Hypertension in Primary Care: Blood Pressure Goals for Adults Aged 60 and Older

B.C. Provincial Academic Detailing Service **November 2017**

Background

Clinical practice guidelines recommend varied systolic blood pressure goals for adults aged 60 and older with hypertension: < 150 mmHg, < 140 mmHg, < 130 mmHg, ≤ 120 mmHg.[1-6]

Participants in this PAD education session will have the opportunity to discuss:

1. How guidelines weigh different sources of evidence when formulating recommendations with specific attention given to systolic blood pressure goals in older adults
2. Relevant clinical considerations when prescribing and monitoring patients receiving antihypertensive medications with a focus on four antihypertensive classes

For systolic blood pressure (SBP) goals, consider the strength of recommendations from two guidelines published in 2017, their corresponding grading of the quality of evidence, and definitions of intensive management:

The American College of Physicians and the American Academy of Family Physicians 2017 guideline for hypertension in adults aged 60 and older[5]

General Goal of Therapy:	In adults aged ≥ 60 years with SBP persistently ≥ 150 mmHg, initiate treatment to achieve SBP < 150 mmHg; select goals based on periodic discussion of the benefits and harms [High Quality Evidence; Strong Recommendation]
Intensive Management:	In some adults aged ≥ 60 at high cardiovascular risk, consider initiating or intensifying pharmacologic treatment to achieve SBP < 140 mmHg; select goals based on periodic discussion of the benefits and harms [Low Quality Evidence; Weak Recommendation]

Hypertension Canada's 2017 guideline for hypertension in adults[6]

General Goal of Therapy:	Goal systolic blood pressure (SBP) < 140 mmHg [Grade C Evidence; Strong Recommendation] Goal diastolic blood pressure (DBP) < 90 mmHg [Grade A Evidence; Strong Recommendation]
Intensive Management:	In high-risk patients, aged ≥ 50 years, with SBP ≥ 130 mmHg, intensive management to target SBP ≤ 120 mmHg should be considered; intensive management should be guided by automated office blood pressure measurements [Grade B Evidence; Strong Recommendation]

The guideline identifies the following people as "candidates for intensive management":[6]

- Age ≥ 75 years, or
- Clinical or subclinical cardiovascular disease, or
- Chronic kidney disease [nondiabetic nephropathy, proteinuria < 1 g/d, estimated eGFR 20-59 mL/min/1.73 m^2], or
- Estimated 10-year cardiovascular risk ≥ 15% [Framingham Risk Score]

And delineates several "cautions and contraindications":[6]

- Limited or no evidence → heart failure [ejection fraction < 35%], recent myocardial infarction [within past 3 months], indication for but not currently receiving a beta blocker, institutionalized elderly patient
- Inconclusive evidence → diabetes mellitus, previous stroke, eGFR < 20 mL/min/1.73m^2
- Contraindications → patient unwilling or unable to adhere to multiple medications, standing SBP < 110 mmHg, inability to measure SBP accurately, secondary causes of hypertension

What is the evidence for treating hypertension in adults aged 60 and older?

Cochrane Systematic Review 2009[1] authors' conclusion [15 RCTs, N=24,055; 4.5 years]: "Treating healthy persons (60 years or older) with moderate to severe systolic and/or diastolic hypertension reduces all-cause mortality and cardiovascular morbidity and mortality." Cardiovascular morbidity & mortality were reduced by approximately 40 events per 1000 people over 4.5 years.

COCHRANE 2009[1] Pharmacotherapy for hypertension in adults aged 60+			15 RCTs; N=24,055	4.5 years
all-cause mortality	ARR 1.2%	NNTB 23 [CV morb & mort]	RR 0.90 [95%CI 0.84, 0.97]	low quality
cardiovascular morbidity & mortality	ARR 4.3%		RR 0.72 [95%CI 0.68, 0.77]	high quality

Applicability mainly a primary prevention population with mean baseline SBP ≥ 160 mmHg [average across trials = 182/95 mmHg; 172/81 mmHg in isolated systolic hypertension trials] | community dwelling | mean age 74 [28% aged ≥ 80] | 60% women
Stepped care approach used by majority of trials | achieving SBP < 150-160 mmHg | thiazide first-line drug in > 70% of trials

What is the evidence for treating hypertension in adults aged 80 and older?

Cochrane Systematic Review 2009[1] authors' conclusion [8 RCTs, N=6701; 2.2 years]: "In very elderly patients ≥ 80, the reduction in total cardiovascular morbidity and mortality was similar to adults aged 60+ [RR 0.75, 95%CI 0.65, 0.87; moderate quality evidence], however there was no reduction in all-cause mortality" [RR 0.98, 95%CI 0.87, 1.10; low quality evidence] … "trials with longer duration of treatment in the very elderly are warranted."

What is the evidence for a goal BP < 140/90 mmHg compared to < 150-160/95-100 mmHg in adults aged 65 and older?

Cochrane Systematic Review 2017[2] authors' summation [3 RCTs, N=8221; 2.6 years]: "There is insufficient evidence at present to determine whether a SBP target < 150-160 mmHg, as compared to a lower SBP target < 140 mmHg, conveys meaningful differences in benefit or harm to older adults with hypertension." The reviewers note that the relative effect on all-cause mortality and cardiovascular morbidity & mortality, while not statistically significantly reduced, favoured a lower blood pressure target but firm conclusions could not be drawn.

Trials comparing BP goals of < 140/90 mmHg versus < 150-160/95-100 mmHg were included.
Trials comparing more intensive SBP goals of < 120 mmHg versus < 140 mmHg were not included.

What is the evidence for a goal BP ≤ 135/85 mmHg in people with hypertension and cardiovascular disease compared to ≤ 140-160/90-100 mmHg?

Cochrane Systematic Review 2017[3] authors' conclusion [6 RCTs, N=9795; 3.7 years]: "No evidence of a difference in total mortality and serious adverse events was found between treating to a lower or to a standard blood pressure target in people with hypertension and cardiovascular disease. This suggests no net health benefit from a lower SBP target despite the small absolute reduction in total cardiovascular serious adverse events [ARR 1.6%; 16 fewer per 1000 people; NNTB 63 over 4 years; low quality evidence]. There was very limited evidence on adverse events, which lead to high uncertainty." The reviewers note that additional trials in participants with cardiovascular disease are ongoing.

Trials comparing BP goals of ≤ 135/85 versus ≤ 140-160/90-100 mmHg were included.
Trials comparing more intensive SBP goals of < 120 mmHg versus < 140 mmHg were included.

RCT=randomized controlled trial; **ARR**=absolute risk reduction; **ARI**=absolute risk increase; **RR**=relative risk; **HR**=hazard ratio; **95%CI**=95% confidence interval
N=number of participants; **NNTB**=number needed to treat for an additional beneficial outcome; **NNTH**=number needed to treat for an additional harmful outcome

Which sources of evidence contribute to recommendations for systolic blood pressure goals?

The American College of Physicians and the American Academy of Family Physicians 2017 weak recommendation for a SBP goal < 140 mmHg in adults aged 60 and older was informed by a systematic review which included SPRINT 2015 and five other RCTs comparing more intensive versus less intensive BP goals.[4,5]

WEISS 2017[5] authors' summation [6 RCTs, N=41,491; 2-5 years]: "Tighter control may prevent, on average, roughly 10 to 20 events for every 1000 high-risk patients treated over 5 years across a population, but more aggressive treatment is likely associated with greater medication burden and higher risk for adverse effects".

Trials comparing BP goals of < 140/≤ 85 mmHg versus < 150-160/≤ 90 mmHg were included.
Trials comparing more intensive SBP goals of < 120 mmHg versus < 140 mmHg were included.

WEISS 2017[5] Benefits and harms of intensive blood pressure in adults aged ≥ 60	6 RCTs; N=41,491	2-5 years

all-cause mortality	ARR 0.8%	Roughly 10 to 20 fewer events for every 1000 high-risk patients treated over 5 years	RR 0.86 [95%CI 0.69, 1.06] low quality
fatal and nonfatal stroke	ARR 0.5%		RR 0.79 [95%CI 0.59, 0.99] moderate quality
fatal and nonfatal coronary events	ARR 0.9%		RR 0.82 [95%CI 0.64, 1.00] low quality

Two RCTs contributed the most weight to WEISS 2017; both trials compared SBP < 120 mmHg versus SBP < 140 mmHg
ACCORD-BP 2010: N=4733, 4.7 years follow up, type 2 diabetes with CV risk factors, CVD 34%, baseline BP 139/76 mmHg[6]
SPRINT 2015: N=9361, 3.3 years follow up, CV risk factors but without diabetes, CVD 20%, baseline BP 140/78 mmHg[7]

Discordant results all-cause mortality
ACCORD-BP 2010: HR 1.07 [95%CI 0.85, 1.35][6]
SPRINT 2015: HR 0.73 [95%CI 0.60, 0.90][7]

Concordant results serious adverse events attributed to treatment
ACCORD-BP 2010: ARI 2.0%; 20 more per 1000 [P < 0.001][6]
SPRINT 2015: ARI 2.2%; 22 more per 1000 [P < 0.001][7]

Total serious adverse events [net benefit]: this systematic review did not analyze total serious adverse events

Hypertension Canada's strong recommendation for a SBP goal ≤ 120 in 'high-risk' adults [including those aged 75 and older] was defined principally by the SPRINT 2015 trial.[7,8]

SPRINT 2015[7] Randomized trial of intensive versus standard blood-pressure control	1 RCT; N=9361	3.3 years

Age ≥ 50 and SBP 130-180 mmHg with cardiovascular risk factors: A) age ≥ 75 [28%], or B) clinical or subclinical cardiovascular disease [20%], or C) chronic kidney disease with eGFR 20-59 mL/min/1.73 m^2 [28%], or D) Framingham 10-year cardiovascular risk score ≥ 15% [61%]
Without diabetes, prior stroke, heart failure, polycystic kidney disease, eGFR < 20 mL/min/1.73 m^2, adherence concerns, residence in assisted-living or long-term care facility, or standing SBP < 110 mmHg

mean age 68, 36% women	baseline 140/78 mmHg	91% receiving antihypertensives at baseline
SBP goal 135-139 mmHg	achieved 136/76 mmHg	# antihypertensives ≤ 2 = 77% | 3 = 17% | ≥ 4 = 7%
SBP goal < 120 mmHg	achieved 121/69 mmHg	# antihypertensives ≤ 2 = 45% | 3 = 32% | ≥ 4 = 24%

all-cause mortality	ARR 1.2%	NNTB 63 [CV morb & mort] NNTH 45 [serious adverse*]	HR 0.73 [95%CI 0.60, 0.90] single RCT
cardiovascular morbidity & mortality	ARR 1.6%		HR 0.75 [95%CI 0.64, 0.89] single RCT
serious adverse events*	ARI 2.2%		HR 1.88; P < 0.001 single RCT

Primary cardiovascular composite outcome first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure or cardiovascular death
Serious adverse events possibly or definitely related to the intervention*: ↑ hypotension, syncope, electrolyte abnormalities, acute kidney injury | Total serious adverse events intensive treatment group = 38.3%; standard treatment group = 37.1% [HR 1.04; P = 0.25]
BP measurement method average of 3 automated office readings while seated after 5 minutes of quiet rest; the American College of Cardiology/American Heart Association 2017 high blood pressure guideline identifies that this may limit confident extrapolation of an SBP goal < 120 mmHg to general clinical practice if the same BP measurement method is not used[9]
SBP goal < 120 mmHg achieved by < 50% participants in the intensive group | Unscheduled clinic visits 30% more in intensive group[10]
Baseline SBP ≥ 160 mmHg = 10% [N=976][11] | Older adults age ≥ 75 = 28% [N=2636] age ≥ 80 = 12% [N=1159][12]
Early trial termination 3.3 years versus planned 5 years | Open label | Lost to follow up or withdrew consent 5.5% [N=520]

RCT=randomized controlled trial; **ARR**=absolute risk reduction; **ARI**=absolute risk increase; **RR**=relative risk; **HR**=hazard ratio; **95%CI**=95% confidence interval
N=number of participants; **NNTB**=number needed to treat for an additional beneficial outcome; **NNTH**=number needed to treat for an additional harmful outcome

Thiazides	average BP lowering efficacy[1] SBP ↓ 9 mmHg, DBP ↓ 4 mmHg	Dose: monograph starting dose for hypertension [daily dosage range]	Cost of starting dose [annual approximate without fee, markup][2]	BC PharmaCare coverage
CHLORTHALIDONE 50 mg tabs generic ⊕ ARB no PharmaCare coverage		12.5 mg once a day [12.5 - 50 mg][3] *max SBP lowering efficacy @ 12.5 mg*[1] *max DBP lowering efficacy @ 25 mg*[1]	$12 quarter tablet = 12.5 mg	Regular Coverage
HYDROCHLOROTHIAZIDE 12.5, 25, 50, 100 mg tabs generic ⊕ amiloride [50 mg hydrochlorothiazide + 5 mg amiloride] generic ⊕ triamterene [25 mg hydrochlorothiazide + 50 mg triamterene] generic ⊕ ACEI least costly combination products ⊕ ARB		12.5 mg once a day [12.5 - 50 mg][3] *80% max BP lowering efficacy @ 25 mg*[1]	$12	Regular Coverage
INDAPAMIDE 1.25, 2.5 mg tabs Lozide, generic ⊕ ACEI no PharmaCare coverage		1.25 mg once a day [1.25 - 2.5 mg][4] *max BP lowering efficacy @ 1.25 mg*[1]	$30	Limited Coverage Special Authority

From the Cochrane Library of Systematic Reviews in Hypertension

- ❖ As first line medications for hypertension, thiazides improve cardiovascular morbidity and mortality outcomes compared to placebo [2009 Cochrane Review: 19 RCTs, N=39,713][5]
  - In a primary prevention population with moderate to severe hypertension, the authors estimate that if 20 patients are treated with a low-dose first-line thiazide for approximately 5 years one person fewer will experience a cardiovascular event[5]
- ❖ Compared to renin angiotensin system inhibitors (ACEI, ARB, direct renin inhibitors), first-line thiazides were superior for stroke and heart failure outcomes but all-cause death did not differ (2015 Cochrane Review; ALLHAT 2002 contributes majority of data: chlorthalidone versus lisinopril)[6,7]
- ❖ Compared to calcium channel blockers, first-line thiazides were superior for heart failure outcomes but all-cause death did not differ [2010 Cochrane Review; ALLHAT 2002 contributes majority of data: chlorthalidone versus amlodipine][7,8]

Clinical Considerations

- ➢ **thiazide-type (eg, hydrochlorothiazide) versus thiazide-like (eg, chlorthalidone, indapamide) diuretics**
  - absence of direct RCT comparisons evaluating cardiovascular morbidity and mortality outcomes; Veterans Affairs Cooperative Study 597 ongoing[9]
  - 2015 meta analysis, indirect RCT comparisons → primary analysis with near identical relative risks and 95% confidence intervals[10]
    thiazide-type diuretics versus placebo [8 RCTs; 21,310 participants] → cardiovascular events: RR 0.67, 95%CI 0.56-0.81 | all-cause death: RR 0.86, 95%CI 0.75-1.00
    thiazide-like diuretics versus placebo [3 RCTs; 9132 participants] → cardiovascular events: RR 0.67, 95%CI 0.60-0.75 | all-cause death: RR 0.84, 95%CI 0.74-0.96
- ➢ **withdrawals due to adverse events** high-dose thiazides vs placebo: RR 4.48 [95%CI 3.83, 5.24] | low-dose thiazides vs placebo: RR 2.38 [95%CI 2.06, 2.75][5]
- ➢ **metabolic effects** dose related | ↓ potassium: 0.25 mmol/L | ↑ uric acid: 38.2 umol/L | ↑ glucose: 0.03 mmol/L [estimate from pooled high and low-dose RCTs][1]
- ➢ **hyponatremia** dose related | risk factors include → low body mass, female gender, concomitant antidepressant use, concomitant potassium sparing diuretic[11]
- ➢ **hypokalemia** potassium < 3.2 mmol/L → ALLHAT 2002 @ 1 year: chlorthalidone 12.5-25 mg 3.5% | amlodipine 2.5-10 mg 0.3% | lisinopril 10-40 mg 0.2%[12]
- ➢ **hydrochlorothiazide + potassium sparing diuretic combinations** amiloride 5 mg, triamterene 50 mg → the limited evidence available does not indicate an additive BP lowering effect at these doses[13]| potassium sparing diuretics (eg, amiloride) ↑ potassium 0.14-0.29 mmol/L on average[14]
- ➢ **chronic kidney disease** limited evidence for/against antihypertensive efficacy when eGFR < 30 mL/min[15-18]

COST calculated from McKesson Canada [accessed: 22 November 2017]; **Special Authority** www.gov.bc.ca/pharmacarespecialauthority

Angiotensin Converting Enzyme Inhibitors [ACEI]	average BP lowering efficacy[1] SBP ↓ 8 mmHg, DBP ↓ 5 mmHg	Dose: monograph starting dose for hypertension [daily dosage range]	Cost of starting dose [annual approximate without fee, markup][2]	BC PharmaCare coverage
RAMIPRIL 1.25, 2.5, 5, 10, 15 mg caps Altace, generic		2.5 mg once a day [1.25 - 20 mg][3]	$50	RDP Reference Drug Regular Coverage
⊕ hydrochlorothiazide 2.5/12.5, 5/12.5, 5/25, 10/12.5, 10/25 mg Altace HCT, generic			$80	
BENAZEPRIL 5, 10, 20 mg tabs Lotensin, generic		10 mg once day [5 - 40 mg][4]	$370	RDP Partial Coverage Special Authority
CILAZAPRIL 1, 2.5, 5 mg tabs Inhibace, generic		2.5 mg once a day [0.5 - 10 mg][5]	$70	
⊕ hydrochlorothiazide 5/12.5 mg Inhibace Plus, generic			$165	
ENALAPRIL 2.5, 5, 10, 20 mg tabs Vasotec, generic		5 mg once a day [2.5 - 40 mg][6]	$90	
⊕ hydrochlorothiazide 5/12.5, 10/25 mg Vaseretic, generic			$295	
FOSINOPRIL 10, 20 mg tabs generic		10 mg once a day [10 - 40 mg][7]	$85	
LISINOPRIL 5, 10, 20 mg tabs Prinivil, Zestril, generic		10 mg once a day [5 - 80 mg][8,9]	$65	
⊕ hydrochlorothiazide 10/12.5, 20/12.5, 20/25 mg Zestoretic, generic			$80	
PERINDOPRIL 2, 4, 8 mg tabs Coversyl		4 mg once a day [2 - 8 mg][10]	$330	
⊕ indapamide 2/0.625, 4/1.25, 8/2.5 mg Coversyl Plus			$345 no PharmaCare coverage	
⊕ amlodipine 3.5/2.5, 7/5, 14/10 mg Viacoram			$375 no PharmaCare coverage	
QUINAPRIL 5, 10, 20, 40 mg tabs Accupril, generic		10 mg once a day [2.5 - 40 mg][11]	$90	
⊕ hydrochlorothiazide 10/12.5, 20/12.5, 20/25 mg Accuretic, generic			$270	
TRANDOLAPRIL 0.5, 1, 2, 4 mg caps Mavik		1 mg once a day [0.5 - 4 mg][12]	$265	
⊕ verapamil sustained release 2/240, 4/240 mg Tarka			$700 no PharmaCare coverage	

lower doses for those receiving concomitant diuretics,[3-12] older adults,[5,6,10,12] hepatic impairment,[5,12] renal impairment[3-6,8-12]

From the Cochrane Library of Systematic Reviews in Hypertension

- ❖ As first-line medications, ACEI improve cardiovascular morbidity and mortality outcomes compared to placebo [2009 Cochrane Review: 3 RCTs, N=6002][13]
- ❖ Dose response: 60-70% of the blood pressure lowering effect occurs with starting doses | half the maximum dose achieves 90% of the maximum blood pressure lowering effect [2008 Cochrane Review][1]

Clinical Considerations

- ➢ **dual blockade of renin angiotensin system** 2014 Health Canada warning that combined use of an ACEI or ARB or renin inhibitor (aliskiren) increases the risk of hypotension, hyperkalemia, renal impairment | ACEI or ARB combined with aliskiren also increases risk of stroke and syncope in people with diabetes or chronic kidney disease;[14] combined use not recommended for hypertension[15]
- ➢ **hyperkalemia** potassium > 5.4 mmol/L → ALLHAT 2002 @ 1 year: chlorthalidone 12.5-25 mg 1.2% | amlodipine 2.5-10 mg 1.9% | lisinopril 10-40 mg 3.6%[16]
- ➢ **hyperkalemia** risk factors include → renal insufficiency, volume depletion, potassium sparing medications, trimethoprim, advanced age, decompensated heart failure, diabetes[17]
- ➢ **angioedema** facial, upper airway, intestinal[18]| ACEI contraindicated if history of hereditary/idiopathic angioedema or angioedema related to previous ACEI[3-12]| onset may be delayed weeks or months, may recur episodically[18]| concomitant sacubitril/valsartan contraindicated due to increased risk of angioedema[19]
- ➢ **cough** dry, non-productive, persistent[18]| estimated incidence 5-20%[20]| onset generally first few weeks but variable[18]| resolution days to months after drug discontinuation[18,21]

COST calculated from McKesson Canada [accessed: 22 November 2017]; **RDP** Reference Drug Program www.gov.bc.ca/pharmacare/rdp-pro; **Special Authority** www.gov.bc.ca/pharmacarespecialauthority

Angiotensin II Receptor Antagonists [ARB]	average BP lowering efficacy[1] SBP ↓ 8 mmHg, DBP ↓ 5 mmHg	Dose: monograph starting dose for hypertension [daily dosage range]	Cost of starting dose [annual approximate without fee, markup][2]	BC PharmaCare coverage
CANDESARTAN 4, 8, 16, 32 mg tabs Atacand, generic		16 mg once a day [4 - 32 mg][3]	$110 4 mg: no PharmaCare coverage	RDP Reference Drug Limited Coverage Special Authority
⊕ hydrochlorothiazide 16/12.5, 32/12.5, 32/25 mg Atacand Plus, generic			$120	
LOSARTAN 25, 50, 100 mg tabs Cozaar, generic		50 mg once a day [25 - 100 mg][4]	$100	
⊕ hydrochlorothiazide 50/12.5, 100/12.5, 100/25 mg Hyzaar, Hyzaar DS, generic			$100	
TELMISARTAN 40, 80 mg tabs Micardis, generic		80 mg once a day [40 - 80 mg][5]	$110	
⊕ hydrochlorothiazide 80/12.5, 80/25 mg Micardis Plus, generic			$110	
⊕ amlodipine 40/5, 40/10, 80/5, 80/10 mg Twynsta			$275	
VALSARTAN 40, 80, 160, 320 mg tabs Diovan, generic		80 mg once a day [80 - 320 mg][6]	$115	
⊕ hydrochlorothiazide 80/12.5, 160/12.5, 160/25, 320/12.5, 320/25 mg Diovan HCT			$115	
EPROSARTAN 400, 600 mg tabs Teveten		600 mg once a day [400 - 600 mg][7]	$435 400 mg: no PharmaCare coverage	RDP Partial Coverage Limited Coverage Special Authority
⊕ hydrochlorothiazide 600/12.5 mg Teveten Plus			$435	
IRBESARTAN 75, 150, 300 mg tabs Avapro, generic		150 mg once a day [75 - 300 mg][8]	$120	
⊕ hydrochlorothiazide 150/12.5, 300/12.5, 300/25 mg Avalide, generic			$120	
OLMESARTAN 20, 40 mg tabs Olmetec, generic		20 mg once a day [20 - 40 mg][9]	$110	
⊕ hydrochlorothiazide 20/12.5, 40/12.5, 40/25 mg Olmetec Plus, generic			$220	
AZILSARTAN 40, 80 mg tabs Edarbi		40 mg once a day [40 - 80 mg][10]	$475	No Coverage
⊕ chlorthalidone 40/12.5, 40/25, 80/12.5mg Edarbyclor			$475	

lower doses for those receiving concomitant diuretics,[3,8] older adults,[7] hepatic impairment,[3,4,5,7,10] renal impairment[3,7,8]

From the Cochrane Library of Systematic Reviews in Hypertension

- As first-line medications, the effect of ARBs on cardiovascular morbidity and mortality outcomes is less certain compared to ACEIs [2009 Cochrane Review][11]
- Compared to ACEIs, there are limited direct comparisons evaluating cardiovascular morbidity and mortality outcomes [2014 Cochrane Review][12]
- Compared to ACEIs, approximately 2 fewer people per 100 discontinue ARB therapy due to adverse events; mainly due to a higher incidence of dry cough with ACEI [2014 Cochrane Review][12]
- Dose response: 60-70% of the blood pressure lowering effect occurs with starting doses | half the maximum dose achieves 80% of the maximum blood pressure lowering effect [2008 Cochrane Review][1]

Clinical Considerations

- **dual blockade of renin angiotensin system** 2014 Health Canada warning that combined use of an ACEI or ARB or renin inhibitor (aliskiren) increases the risk of hypotension, hyperkalemia, renal impairment | ACEI or ARB combined with aliskiren also increases risk of stroke and syncope in people with diabetes or chronic kidney disease;[13] combined use not recommended for hypertension[14]
- **hyperkalemia** risk factors include → renal insufficiency, volume depletion, potassium sparing medications, trimethoprim, advanced age, decompensated heart failure, diabetes[15]
- **angioedema** 2012 meta analysis RCTs: incidence ACEI 0.30% | ARB 0.11% | direct renin inhibitor 0.13%[16]
- **olmesartan & sprue-like enteropathy** U.S. Food & Drug Administration 2013 warning → severe chronic diarrhea and weight loss[17]
- **telmisartan & food** food reduces maximum plasma-concentration up to 56% → monograph advises taking with or without food but should be consistent[5]
- **azilsartan** CADTH 2013 Common Drug Review: evidence does not support greater efficacy or safety versus less costly alternative treatments[18]

COST calculated from McKesson Canada [accessed: 22 November 2017]; **RDP** Reference Drug Program www.gov.bc.ca/pharmacare/rdp-pro; **Special Authority** www.gov.bc.ca/pharmacarespecialauthority

Calcium Channel Blockers [CCB]	average BP lowering efficacy[1] SBP ↓ 9 mmHg, DBP ↓ 5 mmHg	Dose: monograph starting dose for hypertension [daily dosage range]	Cost of starting dose [annual approximate without fee, markup][2]	BC PharmaCare coverage
dihydropyridines				
AMLODIPINE 2.5, 5, 10 mg tabs Norvasc, generic		5 mg once a day [2.5 - 10 mg][3]	$80	RDP Reference Drug Regular Coverage
⊕ telmisartan 40/5, 40/10, 80/5, 80/10 mg Twynsta			$275	
⊕ perindopril 3.5/2.5, 7/5, 14/10 mg Viacoram			$375 no PharmaCare coverage	
FELODIPINE extended release tabs 2.5, 5, 10 mg Plendil, generic		5 mg once a day [2.5 - 10 mg][4]	$135	RDP Partial Coverage Special Authority
NIFEDIPINE extended release tabs 20, 30, 60 mg Adalat XL, generic		20 or 30 mg once a day [20 - 90 mg][5]	$240	
non dihydropyridines				
DILTIAZEM controlled delivery caps (CD) 120, 180, 240, 300 mg generic		120 - 240 mg once a day [120 - 360 mg][6-8]	$140 CD	Regular Coverage
extended release caps (ER) 120, 180, 240, 300, 360 mg Tiazac, generic			$85 ER	
extended release tabs (XC) 120, 180, 240, 300, 360 mg Tiazac XC			$340 XC	
VERAPAMIL 120, 180, 240 mg sustained release tabs Isoptin SR, generic		180 or 240 mg once a day [120 - 480 mg][9]	$205	
⊕ trandolapril 2/240, 4/240 mg Tarka		with food [divide doses > 240 mg per day]	$700 no PharmaCare coverage	

lower doses for older adults,[3,4,6,9] hepatic impairment [nifedipine contraindicated in moderate to severe hepatic impairment][3,4,5,9]

From the Cochrane Library of Systematic Reviews in Hypertension

- As first-line medications, CCBs improve cardiovascular morbidity and mortality outcomes compared to placebo [2009 Cochrane Review: 1 RCT, N=4695][1]
- Compared to thiazides, first-line CCBs were inferior for heart failure outcomes but all-cause death did not differ [2010 Cochrane Review; ALLHAT 2002 contributes majority of data: amlodipine versus chlorthalidone][10,11]
- Compared to renin angiotensin system inhibitors (ACEI, ARB, direct renin inhibitors), first-line CCBs were superior for stroke outcomes, were inferior for heart failure outcomes, but all-cause death did not differ [2015 Cochrane Review; ALLHAT 2002 contributes majority of data: amlodipine versus lisinopril][11,12]
- Dose response: Cochrane Review is at protocol stage[13]

Clinical Considerations

- **negative inotropic, negative chronotropic [non dihydropyridines: diltiazem, verapamil]** precautions include severe left ventricular dysfunction, atrioventricular block, bradycardia | caution concomitant use with beta blockers[6-9]
- **heart failure** not recommended for routine use in patients with heart failure with reduced ejection fraction[14]
- **peripheral edema** dose related | dihydropyridine monographs indicate 3-5% incidence on lower doses, 10-30% incidence on higher doses[3,4,5] | 2011 meta analysis: incidence increases with duration of therapy with > 5% of patients discontinuing therapy due to peripheral edema[15]
- **diltiazem formulations** product monographs indicate not interchangeable[6-8] however the clinical implications of the reformulations are unclear | peak plasma levels: diltiazem controlled delivery (CD) caps @ 10-14 hrs; diltiazem extended release caps (Tiazac) @ 8 hrs; diltiazem extended release tablets (Tiazac XC) @ 11-18 hrs[6-8]
- **gingival hyperplasia** risk factors include → gingival inflammation, male gender, poor oral hygiene[16,17]
- **cytochrome P450 3A4 drug interactions** substrates: amlodipine, felodipine, nifedipine, diltiazem, verapamil[18,19] | co-prescription of erythromycin, clarithromycin: ↑ risk of hospitalization for acute kidney injury and hypotension in older adults[20,21]
- **cytochrome P450 3A4 drug interactions** inhibitors: diltiazem, verapamil | recommendations include dose reductions or therapy modification for numerous medications including but not limited to → atorvastatin, colchicine, domperidone, simvastatin, zopiclone, fentanyl[18,19]
- **grapefruit juice interaction** product monographs include conflicting recommendations | Lexicomp indicates avoid combination or consider therapy modification → felodipine, nifedipine; monitor therapy → amlodipine, diltiazem, verapamil[18] | Cochrane Review is at the protocol stage[22]

COST calculated from McKesson Canada [accessed: 22 November 2017]; **RDP** Reference Drug Program www.gov.bc.ca/pharmacare/rdp-pro; **Special Authority** www.gov.bc.ca/pharmacarespecialauthority

What is the role for beta blockers in adults aged 60 and older with hypertension?

- As first-line medications, beta blockers improve stroke but not coronary heart disease or mortality outcomes compared to placebo [2017 Cochrane Review; 4 RCTs, N=23,613; 5 years][1]
- Compared to other first-line medications (thiazides, renin angiotensin system inhibitors, calcium channel blockers), beta blockers do not reduce the risk of any cardiovascular outcomes and have higher rates of stroke and withdrawals due to adverse events [2017 Cochrane Review][1]
- Hypertension Canada's 2017 guideline does not recommend beta blockers as a first-line therapy for hypertension in adults aged ≥ 60 unless recent myocardial infarction, stable angina or heart failure[2]
- U.S. Department of Veterans Affairs' 2014 hypertension guideline recommends thiazides as first-line therapy for hypertension including patients with coronary artery disease, prior myocardial infarction, diabetes[3]

What is the applicability of the hypertension evidence to those with frailty and multimorbidity?

The American College of Physicians and the American Academy of Family Physicians 2017 guideline was informed by a systematic review sponsored by the U.S. Department of Veterans Affairs [WEISS 2017].[4,5]
The systematic review found:[5]

- The hypertension pharmacotherapy evidence for adults who are frail and for those with multimorbidity is limited → most hypertension trials do not assess the effect of frailty on benefits and harms
- Trials generally included participants who were community dwelling and excluded persons with dementia, significant multimorbidity or limited life expectancy

What is the evidence for initiating antihypertensive therapy as combination drug therapy?

- Cochrane Systematic Review 2017[6] [3 RCTs, N=568; 1-3 years]: Initiating antihypertensive therapy with a combination of antihypertensives as compared to monotherapy has not been shown to improve cardiovascular morbidity or mortality outcomes however the numbers of participants and events were too few to draw conclusions[6]
- The European Society of Hypertension – European Union Geriatric Medicine 2016 hypertension working group advises against initial high dose or combination therapy in adults aged ≥ 80 or in those with frailty[7]

Summary

1. When considering treatment for high blood pressure in adults aged 60 and older, systematic reviews identify the greatest absolute reduction in cardiovascular events in randomized controlled trials:
   a) when the mean baseline SBP is 160 mmHg or higher
   b) where a stepped care approach achieved SBP < 150-160 mmHg
   c) with strategies that commonly include a thiazide diuretic as the first-line drug
2. Aiming for intensive blood pressure targets in people at high cardiovascular risk affords a smaller absolute reduction in cardiovascular events and increases serious adverse events attributable to antihypertensive therapy
3. The generalizability of drug-therapy evidence for hypertension to those who are frail or have multimorbidity is limited
4. For many antihypertensive medications, near maximum blood pressure lowering occurs with the starting dose or half of the maximum recommended dose

Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist.
For more information, or to schedule an academic detailing session, please contact:
BC Provincial Academic Detailing Service
Phone: 604 660-2101 | Fax: 604 660-2108 | Email: PAD@gov.bc.ca | Web: www.bcpad.ca