled trials without randomization **II-2:** Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group **II-3:** Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in the category **III:** Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	**A.** There is good evidence to recommend the clinical preventive action **B.** There is fair evidence to recommend the clinical preventive action **C.** The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making **D.** There is fair evidence to recommend against the clinical preventive action **E.** There is good evidence to recommend against the clinical preventive action **L.** There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

GRADE Definitions for Quality of Evidence and Strength of Recommendations used by SOGC:[3]

Quality of the evidence:	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect
Strength of recommendations:	
Strong:	
For patients/public	We believe most people in this situation would want the recommended course of action and only a small number would not
For clinicians	The recommendation would apply to most individuals. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences
For policy makers and developers of quality measures	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator

Weak:	
For patients/public	We believe that most people in this situation would want the recommended course of action, but many would not. Different choices are acceptable for each person and clinicians should support patients and discuss their values and preferences to reach a decision. Decision aids may support people in reaching these decisions
For clinicians	We recognize that different choices may be appropriate for individual patients. Clinicians should support each patient in reaching a management decision consistent with his or her values and preferences. Decision aids may support individuals in reaching such decisions
For policy makers and developers of quality measures	Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as quality indicator

Hypertension Canada Grading Scheme for Recommendations:[1]

Grade A	Recommendations are based on randomized trials (or systematic reviews of trials) with high levels of internal validity and statistical precision, and for which the study results can be directly applied to patients because of similar clinical characteristics and the clinical relevance of the study outcomes.
Grade B	Recommendations are based on randomized trials, systematic reviews or pre-specified subgroup analyses of randomized trials that have lower precision, or there is a need to extrapolate from studies because of differing populations or reporting of validated intermediate/surrogate outcomes rather than clinically important outcomes.
Grade C	Recommendations are based on trials that have lower levels of internal validity and/or precision, or trials reporting unvalidated surrogate outcomes, or results from non-randomized observational studies.
Grade D	Recommendations are based on expert opinion alone

Appendix 3: Risk Markers for Preeclampsia, According to the SOGC 2014 Guidelines:[3]

Demographics and family history	Past medical or obstetric history	Current pregnancy	
		First trimester	Second or third trimester
Maternal age ≥40 years	**Previous preeclampsia**	**Multiple pregnancy**	Elevated BP (gestational hypertension)ǂ
Family history of preeclampsia (mother or sister)	**Anti-phospholipid antibody syndrome**	Overweight/obesity	Abnormal AFP, hCG, inhA or E_3 (see guidelines for more details)
Family history of early-onset cardiovascular disease	**Pre-existing medical condition(s)** • **Pre-existing hypertension or booking diastolic BP ≥90 mmHg** • **Pre-existing renal disease or booking proteinuria** • **Pre-existing diabetes mellitus**	First ongoing pregnancy	Excessive weight gain in pregnancy
		New partner	Infection during pregnancy (e.g., UTI, periodontal disease)
		Short duration of sexual relationship with current partner	Abnormal uterine artery doppler
		Reproductive technologies (subfertility and its treatment)	IUGR
	Lower maternal birthweight and/or preterm delivery	Inter-pregnancy interval ≥10 years	Investigational laboratory Markers**
	Heritable thrombophilias*	Booking SBP ≥130 mmHg, or booking DBP ≥80 mmHg	
	Increased pre-pregnancy triglycerides	Vaginal bleeding in early pregnancy	
	Non-smoking	Gestational trophoblastic disease	
	Cocaine and metamphetamine use	Abnormal PAPP-A or free ßhCG	
	Previous miscarriage at ≤10 weeks with same partner	Investigational laboratory markers**	

Bolded risk factors are strong risk factors.
AFP, alfafetoprotein; Booking, first antenatal visit, usually early in pregnancy; DBP, diastolic blood pressure; E_3, oestriol; hCG, human chorionic gonadotropin; inhA, inhibin A; IUGR, intrauterine fetal growth restriction; MSS, maternal serum screening; PAPP-A, pregnancy-associated plasma protein A; SBP, systolic blood pressure; UTI, urinary tract infection.
*Heritable thrombophilia includes Factor V Leiden gene mutation and Protein S deficiency.
**Investigational markers include, in the first trimester: PAPP-A, PlGF, PP-13, and in the second trimester: elevated sFlt-1/PlGF (soluble fms-like tyrosine kinase, placental growth factor), PAI-1/PAI-2 (plasminogen activator inhibitor), von Willebrand factor, and leptin.
ǂ Elevated BP is defined as DBP ≥110 mmHg before 20 weeks, 2nd trimester mean arterial pressure of ≥85 mmHg, or a 2nd trimester SBP ≥120 mmHg.

Women at increased risk (who should be considered for specialty referral) are those with one of the **bolded** markers, or two or more of the unbolded markers.

Appendix 4: Normative Blood Pressure Tables from the National Heart, Lung, and Blood Institute's 2004 Fourth Report

Blood Pressure Levels for Boys by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

Blood Pressure Levels for Boys by Age and Height Percentile (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

Blood Pressure Levels for Girls by Age and Height Percentile

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

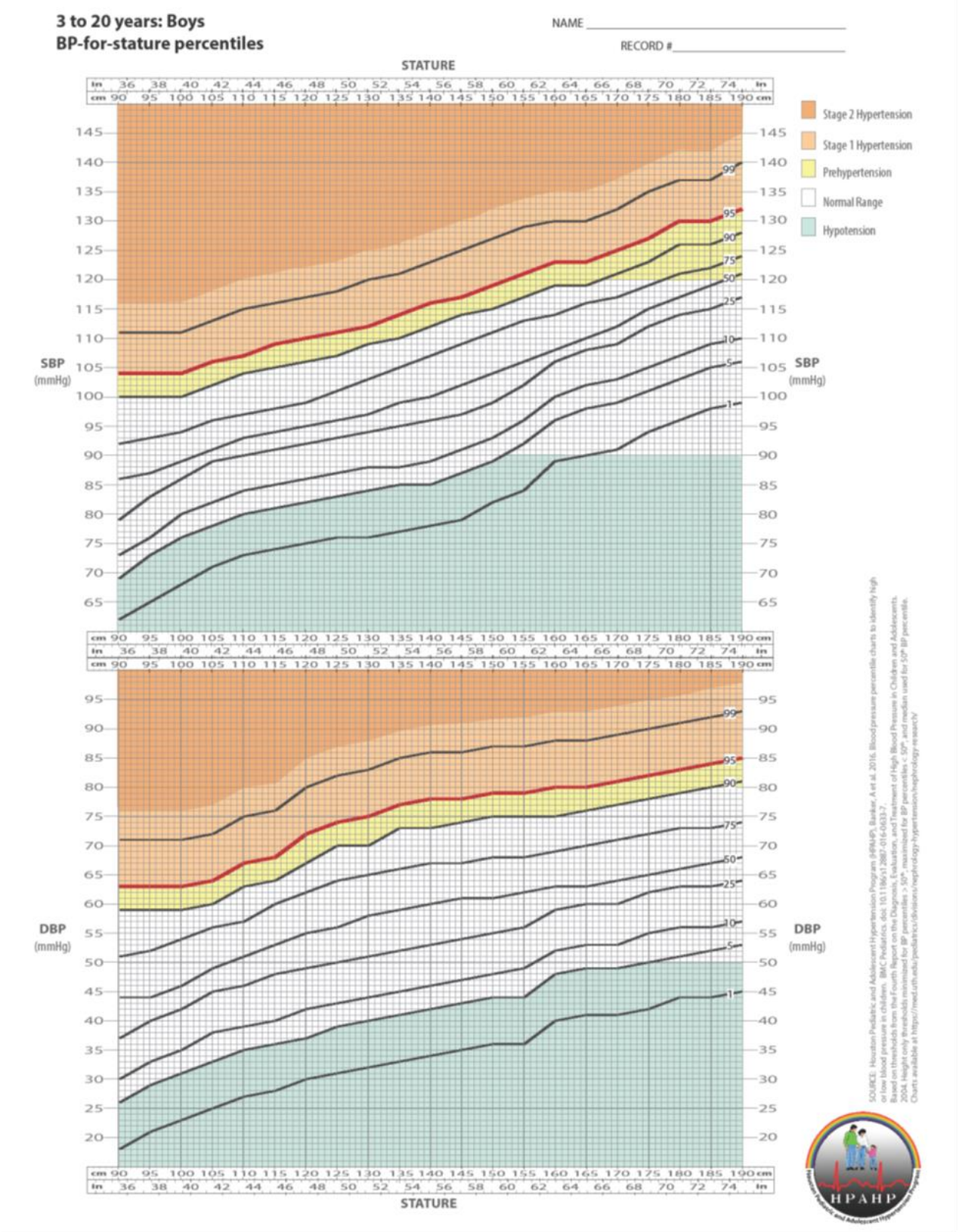
Blood Pressure Levels for Girls by Age and Height Percentile (Continued)

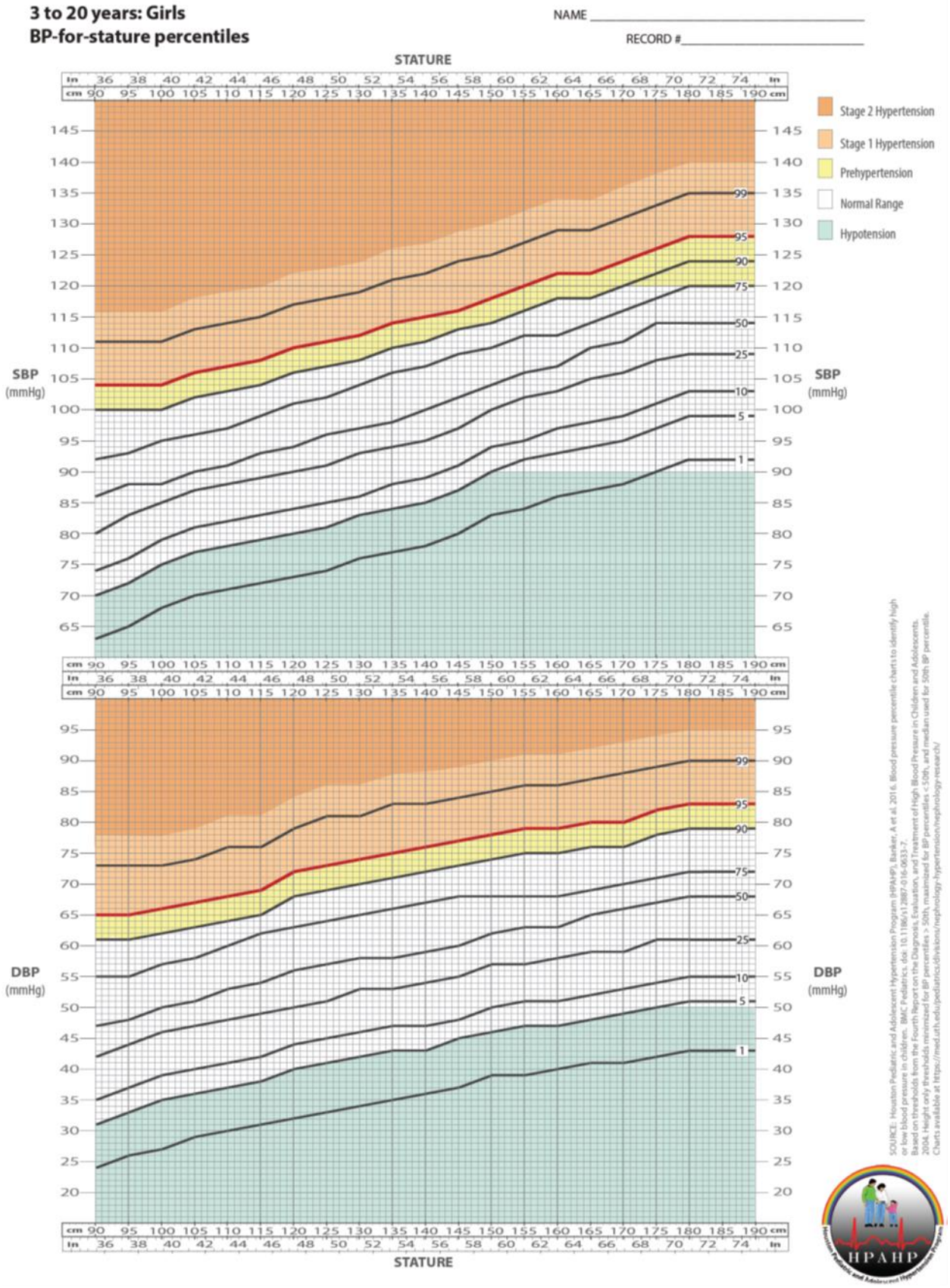
Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP, blood pressure

* The 90th percentile is 1.28 SD, 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

Appendix 5: Simplified Blood Pressure Chart Screening Tool by Banker et al.[22]




3 to 20 years: Girls
BP-for-stature percentiles
NAME
RECORD #
STATURE
Stage 2 Hypertension
Stage 1 Hypertension
Prehypertension
Normal Range
Hypotension
SBP (mmHg)
DBP (mmHg)
99
95
90
75
50
25
10
5
1
SOURCE: Houston Pediatric and Adolescent Hypertension Program (HPAHP), Flynn, J. et al. 2016. Blood pressure percentile charts to identify high or low blood pressure in children. BMC Pediatrics. doi: 10.1186/s12887-016-0633-7.
Based on thresholds from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. 2004. Height only thresholds minimized for BP percentiles > 50th, maximized for BP percentiles < 50th, and median used for 50th BP percentile.
Charts available at https://med.uth.edu/pediatrics/divisions/nephrology-hypertension/nephrology-research/
HPAHP