

# Issues in Hypertension 2011

Academic  
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Service





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“Seek simplicity, and mistrust it.”  
Alfred North Whitehead



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## Definitions and Abbreviations

ACCF/AHA	American College of Cardiology Foundation / American Heart Association
ACEI	Angiotensin converting enzyme inhibitor
ACR	Albumin to creatinine ratio
ARB	Angiotensin receptor blocker
ARR	Absolute risk reduction
BP	Blood pressure
CDA	Canadian Diabetes Association
CHEP	Canadian Hypertension Education Program
CHF	Congestive heart failure
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CV	Cardiovascular
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
HF	Heart failure
HCTZ	Hydrochlorothiazide
KDOQI	Kidney Disease Outcomes Quality Initiative
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
NNH	Number needed to harm
NNT	Number needed to treat
RCT	Randomized controlled trial
RRR	Relative risk reduction
SBP	Systolic blood pressure
SrCr	Serum creatinine
TIA	Transient ischemic attack



## SUMMARY STATEMENTS

### Question 1: What is the evidence for a treatment target of <140/90 mmHg in the elderly? Page 15

- Definitions vary but the elderly are usually defined as  $\geq 60$  or 65 years old and the very elderly as  $\geq 80$  years old.
- The **frail** elderly are not defined by age alone and have multiple chronic illnesses and associated vulnerability including dementia, functional decline, and geriatric syndromes, such as falls and impaired mobility.
- A Cochrane review indicates that antihypertensive therapy confers benefit in the elderly and the very elderly.
- There is uncertainty about the optimal level of blood pressure that should be maintained, which leads to **two questions**.
- **Question A: At what SBP should pharmacotherapy be started in people >65 years old ?**
  - Evidence supports initiating pharmacotherapy at a SBP  $\geq 160$  mmHg.
  - Major trials enrolled elderly patients only if they had SBP  $\geq 160$  mmHg. Therefore the current guideline recommendations on initiating therapy at SBP values between 140 and 159 mmHg in the elderly are **uncertain** and not based on results from trials.
    - CHEP recommends to strongly consider therapy at SBP level 140 to 159 mmHg in the general population and stipulates that target organ damage be present (**Grade C**).
    - This recommendation is extrapolated to the elderly.
- **Question B: What should the SBP treatment target be in people >65 years old?**
  - Evidence supports a SBP target of <160 mmHg in the elderly.
  - The optimal SBP target below 160 mmHg is uncertain.
  - Evidence addressing a SBP target of <140 mmHg is limited.
    - The only trial that randomized patients to different blood pressure targets in the elderly (SBP <140 mmHg vs 140 to 160 mmHg) showed **no** statistically significant **difference** between groups in any outcome.
- **Opinions of local experts are in the following comments.**
  - Most elderly should achieve a SBP of <160 mmHg.
    - Below 160 mmHg, initiation of treatment and setting BP target levels should consider the patient's overall risk assessment and not simply a numerical value.
    - In patients with SBP 140 to 159 mmHg without target organ damage or risk factors, encourage lifestyle change for at least 6 months but strongly consider drug therapy if inadequate response.
    - In general, aim for <140/<90 in every patient if tolerated even in the healthy elderly while monitoring potassium, creatinine, orthostasis, and side effects.





- In patients with SBP 140 to 159 mmHg without target organ damage or risk factors, encourage lifestyle change for at least 6 months but strongly consider drug therapy if inadequate response.
- In the **frail** elderly
  - If treatment is initiated, a reasonable target is SBP 140 to 160 mmHg while sitting as long as there is no orthostatic drop to <140 mmHg while standing.
  - With **short** life expectancy, a SBP range of 160 to 190 mmHg may be reasonable.
  - In general use no more than 2 medications.
- Make reasonable attempts to control hypertension, while taking heed to avoid harmful effects from treatment, which might be more likely or of greater consequence in certain patients, such as the frail or very elderly.

## Question 2: What is the evidence for a treatment target of <130/80 mmHg in patients with diabetes? Page 27

- Together, diabetes and hypertension account for more than two-thirds of CV disease risk.
- It is important to treat hypertension in people with diabetes, however the same questions about hypertension in the elderly apply to persons with diabetes:

### Question A: At what SBP should pharmacotherapy be started in people with diabetes?

- No studies compared the effect of starting therapy in patients with SBP of 130 to 139 mmHg vs patients with SBP >140 mmHg.
- The CDA recommends treatment be initiated at a BP of  $\geq 130/80$  mmHg.
  - This is a Grade D (**consensus**) recommendation.
- The above information indicates the uncertainty in the evidence for starting therapy at SBP 130 to 139 mmHg vs  $\geq 140$  mmHg in patients with diabetes.

### Question B: What should the SBP treatment target be in people with diabetes?

- The CHEP and CDA guidelines make the following recommendation:
  - Persons with diabetes and hypertension should be treated to attain
    - SBP <130 mm Hg [CDA: Grade C, Level 3 and CHEP: Grade C]
- ACCORD BP randomized patients with diabetes to different SBP targets (<120 mmHg vs <140 mmHg).
  - There was **no** statistically significant **difference** between the 2 target groups in the **primary** outcome of non-fatal MI, non-fatal stroke, or cardiovascular death.
  - There was benefit in the **secondary** outcome of **stroke** though the absolute benefit was small.
  - The ACCORD authors conclude "The results provide no evidence that the strategy of intensive BP control reduces the rate of a **composite of major cardiovascular events** in the study patients."



- The current CHEP guidelines have not made any changes to recommendations since publication of ACCORD BP.
- Patients with diabetes should be screened annually for **kidney damage** with a routine urinalysis and urinary albumin-creatinine ratio (ACR).
- In patients with diabetes and kidney damage **expert opinion** suggests it may be reasonable to aim for a target BP of <130/80 although definitive evidence is lacking.
- The above information indicates the uncertainty for a treatment target of <130/80 mmHg in patients with diabetes.
- It may be difficult to reach a SBP of <130 mmHg without excessive lowering of DBP ( $\leq 70$  mmHg) which may lead to increased cardiovascular events particularly in the elderly and people with diabetes or coronary heart disease.

### **Question 3: What is the role of adhering to a low sodium diet and assuring good compliance with medications in managing hypertension?**

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- Epidemiological studies have consistently shown an association between salt intake and cardiovascular disease.
- We found no RCTs that examined the effect of lowering dietary sodium and hard clinical outcomes like stroke and cardiovascular disease.
- Based on a Cochrane review, decreasing sodium intake by approximately 2400 mg could reduce SBP by 7.2 mmHg and DBP by 3.8 mmHg in hypertensive patients.
- A local study indicates that following a low-sodium diet and taking medications as prescribed are the two factors most strongly associated with achieving BP targets in patients with diabetes.
  - Frequent self-monitoring of BP was not associated with better BP control.



## Question 4: What is evidence for the efficacy and harms of aliskiren (Rasilez), a direct renin inhibitor, in hypertension?

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- Aliskiren is the only direct renin inhibitor currently marketed in Canada.
- We found **no studies** of aliskiren that addressed **hard clinical** outcomes.
- A 2009 Cochrane review found that compared to **placebo** aliskiren reduced SBP and DBP in a dose-related manner:
  - 150 mg dose decreased SBP by 5.5 mmHg and DBP by 3 mmHg
  - 300 mg dose decreased SBP by 8.7 mmHg and DBP by 5 mmHg
- Aliskiren has been found to be as effective in lowering BP as ACEIs, ARBs, and HCTZ.
- In most studies, aliskiren at doses up to 300 mg daily was as well tolerated as placebo.
- There is no long-term safety data available for aliskiren.
- Aliskiren is more expensive than other drugs which have proven benefit in reducing cardiovascular and cerebrovascular outcomes.



## Introduction

This topic has been developed in conjunction with a provincial initiative to increase awareness about the risks, prevention, and management of high blood pressure among health care providers and the public.

- Using the slogan “Come on Nova Scotia, Check It”, persons with or without hypertension will be encouraged to discuss high blood pressure with their health care providers and record their readings on a wallet-sized card (My Blood Pressure Card).
- Health care providers will be receiving a packet including the wallet-sized cards, patient brochures, and a poster for office use.
- Provincial organizations leading this initiative are
  - The Diabetes Care Program of Nova Scotia
  - Cardiovascular Health Nova Scotia
  - Nova Scotia Renal Program
- Material reviewed for this topic includes
  - The 2011 Canadian Hypertension Education Program (CHEP) recommendations<sup>1</sup>
  - The 2008 Canadian Diabetes Association Guideline<sup>2</sup>
  - A reappraisal of the European guidelines on hypertension management<sup>3</sup>
  - Canadian guidelines for the management of Chronic Kidney Disease<sup>4</sup>
  - KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and CKD<sup>5</sup>
  - Cochrane reviews<sup>6-8</sup>
  - ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly<sup>9</sup>
  - Original publications cited in the above documents.
- The intention is to synthesize important points from the above documents with a view to complementing current guidelines.
- We also provide our own comments which are designated “**Academic Detailing Comments**”.
- Comments of our clinical experts are designated “**Expert Opinion**” and represent individual opinion, not consensus.
- Cardiovascular disease is a term used to describe a variety of heart diseases, illnesses, and events that affect the heart and circulatory system. Conditions include arteriosclerosis, coronary artery disease, heart valve disease, arrhythmia, heart failure, hypertension, orthostatic hypotension, shock, endocarditis, diseases of the aorta and its branches, disorders of the peripheral vascular system (all vessels outside the coronary system including the cerebral vessels) and congenital heart diseases.
- Definitions of **cardiovascular** outcomes vary among studies but generally include **any** of the following:



- Coronary heart disease/coronary artery disease/ischemic heart disease outcomes e.g. fatal and non-fatal myocardial infarction (MI) and heart failure (HF).
- Cerebrovascular outcomes e.g. fatal and non-fatal stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or subarachnoid hemorrhage.
- Cardiovascular death e.g. sudden cardiac death, death from MI, stroke or HF.
- There are notable ethnic and gender differences in diagnosis, treatment and control of hypertension.
  - Blood pressure is not regularly measured in those who are male, of a younger age, have no family doctor, are of a visible minority ethnic background or are of Aboriginal descent.<sup>10</sup>
  - People of African descent are more likely to have hypertension and receive drug therapy. However, they are less likely to achieve blood pressure control compared to Caucasians.<sup>11</sup>
  - People of African or South Asian descent are 3 times more likely to have hypertension than Caucasian people.<sup>10</sup>
- Over the past twenty years, the prevalence of hypertension in Canada has remained at approximately 20%. However the percent of people whose BP is controlled has risen 5-fold, from 13% to 65% in the same period.<sup>12</sup>
- In Nova Scotia<sup>13,14</sup>
  - Hypertension is reported in 28% of residents  $\geq$  20 years old.
  - The prevalence of hypertension is slightly higher in females than males in all age categories and varies by age group, peaking in those 75 years and older at over 75%.
  - In persons with **diabetes**, close to 70% have hypertension.
    - Hypertension prevalence is over 85% in females with diabetes between the ages of 70 to 79.
  - In younger age groups, 30-39 and 40-49, hypertension is present in 27% and 44% of the diabetes population, respectively.
- In addition to the above points, there are several reasons for providing the information covered in this topic.
  - In managing hypertension, targets have been widely promoted. However, less widely discussed are the details of the target recommendations and uncertainties behind them, especially the strength of the evidence used to determine some targets. Awareness of these details and uncertainties can lead to more fully informed clinical decision-making. In addition there may be uncertainty about the application of recommendations to different populations such as the elderly.
  - There is new evidence from the ACCORD BP study regarding optimal SBP targets in persons with diabetes. It is important to review this new evidence in relation to previous evidence cited to support SBP target recommendations in persons with diabetes.



- Simple measures can improve the management of hypertension and effectiveness of medications in achieving BP goals and are part of provincial anti-hypertension activities. We shall review those measures and some of the evidence behind them.
- A renin blocker, a new class of antihypertensive, has become available and it is important that family physicians be aware of the evidence for its efficacy and safety.

**This review will address four questions:**

1. What is the evidence for a treatment target of <140/90 mmHg in the elderly?
2. What is the evidence for a treatment target of <130/80 mmHg in persons with diabetes?
3. What is the role of adhering to a low sodium diet and assuring good compliance with medications in managing hypertension?
4. What is the evidence for the efficacy and safety of aliskiren (Rasilez), a direct renin inhibitor, in hypertension?



## Background information

### Levels of Evidence and Strength of Recommendations

The systems of rating strength of recommendations for the CHEP<sup>1</sup> and CDA<sup>2</sup> guidelines are shown in Table 1 and Table 2 respectively.

**Table 1 CHEP system for rating strength of recommendations**

CHEP rating of strength of recommendations	
Grade A	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	Based on randomized trials, systematic reviews or prespecified subgroup analyses of randomized trials that have lower precision, or if 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	Based on trials that have lower levels of internal validity and/or precision, or report unvalidated surrogate outcomes, or results from nonrandomized observational studies
Grade D	Based on expert opinion alone

**Table 2 CDA system for rating evidence and strength of recommendations**

CDA rating of evidence	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs OR Appropriately designed RCT with adequate power to answer the question posed by the investigators
Level 1B	Nonrandomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Nonrandomized clinical trial or cohort study
Level 4	Other
CDA rating of strength of recommendations	
Grade A	The best evidence was at level 1
Grade B	The best evidence was at level 2
Grade C	The best evidence was at level 3
Grade D	The best evidence was at level 4



## Categorization of hypertension

- The CHEP recommendations for drug therapy in relation to various levels of blood pressure and other factors are in Table 3.
- Current CHEP recommendations do **not** cite the studies on which the grades of recommendations are based.
- Current thinking considers SBP as the most relevant component of BP for determining risk for cardiovascular and other events in hypertensive patients, particularly those >50 years of age. Earlier treatment guidelines emphasized control of DBP.<sup>9,15,16</sup>
  - However pulse pressure, the difference between DBP and SBP is also emerging as an important predictor of coronary artery disease in persons aged 60 to 79.
    - SBP rises gradually throughout adult life, while DBP peaks and plateaus in late middle-age, declining slightly thereafter.<sup>9</sup>
- Because of the current emphasis on SBP, we will focus on this component of BP in this document.

**Table 3 Summary of CHEP recommendations about initiating drug therapy for adults with hypertension<sup>1</sup>**

BP	Other Factors	Recommendation	Grade of Recommendation
SBP ≥ 160 or DBP ≥ 100		Prescribe therapy	Grade A
DBP ≥ 90	Presence of macrovascular target organ damage or other CV risk factors	Strongly consider therapy	Grade A
SBP 140 to 159	Presence of macrovascular target organ damage	Strongly consider therapy	Grade C
Consider therapy in all patients meeting the above indications regardless of age. Exercise caution in elderly patients who are frail.			Grade B  No grade given

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





### CHEP recommendations about BP treatment targets for adults with hypertension

- The DBP treatment goal is <90 mmHg (**Grade A**).
- The SBP treatment goal is <140 mmHg (**Grade C**).
- Following the acute phase of a stroke, patients should have their blood pressure chronically controlled to a target of less than 140/90 mmHg (**Grade C**).
- For patients with nondiabetic chronic kidney disease, the target blood pressure is lower than 130/80 mmHg (**Grade C**).
- Persons with diabetes mellitus should be treated to attain SBP of less than 130 mmHg (**Grade C**) and DBP of less than 80 mmHg (**Grade A**).
- Combination therapy using two first-line agents may also be considered as initial treatment of hypertension (**Grade B**) if SBP is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target.
  - However, caution should be exercised in patients in whom a substantial fall in blood pressure is more likely or poorly tolerated (e.g. elderly patients and patients with autonomic neuropathy).
- **Academic Detailing Comment:** Note that the recommendation to strongly consider therapy in patients with SBP 140 to 159 mmHg specifies that macrovascular target organ damage be present.
  - Other recommendations consider the presence of other cardiovascular risk factors (Table 4).
- CHEP
  - Suggests the use of a global **risk assessment** tool (e.g. Framingham model) to more accurately assess cardiovascular risk to help decide at what BP level to initiate drug therapy.
  - Emphasizes the importance of **lifestyle** change before or in conjunction with pharmacotherapy.



**Table 4 Examples of target organ damage and cardiovascular risk factors from CHEP<sup>17</sup>**

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

<sup>a</sup> CHEP 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.



## Question 1: What is the Evidence for a Treatment Target of < 140/90 mmHg in the Elderly?

### SUMMARY

- Definitions vary but the elderly are usually defined as  $\geq 60$  or 65 years old and the very elderly as  $\geq 80$  years old.
- The **frail** elderly are not defined by age alone and have multiple chronic illnesses and associated vulnerability including dementia, functional decline, and geriatric syndromes, such as falls and impaired mobility.
- A Cochrane review indicates that antihypertensive therapy confers benefit in the elderly and the very elderly.
- There is uncertainty about the optimal level of blood pressure that should be maintained, which leads to **two questions**.
- **Question A: At what SBP should pharmacotherapy be started in people >65 years old>**
  - Evidence supports initiating pharmacotherapy at a SBP  $\geq 160$  mmHg.
  - Major trials enrolled elderly patients only if they had SBP  $\geq 160$  mmHg. Therefore the current guideline recommendations on initiating therapy at a SBP values between 140 and 159 mmHg in the elderly are **uncertain** and not based on results from trials.
    - CHEP recommends to strongly consider therapy at SBP level 140 to 159 mmHg in the general population and stipulates that target organ damage be present (**Grade C**).
      - This recommendation is extrapolated to the elderly.
- **Question B: What should the SBP treatment target be in people >65 years old?**
  - Evidence supports a SBP target of <160 mmHg in the elderly.
  - The optimal SBP target below 160 mmHg is uncertain.
  - Evidence addressing a SBP target of <140 mmHg is limited.
    - The only trial that randomized patients to different blood pressure targets in the elderly (SBP <140 mmHg vs 140 to 160 mmHg) showed **no** statistically significant **difference** between groups in any outcome.
- **Opinion of local experts are in the following comments.**
  - Most elderly should achieve a SBP of <160 mmHg.
    - Below 160 mmHg, initiation of treatment and setting BP target levels should consider the patient's overall risk assessment and not simply a numerical value.
    - In patients with SBP 140 to 159 mmHg without target organ damage or risk factors, encourage lifestyle change for at least 6 months but strongly consider drug therapy if inadequate response.
    - In general, aim for <140/<90 in every patient if tolerated even in the healthy elderly while monitoring potassium, creatinine, orthostasis, and side effects.



- In the **frail** elderly
  - If treatment is initiated, a reasonable target is SBP 140 to 160 mmHg while sitting as long as there is no orthostatic drop to <140 mmHg while standing.
  - With **short** life expectancy, a SBP range of 160 to 190 mmHg may be reasonable.
  - In general use no more than 2 medications.
- Make reasonable attempts to control hypertension, while taking heed to avoid harmful effects from treatment, which might be more likely or of greater consequence in certain patients, such as the frail or very elderly.

- Several studies have addressed the treatment of hypertension in the elderly. Definitions of elderly vary
  - A Cochrane review defines "elderly" as  $\geq 60$  years old and "very elderly" as  $\geq 80$  years old.<sup>6</sup>
  - The ACCF/AHA consensus document defines elderly as  $\geq 65$  years old but also differentiates patients  $\geq 80$  years old in some discussion points.<sup>9</sup>
- A 2010 Cochrane review looked at the efficacy of anti-hypertensive therapy in the elderly with mild to moderate hypertension for the outcomes of
  - All-cause mortality
  - Cardiovascular morbidity and mortality
  - Withdrawals for adverse events.
- The review included 15 studies and 24,000 subjects.
  - For the **elderly** ( $\geq 60$  years) data came from 13 studies with 23,000 subjects.
  - For the **very elderly** ( $\geq 80$  years) data came from 8 studies with 6500 subjects.
  - Inclusion criteria: SBP  $\geq 140$  and/or DBP  $\geq 90$
  - Mean age was 74 years.
  - 60% of subjects were female.
  - Four studies were  $\leq 2$  years long, the rest were 3 to 6 years long.
  - Mean duration in elderly was 4.5 years.
  - Mean duration in very elderly was 2.2 years.
  - Mean BP at entry in most studies was 182/95.
  - No studies included in the review compared outcomes at two different target BP levels. Instead, subjects were assigned to take either active medication or placebo and the resulting BPs were recorded.
  - Patients were treated with commonly used antihypertensive medications.
    - In over 70% of the trials a thiazide diuretic was the first line drug used in the treatment group.
- Results are in Table 5.
  - In the **elderly** there was benefit in all outcomes including total mortality.



- In the **very elderly** there was a significant reduction in cardiovascular and cerebrovascular events when fatal and non-fatal events were combined.
  - However, all-cause mortality was not significantly different when analyzed alone.
- **Author conclusions**
  - 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.
  - The decrease in all-cause mortality was limited to persons 60 to 80 years old.

**Table 5 Results of antihypertensive therapy in subjects  $\geq 60$  years old and  $\geq 80$  years old<sup>6</sup>**

Outcome	Event Rate		ARR (ARI)	RRR (RRI)	NNT for ~4.5 yrs	
	Placebo	Drug			NNT	95% CIs
<b>Elderly (<math>\geq 60</math> yrs)</b>						
Total mortality	15%	14%	1.1% <sup>a</sup>	10%	91	53 to 333
Cardiovascular mortality and morbidity	21%	14%	4.3% <sup>a</sup>	18%	23	16 to 42
Cerebrovascular mortality and morbidity	7.1%	4.2%	1.9% <sup>a</sup>	44%	53	42 to 77
Coronary heart disease mortality and morbidity	4.8%	3.7%	0.9%	21%	111	67 to 250
<b>Very elderly (<math>\geq 80</math> yrs)</b>					<b>NNT for ~2.2 yrs</b>	
Total mortality	16%	19%	(2%) <sup>a,b</sup>	(20%) <sup>b</sup>	NS	
Cardiovascular mortality and morbidity	14%	10%	2.8% <sup>a</sup>	25%	36	23 to 71
Cerebrovascular mortality and morbidity	7.9%	4.6%	1.8% <sup>a</sup>	44%	56	36 to 125
Coronary heart disease mortality and morbidity	3.5%	3.4%	0.3% <sup>a</sup>	14%	NS	

ARR, absolute risk reduction; ARI, absolute risk increase; RRR, relative risk reduction; RRI, relative risk increase; NNT, number needed to treat; CI, confidence interval; NS, not statistically significant.

a Results calculated by Dalhousie Academic Detailing Service from data provided in publication using meta-analysis program called Comprehensive Meta-analysis. ARR values are calculated by doing meta-analysis of ARRs from all studies and not from subtracting event rates in drug group from placebo group. NNTs are calculated from ARRs in table.

b Event rate in drug group is higher than in placebo group so values are absolute and relative risk **increase**

- Total mortality means deaths from all causes.
- Cardiovascular morbidity and mortality includes coronary heart disease plus cerebrovascular morbidity and mortality plus aneurysms, congestive heart failure, and transient ischemic attacks.
- Cerebrovascular morbidity and mortality includes fatal and nonfatal strokes.
- Coronary heart disease morbidity and mortality includes fatal and non-fatal myocardial infarctions and sudden or rapid cardiac death.



- The Cochrane review indicates that antihypertensive therapy confers **benefit** in the elderly and the very elderly.
  - What is uncertain is the optimal level of blood pressure that should be maintained, which leads to two questions
    - Question A. When should pharmacotherapy be started?
    - Question B. What should the blood pressure treatment target be?

**Question A: At what SBP should pharmacotherapy be started in people >65 years old?**

- A reappraisal of the European guidelines on hypertension management published in 2009 by the European Society of Hypertension<sup>3,18</sup> provides a summary of the major hypertension RCTs involving the elderly published to date.
  - In the studies cited, patients were included only if they had a **SBP  $\geq$ 160** mmHg and all studies except 1 showed benefit in clinical outcomes.
  - Thus evidence supports initiating therapy in patients >65 years old with SBP  **$\geq$  160** mmHg.<sup>3</sup>
    - CHEP makes this recommendation for all ages (**Grade A** Table 3).
      - This applies whether or not target organ damage is present.
  - The CHEP guideline recommends strong consideration be given to starting therapy in the general population if SBP is **140-159** mmHg.
    - This recommendation applies **only** in the **presence** of macrovascular target organ damage.
      - This is a **Grade C** recommendation.
  - CHEP states to consider therapy in all patients meeting the above indications **regardless of age**.
    - This is a **Grade B** recommendation.
  - The authors of the European guideline reappraisal state
    - "Current guidelines recommendations on BP values at which to initiate drug treatment in the elderly [SBP 140 to 159] are not based on results from trials, but derived from other findings
      - and perhaps encouraged by the large benefits of antihypertensive therapy in all available trials in the elderly, admittedly at **higher** initial blood pressures."
- **Academic Detailing Comment**
  - Evidence supports initiating pharmacotherapy at a SBP  $\geq$ 160 mmHg.
  - The Grade C level of the CHEP recommendation for the general population indicates the uncertainty about starting antihypertensive therapy at SBP levels of 140 to 159 mmHg and as highlighted by the European reappraisal document, this recommendation has not been studied in RCTs of the elderly.
  - It is important to note that the CHEP consideration to start therapy at SBP levels of 140 to 159 mmHg applies only in the presence of target organ damage.



- **Expert opinion**

- Most of our content experts recognize the limitations of the evidence but this does not override their opinion about starting therapy in patients with target organ damage at SBP  $\geq$  140 mmHg.
- Focus on the patient and the overall risks/benefits of treatment rather than on a specific numerical value.

**Question B: What should the SBP treatment target be in people >65 years old?**

- The CHEP recommendations indicate a SBP treatment target of <140 mmHg regardless of age (**Grade C**).
- The ACCF/AHA consensus document states that in the elderly the generally recommended BP goal of <140/90 is based on **expert opinion** rather than on data from RCTs.<sup>9</sup>
- Table 6 summarizes the studies cited in the 2009 reappraisal document by the European Society of Hypertension (see page 18).<sup>3</sup>
  - The achieved SBP levels are reported for the more active (drug) or less active (control) treatment groups for each of the trials.
  - With the exception of **JATOS**, these studies did not randomize patients to different BP targets. Instead patients were randomized to less active or more active blood pressure therapy to evaluate specific drug regimens.
  - Again, with the exception of **JATOS**, none of the studies achieved a SBP less than 140 mmHg, the currently recommended target. However, they **all** showed some benefit. **JATOS**, described on the next page, did not show difference in any outcomes.

**Table 6 Achieved SBP in studies of the elderly cited in 2009 reappraisal of European guidelines<sup>3</sup>**

Study	N subjects	Duration Years	Achieved SBP			Benefit
			Control	Active	Difference	
EW	840	4.6	172	150	22	Yes
CW	884	4.4	180	162	18	Yes
SHEP	4736	4.5	170	143	27	Yes
STOP	1627	2.1	186	167	19	Yes
MRC-E	4396	5.8	165	156	9	Yes
S Eur	4695	2.0	161	151	10	Yes
S-Ch	2394	3.0	160	151	9	Yes
SCOPE	4937	3.7	148	145	3	Partial <sup>a</sup>
HYVET	3845	2.1	159	144	15	Yes
<b>JATOS</b>	4418	2.0	146	<b>136</b>	10	<b>No</b>

a Significant benefits of more active treatment were limited to some secondary endpoints



- **JATOS** studied 4400 Japanese people 65 to 85 years old; duration 2 years.<sup>19</sup>
  - Subjects were randomized to SBP targets of <140 mmHg vs 140 to 160 mmHg.
    - 56% of patients were on antihypertensive therapy at study entry.
    - The main initial or add-on therapy was a calcium channel blocker, efonidipine but other common antihypertensives were also used.
    - Approximately 7% of patients had pre-existing cardiovascular disease.
  - Baseline BP levels were 172/89.
  - Achieved BP levels were 136/75 vs 146/78.
  - There was **no difference** between target groups in any outcome including
    - The primary composite outcome of stroke, cardiac and vascular disease, and renal failure (4.3% vs 4.3%) (Table 7).
    - Withdrawal from adverse events (1.6% vs 1.6%).
  - 80% of subjects in both groups achieved their target SBP with 1 or 2 medications.

**Table 7 Results of JATOS<sup>19</sup>**

Efficacy outcomes	SBP target		ARR	RRR	NNT for 2.0 yrs	
	140-160	≤ 140			NNT	95% CI
Primary outcome: stroke, cardiac and vascular disease, renal failure (morbidity)	3.9%	3.9%	0%	0%	NS	
Primary outcome: stroke, cardiac and vascular disease, renal failure (mortality)	0.36%	0.41%	0.05%	0%	NS	

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat; NS, not statistically significant.

- In 2009 after completion of the European Society of Hypertension reappraisal document, the **Cardio-sis**<sup>20</sup> trial was published.
  - Cardio-sis, if available, might have been included in Table 6 since 67% of the population consisted of patients ≥ 63 years old and 33% were >70.
  - Like JATOS, Cardio-sis also tested different SBP targets in patients with hypertension.
  - Cardio-sis studied 1,111 Italian people ≥ 55 years old without diabetes; duration 2 years.
  - Subjects were randomized to SBP targets of <130 mmHg vs <140 mmHg.
  - 100% of patients were already on antihypertensive therapy for at least 12 weeks at study entry.
  - Approximately 23% of patients had pre-existing cardiovascular disease.
  - Baseline BP levels were 163/90.





- Achieved BP levels were 132/77 vs 136/79.
- There was a **significant difference** in the primary outcome of the rate of electrocardiographic left ventricular hypertrophy between the tight and usual control groups at study endpoint (17% vs 11.4%).
  - While this primary endpoint is a surrogate outcome reported to be a strong predictor of cardiovascular outcomes, the clinical significance of the result is uncertain and according to the authors should be viewed as hypothesis-generating.
  - There was also benefit in the secondary composite outcome consisting of 13 individual outcomes.
    - Only 2 individual outcomes of the composite were positive – new onset of atrial fibrillation and coronary revascularization.
    - This secondary outcome was **not pre-specified** in the trial registry.
- The above 2 trials address SBP targets with JATOS addressing targets exclusively in the elderly (65 to 85 years old).
- HYVET, a recent trial involving the **very elderly** ( $\geq 80$  years old) was **not** designed to evaluate different blood pressure targets.<sup>21</sup>
  - It was designed to evaluate the benefit of treatment with indapamide with or without perindopril vs placebo.
  - HYVET enrolled the **very elderly** (all  $\geq 80$  years old) N=3845; duration 2.1 years.
    - Patients with SBP  $\geq 160$  (and standing SBP  $\geq 140$ ) were randomized to receive either
      - placebo or indapamide 1.5 mg +/- perindopril 2 or 4 mg to get to a BP of  $<150/<80$ .
    - Patients were taken off previous meds if they were on any.
    - Patients were community-living and generally healthy.
      - Approximately 12% had macrovascular target organ damage.
    - In the two groups BP went from 173/91 to
      - 144/78 vs 159/84
    - There was **no** statistically significant **benefit** in the **primary** outcome of fatal and non-fatal **stroke**.
    - However the study was stopped early at a mean of 2.1 years because of benefit in death from any cause.
      - Had the trial continued longer the benefit in stroke reduction may have become statistically significant.
      - In addition, HYVET was included in the Cochrane meta-analysis<sup>6</sup> which showed overall statistically significant **benefit** in reduction of fatal and non-fatal stroke with antihypertensive therapy in those  $\geq 80$  years old.

Table 8 Results of HYVET<sup>21</sup>

Outcome	Events per 1000 pt-yr		RRR	P-value
	Placebo	Drug		
Fatal or non-fatal stroke <sup>a,b</sup>	17.7	12.4	30%	0.06
Fatal or non-fatal heart failure <sup>a</sup>	14.8	5.3	64%	<.001 <sup>c</sup>
Fatal or non-fatal cardiovascular event <sup>a</sup>	51	34	34%	<.001 <sup>c</sup>

	Event Rate		ARR	RRR	NNT for 2.1 yrs	
	Placebo	Drug			NNT	95% CI
Death from any cause	12.3%	10.1%	2.2%	18%	46	24 to 637
Death from stroke	2.2%	1.4%	0.8%	36%	125	-2500 to 61 <sup>d</sup>

a Results reported as hazards and hazard ratios of numbers of events rather than number of patients having an event so it is not possible to calculate ARR and NNT.

b Fatal or non-fatal stroke was the **primary** outcome. Result was **not** statistically significant: hazard ratio 0.70 (95% CI: 0.49 to 1.01) p = 0.06.

c These composite secondary outcomes were **not** pre-specified in the clinical trial registry.

d Results were calculated by Dalhousie Academic Detailing Service from data provided in publication. Negative confidence interval indicates non-significant result. However, published result was **statistically significant**.

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat; pt-yr, patient year.

#### Academic Detailing Comments on HYVET

- HYVET supports that there is benefit from treating hypertension in the very elderly with indapamide and perindopril but does not provide evidence to support treating to a specific target.
  - The ACCF/AHA Consensus Document states that HYVET did not address the optimal BP goal for reducing CV events and mortality.<sup>9</sup>
- The benefit of the achieved blood pressure (144/78) in the very elderly is uncertain because it is difficult to separate the effects of lowering blood pressure from the effects of the medication given to the active treatment group.
  - Angiotensin converting enzyme inhibitors (ACEI) may have beneficial effects beyond reducing blood pressure and since this was a placebo-controlled trial, may have contributed to the benefit found in the active group.
- It is noteworthy that the benefits occurred despite over half (52%) of subjects not achieving the specified BP of <150/<80.<sup>21</sup>



## Various Interpretations and Recommendations For the Elderly

- The CHEP recommendations for starting therapy and for targets are the same regardless of age while exercising caution in the frail elderly.<sup>1</sup>
- The **2011 ACCF/AHA Consensus Document**<sup>9</sup> states
  - Studies have shown clinical benefits with achieved SBP values averaging in the 140s, 150s, and 160s.
  - The target of <140/90 in uncomplicated elderly patients is based on **expert opinion**.
  - There is **limited evidence** to
    - Support a value of 140 mmHg as a diagnostic and therapeutic threshold.
    - Determine if patients with initial SBP between 150 and 159 would benefit from treatment.
- Nevertheless the Consensus Document considers
  - For those  $\leq 79$  years old achieved SBP values <140 mmHg are appropriate.
  - For those  $\geq 80$  years old achieved SBP levels of 140 to 145 mmHg if tolerated can be acceptable with the following **exceptions**
    - If patient has achieved SBP <150 mmHg on 1 or 2 meds with no problems, try for <140 mmHg even though there is no firm evidence to support this target.
    - If SBP is  $\geq 150$  mmHg under following 3 circumstances
      1. Taking 4 drugs
      2. Having unacceptable adverse effects, especially postural hypotension
      3. DBP is being reduced to <65 mmHg
        - For the above 3 circumstances the lowest safely achieved SBP  $\geq 150$  mmHg is acceptable.
- The Consensus Document also states there is **no data** to support lower BP targets in patients at high risk because of conditions such as diabetes, CKD, or CAD.<sup>9</sup>
- The Consensus Document did not report results of JATOS but communication with the authors indicates they would not change recommendations based on it.
- **Opinions of local experts are in the following comments.**
  - Most elderly should achieve a SBP of <160 mmHg.
    - Below 160 mmHg, initiation of treatment and setting BP target levels should consider the patient's overall risk assessment and not simply a numerical value.
    - In patients with SBP 140 to 159 mmHg without target organ damage or risk factors, encourage lifestyle change for at least 6 months but strongly consider drug therapy if inadequate response.
    - In general, aim for <140/<90 in every patient if tolerated even in the healthy elderly while monitoring potassium, creatinine, orthostasis, and side effects.



- In the **frail** elderly
  - If treatment is initiated, a reasonable target is SBP 140 to 160 mmHg while sitting as long as there is no orthostatic drop to <140 mmHg while standing.
  - With **short** life expectancy, a SBP range of 160 to 190 mmHg may be reasonable.
  - In general use no more than 2 medications.
- Make reasonable attempts to control hypertension, while taking heed to avoid harmful effects from treatment, which might be more likely or of greater consequence in certain patients, such as the frail or very elderly.
- **Academic Detailing Comments**
  - A Cochrane review indicates that antihypertensive therapy confers benefit in the elderly and the very elderly.
  - Evidence supports a SBP target of <160 mmHg in the elderly.
  - The optimal target **below 160** is **uncertain**.
  - Evidence addressing a SBP target of <140 mmHg is limited.
    - JATOS, the only trial that randomized exclusively elderly patients to different SBP targets (<140 mmHg vs 140 to 160 mmHg) showed **no difference** in any outcome between the two targets.
      - Only 7% of patients in this study had pre-existing cardiovascular disease.

### The frail elderly

- Frailty is defined as the accumulation of multiple chronic illnesses and associated vulnerability. (See Appendix 2.)
  - The frail elderly commonly have dementia, functional decline, and geriatric syndromes, such as falls and impaired mobility.
  - They are at higher risk for adverse outcomes such as hospitalization delirium; adverse drug reactions which frequently present atypically;<sup>22</sup> and death, compared with those who are not frail.<sup>23</sup>
  - Older adults living in long-term care facilities tend to be very frail or very severely frail with limited life expectancy.
  - As life-expectancy is shorter in frail individuals, time required to achieve benefit should be considered in therapeutic decisions.
- The defining characteristics of frailty require a unique approach.
- Most trials enroll subjects who are at most, mildly frail and do not address hypertensive treatment in those who are severely frail or very severely frail.



- As the main concern in frailty is to decrease disability, it is important to focus on the possibility of **stroke** prevention.
  - In studies of the **non-frail** elderly, antihypertensive therapy required 1 to 2 years<sup>24-26</sup> or longer<sup>27, 28</sup> to show benefit in fatal and non-fatal stroke.
  - In contrast, HYVET did not show statistically significant reduction in fatal and non-fatal stroke after 2 years.<sup>21</sup>
- Advanced age and frailty may result in a greater risk of events such as stroke. Therefore the benefits of therapy **may** appear earlier than in the non-frail. However, no studies have been done to explore this.
- The potential for **adverse effects** from therapies also requires consideration.
  - The frail elderly, especially those with dementia, may not be able to communicate symptoms of drug-related adverse effects.
  - Polypharmacy is common and with each additional medication, there is an increased risk of medication-related adverse effects.<sup>29, 30</sup>
  - Age-related physiologic changes may alter the disposition and pharmacologic actions of drugs (e.g., onset, duration and magnitude of effect) and can result in considerable interindividual variation in response.<sup>31</sup>
  - **Orthostatic hypotension** is a particular concern and may lead to falls.
    - In long-term care facilities, blood pressure is frequently measured in the supine position, which may over-estimate the sitting or standing blood pressure.
- In most RCTs that included the elderly, beneficial effects were achieved with **1 or 2** anti-hypertensive medications.
  - No trial was designed to look at the benefit or risks of using 3 or more therapies. Thus, there is no definitive evidence that using more than 2 drugs to control hypertension in frail older adults is beneficial.
- RCTs exclude the very frail or very severely frail elderly and thus, recommendations for BP treatment are based on **local expert consensus**.
- When managing the frail elderly, it is worth considering the following questions:<sup>32</sup>
  - Is the person's life expectancy long enough to achieve benefit?
  - Are there clinically significant drug-drug interactions?
  - Are there clinically significant adverse effects?
  - Does the medication match the patient's goals of care?
  - Is this drug the least expensive alternative compared with others of equal usefulness?



### **Local Expert Consensus on Treatment of Hypertension in the Frail Elderly**

#### Considerations before treating:

- Carefully review the risks and potential, but unproven, benefits.
- Do not make treatment decisions based only on supine measurements.

#### Measuring blood pressure

- When measuring BP, take readings when sitting.
- To evaluate orthostasis, measure BP lying, then immediately on standing and after 2 minutes. Ask the patient if they feel lightheaded or dizzy when standing.

#### Starting treatment:

- Consider starting treatment when SBP is **≥160** mmHg.
- Target SBP to **140 to 160** mmHg while sitting as long as
  - There is no orthostatic drop to <140 mmHg using the technique described above.
  - There are no adverse effects from treatment that affect quality of life.
- In the very frail with short life expectancy, a target SBP of 160 to 190 mmHg may be reasonable.
- The blood pressure target does not need to change when there is a history of diabetes.
- In general, use no more than 2 medications.

#### Stopping treatment:

- If sitting SBP is <140 mmHg, medications can be tapered and discontinued.
- However, before discontinuation, consider if the medications are treating additional conditions such as rate control for atrial fibrillation or symptomatic control of heart failure.



## Question 2: What is the evidence for a treatment target of <130/80 mmHg in patients with diabetes?

### SUMMARY

- Together, diabetes and hypertension account for more than two-thirds of CV disease risk.
- It is important to treat hypertension in people with diabetes, however the same questions about hypertension in the elderly apply to persons with diabetes:

#### Question A: At what SBP should pharmacotherapy be started in people with diabetes?

- No studies compared the effect of starting therapy in patients with SBP of 130 to 139 mmHg vs patients with SBP >140 mmHg.
- The CDA recommends treatment be initiated at a BP of  $\geq 130/80$  mmHg.
  - This is a Grade D (**consensus**) recommendation.
- The above information indicates the uncertainty in the evidence for starting therapy at SBP 130 to 139 mmHg vs  $\geq 140$  mmHg in patients with diabetes.

#### Question B: What should the SBP treatment target be in people with diabetes?

- The CHEP and CDA guidelines make the following recommendation:
  - Persons with diabetes and hypertension should be treated to attain
    - SBP <130 mm Hg [*CDA: Grade C, Level 3 and CHEP: Grade C*]
- ACCORD BP randomized patients with diabetes to different SBP targets (<120 mmHg vs <140 mmHg).
  - There was **no** statistically significant **difference** between the 2 target groups in the **primary** outcome of non-fatal MI, non-fatal stroke, or cardiovascular death.
  - There was benefit in the **secondary** outcome of **stroke** though the absolute benefit was small.
  - The ACCORD authors conclude "The results provide no evidence that the strategy of intensive BP control reduces the rate of a **composite of major cardiovascular events** in the study patients."
- The current CHEP guidelines have not made any changes to recommendations since publication of ACCORD BP.
- Patients with diabetes should be screened annually for **kidney damage** with a routine urinalysis and urinary albumin-creatinine ratio (**ACR**).
- In patients with diabetes and kidney damage **expert opinion** suggests it may be reasonable to aim for a target BP of <130/80 although definitive evidence is lacking.
- The above information indicates the uncertainty for a treatment target of <130/80 mmHg in patients with diabetes.
- It may be difficult to reach a SBP of <130 mmHg without excessive lowering of DBP ( $\leq 70$  mmHg) which may lead to increased cardiovascular events particularly in the elderly and people with diabetes or coronary heart disease.



- Diabetes is a risk factor for cardiovascular disease and chronic kidney disease (CKD). Epidemiological data suggest that relative hyperglycemia accounts for **part** but not all of the increased CV and renal disease risk.
- Hypertension is more common in people with diabetes. Together, diabetes and hypertension account for more than two-thirds of CV disease risk.<sup>2</sup>
- Two cohort studies show that blood pressure has a continuous and independent relationship with cardiovascular risk and renal progression in patients with diabetes.<sup>33, 34</sup>
- The same questions about hypertension in the elderly apply to persons with diabetes:
  - Question A. At what blood pressure value should pharmacotherapy be started in people with diabetes?
  - Question B. What should the blood pressure treatment target be in people with diabetes?

**Question A: At what SBP should pharmacotherapy be started in people with diabetes?**

- The same 2009 reappraisal report from the European Society of Hypertension<sup>3</sup> that reviewed achieved SBP in studies of the elderly also summarized studies involving patients with diabetes (Table 10).
  - **No** studies compared the effect of starting therapy in patients with SBP of 130 to 139 mmHg vs patients with SBP  $\geq$ 140 mmHg.
  - One study<sup>35</sup> evaluated the effect of varying blood pressure control in patients with type 2 diabetes who were considered normotensive when the study was done.
    - However, patients were enrolled based on DBP between 80-89 mmHg with “normotension” defined as SBP <160 mmHg which is higher than currently accepted levels. Further details of this trial are provided in Table 11.
- Current Canadian hypertension guidelines<sup>1,2</sup> recommend aggressive treatment of hypertension in all patients with diabetes. It is recommended that treatment be initiated at a BP of  $\geq$ 130/80 mmHg.
  - In the CDA guideline this is a Grade D (**consensus**) recommendation.
- **Academic Detailing Comment:** The above information indicates the uncertainty about the evidence for starting therapy at SBP 130 to 139 mmHg vs  $\geq$ 140 mmHg in patients with diabetes.



**Question B: What should the SBP treatment target be in people with diabetes?**

- The CHEP and CDA guidelines do not differentiate between persons with type 1 and type 2 diabetes. However most evidence is from studies of persons with type 2.
- The guidelines make the following recommendations:
  - Persons with diabetes and hypertension should be treated to attain
    - SBP <130 mm Hg [CDA: Grade C, Level 3 and CHEP: Grade C] and
    - DBP <80 mm Hg [CDA: Grade B, Level 2 and CHEP: Grade A].
- Since SBP is considered more important in management of hypertension we shall place more emphasis on it.
- The CDA states the recommendation for the above **SBP** target
  - Is based on weaker evidence than that for a DBP target of <80 mmHg.
  - Is based on two cohort studies<sup>33, 34</sup> and the ABCD normotensive trial.<sup>35</sup>
- The CDA guideline was written before the publication of ACCORD BP<sup>36</sup> and states that this study would provide stronger evidence to address the question of SBP target.
- **ACCORD BP** has now been published<sup>36</sup> (The full name of the study is Action to Control Cardiovascular Risk in Diabetes - blood pressure.)
  - ACCORD found **no** statistically significant **difference** between the 2 target groups in the **primary** outcome of non-fatal MI, non-fatal stroke, or cardiovascular death.
    - There was benefit in the **secondary** outcome of **stroke** though the absolute benefit was small (Table 9).
  - There were also more **serious adverse events** due to medication (those that were life-threatening, cause permanent disability, or necessitate hospitalization) in the group randomized to a target SBP <120 mmHg, the most common being
    - Hypotension
    - Bradycardia or arrhythmia
  - The authors concluded
    - "The results provide **no evidence** that the strategy of intensive BP control reduces the rate of a **composite of major cardiovascular events** in the study patients."
    - "Although it was not the intent of the trial to test the BP goal of 130 mmHg it would be difficult to argue that such a target would be better than a target of 140 mmHg since even a BP goal of 120 mmHg did not confer benefit."
  - Details of ACCORD are in the box on page 30 and results are in Table 9.
- The current CHEP guidelines have not made any changes to recommendations since publication of ACCORD BP.



### Details of ACCORD BP<sup>36</sup>

- The goal was to test the effect of target SBP <120 on major CV events among high-risk persons with type 2 diabetes.
- N = 4733; mean duration 4.7 years; not blinded although outcome assessors were blinded.
- Patients were either
  - ≥ 40 years old with CV disease or
  - ≥ 55 years old with anatomic evidence of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for CV disease.
- At baseline patients
  - Were overweight (BMI 32) and had type 2 diabetes but had **no substantive evidence of kidney disease**.
  - Had a history of excellent BP control (mean baseline BP 139/76).
- Patients were randomized to receive intensive therapy or standard therapy.
  - Intensive therapy had a SBP target of <120 mmHg
  - Standard therapy had a SBP target of <140 mmHg
- To achieve the targets patients were treated with drugs known to reduce CV events in patients with diabetes. In patients in the intensive therapy group, the initial recommended therapy was a diuretic plus an ACEI or beta-blocker.
  - At 12 months
    - 90% of patients were on ACEIs or ARBs
    - 50% were on beta-blockers
    - 40% were on calcium channel blockers
    - 60% were on statins and platelet inhibitors
- Achieved BP was
  - Intensive group 119/64
  - Standard group 134/71
- Results
  - There was **no** statistically significant **difference** between the 2 target groups in the **primary** outcome of non-fatal MI, non-fatal stroke, or cardiovascular death.
    - There was benefit in the **secondary** outcome of **stroke** though the absolute benefit was small (Table 9).
- The intensive therapy group:
  - Took **more** drugs from every class (mean 3.4 vs 2.1)
  - Had significantly **higher** rates of hypokalemia and serious adverse events attributed to antihypertensive treatment.
  - Had significantly **more** instances of an eGFR <30ml/min/1.73m<sup>2</sup> although only 38 people in the intensive group and 32 in the standard group had ≥ 2 instances of that rate (p=0.46).
  - Had a significantly **lower** mean eGFR at the last visit.
  - Had a significantly **lower** frequency of macroalbuminuria at the last visit.
  - Had a **similar** frequency of end stage renal disease or need for dialysis compared to the standard group.

Table 9 Results of ACCORD BP<sup>36</sup>

Efficacy outcomes	SBP target		ARR	RRR	NNT for 4.7 yrs	
	≤ 140	≤ 120			NNT	95% CI
Primary outcome – non-fatal MI, non-fatal stroke, death from CV causes	10%	8.8%	1.2%	12%	NS	
Strokes	2.6%	1.5%	1.1%	42%	92	53 to 356
Macroalbuminuria	8.7%	6.6%	2.1%	25%	47	27 to 179
Adverse events	≤ 140	≤ 120	ARI	RRI	NNH	95% CI
Total mortality	6.1%	6.3%	0.2%	4.5%	NS	
Serious AEs from BP medication <sup>a</sup>	1.3%	3.3%	2.0%	158%	50	35 to 87
Potassium <3.2 mmol/liter	1.1%	2.1%	1.0%	82%	107	61 to 455
eGFR < 30 ml/min/1.73 m <sup>2</sup>	2.2%	4.2%	2.0%	91%	50	33 to 100

<sup>a</sup> Serious adverse events are those that are life threatening, cause permanent disability, or require hospitalization

ARR, absolute risk reduction; ARI, absolute risk increase; RRR, relative risk reduction; RRI, relative risk increase; NNT, number needed to treat; NNH, number needed to harm; CI, confidence intervals.

- In addition to ACCORD, another study published after the CDA guideline is an **observational secondary analysis of the INVEST** trial.<sup>37</sup> It supports the conclusions of ACCORD BP.
  - INVEST, an open label, blinded end-point RCT published in 2003, randomized patients with hypertension and coronary heart disease to antihypertensive therapy based on either a calcium channel blocker or  $\beta$ -blocker.<sup>38</sup>
    - All patients with diabetes could receive trandolapril as initial therapy.
    - N = 22,576; duration 2.7 years.
  - The 2010 **observational secondary analysis** reports a sub-group analysis of the 6,400 patients with diabetes which explored the primary outcome of all-cause mortality, non-fatal MI or non-fatal stroke in relation to three levels of achieved SBP:
    - <130 mmHg
    - 130-139 mmHg
    - >139 mmHg
  - A long-term follow up of 5 years was conducted in the US patients only (n=5,077) to assess the cumulative effect on all-cause mortality.
  - There was **no significant** difference between the <130 mmHg group and the 130-139 mmHg group for the **primary** outcome
    - Event rates 12.6% vs 12.7% (HR 1.11; 95% CI, 0.93-1.32;  $P=.24$ )



- When adjusted for possible confounding factors the risk of all-cause **mortality** in the US patients followed for an extra 5 years was **increased** in the group that achieved SBP <130 mm Hg vs the 130-139 mmHg group
  - 22.8% vs 21.8% hazard ratio 1.20 (95% CI: 1.01 to 1.32) P=0.04
- The authors conclude
  - For patients with diabetes and coronary heart disease, achieving a SBP of <140 mmHg provides the same reduction in CV events as achieving a SBP <130 mmHg.
  - There is no compelling evidence to indicate that lowering SBP below 130 mmHg is beneficial for patients with diabetes; thus, emphasis should be placed on maintaining systolic BP between 130 and 139 mmHg while focusing on weight loss, healthful eating, and other manifestations of cardiovascular morbidity to further reduce long-term cardiovascular risk.
- **Academic Detailing Comments:**
  - The data provided by the ACCORD BP trial and the INVEST subgroup analyses support a SBP goal of <140 mmHg in the populations studied.
    - However they do not support a SBP goal of <130 mmHg.
  - The most important positive finding of ACCORD BP was the benefit reported for **stroke**. However, this was a secondary outcome in which the primary outcome was negative. Also, the absolute benefit was small.
    - A recent meta-analysis supports the findings of ACCORD BP that intensive BP reduction led to benefit in reducing stroke but not MI.<sup>39</sup>
    - Note that in ACCORD BP, 97.4% of patients in the standard therapy group did not have a stroke.
      - This number increased to 98.5% in the intensive therapy group a difference of 1.1%, NNT 92 (95% CI: 53 to 356) over 4.7 years.
  - ACCORD BP does not answer whether patients with diabetes and **chronic kidney disease** (CKD) would benefit from a BP treatment target of <130/80 mmHg.
    - The majority of patients enrolled in ACCORD BP had normal kidney function. (See page 36 for details on chronic kidney disease, diabetes, and hypertension.)
  - While the secondary analysis of INVEST indicates there is no difference in benefit, and possible increase in all-cause mortality from lowering SBP below 130 mmHg, results should be interpreted with **caution** because of the limitations of post-hoc observational analyses.
- Before publication of ACCORD BP and the INVEST sub-group analysis, the 2009 reappraisal document by the European Society of Hypertension pointed out some of the uncertainty of the evidence for recommended SBP targets in patients with diabetes.
- Table 10 summarizes the studies cited in this publication. The achieved SBP levels are reported for the more active (drug) or less active (control) treatment groups in the randomized controlled trials involving patients with diabetes.
  - (ACCORD BP<sup>36</sup> and the subgroup analysis of INVEST<sup>37</sup> are not included as they were not available when this review was published.)



**Table 10 Achieved SBP in studies of persons with diabetes cited in 2009 reappraisal of European guidelines<sup>3</sup>**

Study	N subjects	Duration Years	Achieved SBP			Benefit
			Control	Active	Difference	
SHEP	583	4.3	155	145	10	Yes
MHOPE	3577	4.5	143	139	4	Yes
S EUR	492	2.0	162	153	9	Yes
IDNT IR	1148	2.6	144	140	4	Partial <sup>b</sup>
IDNT AM	1136	2.6	144	141	3	No
REN	1513	3.4	145	143	2	Partial <sup>b</sup>
PROG	6105	4.0	143	134	9	Yes
ADV	11,140	4.3	140	134	6	Yes
HOT <sup>a</sup>	1501	3.8	148	145	3	Yes
UKPDS 38 <sup>a</sup>	1148	8.4	154	144	10	Yes
ABCD HT <sup>a</sup>	470	5.3	138	132	6	Partial <sup>b</sup>
ABCD NT <sup>a</sup>	480	5.3	137	<b>128</b>	9	Partial <sup>b</sup>

a Only these four trials randomized patients to different blood pressure targets. Only UKPDS 38 evaluated systolic and diastolic targets. HOT, ABCD HT, and ABCD NT evaluated only diastolic targets. See Appendix 1 for details.

b Significant benefits of more active treatment were limited to some secondary endpoints.

- Eight of the 12 trials cited above randomized patients to placebo or active therapy to evaluate specific drug regimens. They were **not designed** to address questions regarding the merit of various blood pressure targets. However, they do provide other relevant information.
  - None of the eight studies achieved a SBP <130 in the drug arm; nevertheless, with the exception of one study, all showed some benefit.
  - IDNT showed
    - **Benefit** from irbesartan in renal outcomes that was **independent** of mean arterial BP.<sup>40</sup>
      - The primary renal outcome was a composite of the doubling of serum creatinine or end-stage renal disease.
    - **No benefit** from amlodipine in any outcome vs placebo despite **lower** BP.
  - RENAAL showed **benefit** from losartan in renal outcomes that was **independent** of BP.<sup>41</sup>
    - The primary outcome was the composite of a doubling of the baseline serum creatinine concentration, end-stage renal disease, or death.



- Four of the 12 trials cited in table 10 were designed to test various BP targets<sup>35, 42-44</sup> (See Appendix 1 for details). Only one trial, ABCD NT, achieved a **SBP** of <130 mmHg. The CDA cites this trial as supporting the currently recommended SBP target of <130 mmHg.
  - CDA does not give findings from the ABCD NT level 1 status because there was no statistical correction for the many secondary outcomes tested, and results of some outcomes (e.g., stroke) were based on small numbers.<sup>2</sup> (See Table 11 for summary of ACCORD BP and ABCD NT.)
- The CDA also cites two **cohort** studies as supporting the SBP target of <130 mmHg.
  - One cohort study is based on an analysis of the UKPDS study which evaluated the relation between mean SBP over the course of the study and the development of micro and macrovascular outcomes.<sup>33</sup>
    - N = 3642; median duration 8.4 years
    - Patients were newly diagnosed with type 2 diabetes.
    - Results were adjusted for age at diagnosis of diabetes, ethnic group, smoking status, presence of albuminuria, hemoglobin A1c, high and low density lipoprotein cholesterol, and triglycerides.
    - For each 10 mmHg drop in SBP, microvascular and macrovascular outcomes, including all-cause mortality, decreased by 12% to 19%.
      - There was no threshold of SBP above or below which this relationship applied. The lower the SBP the lower the risk of complications even below a level of 130 mmHg.
  - The other cohort study prospectively involved patients with childhood-onset type 1 diabetes and analyzed the relation between micro and macrovascular outcomes and DBP and SBP.<sup>34</sup>
    - N = 589; duration 10 years
    - All micro and macrovascular outcomes except development of overt nephropathy showed a statistically significant decrease with decreasing SBP and DBP including below a SBP of <130 mmHg.
- **Academic Detailing Comments**
  - Observational cohort data establish an **association** between blood pressure and cardiovascular or renal events. However, they do **not** provide **definitive evidence** on the level at which antihypertensive therapy should be initiated or what the optimal target should be to decrease the risk of kidney disease or cardiovascular events.
  - The CDA cites ABCD NT as supporting the SBP target of <130 mmHg in persons with diabetes while acknowledging its limitations.
    - Of note, the primary outcome (change in creatinine clearance) was **negative**.
  - ACCORD BP, a much larger trial designed to test different SBP targets provides stronger evidence **not** supporting a SBP target of <120 mmHg.



**Table 11 Summary of ACCORD BP and ABCD NT**

	<b>ACCORD BP</b>	<b>ABCD NT</b>
Goal/Question	Test effect of target SBP <120 on major CV events among high-risk persons with T2DM	Determine the effect of moderate versus intensive DBP control on change in creatinine clearance
N	4733	480
Duration	4.7 years	5.3 years
Population	Type 2 diabetes	Type 2 diabetes
CVD	34%	24% intensive group 31% control group
Age	Inclusion ≥ 40	40 to 74
	Baseline 62	59
Drugs	Both groups able to take diuretic, B-blocker, ACE, ARB, CCB	Nisoldopine or enalapril vs placebo
Inclusion SBP	130-170 if on 0 to 3 meds	
Inclusion DBP		80 to 89 on no meds
Target SBP	Intensive: <120 Moderate: <140	
Target DBP		Intensive: 10 mmHg lower than on entry Moderate: 80 to 89
Baseline BP	139/76	136/84
Achieved SBP	119 vs 134	128 vs 137
Achieved DBP	64 vs 71	75 vs 81
Primary outcome	MI, stroke, cardiovascular death	Change in 24 hr creatinine clearance
Results	- No difference in primary outcome - No difference in most secondary outcomes with the exception of stroke	- No difference in primary outcome - Benefit in stroke, proteinuria, retinopathy
CDA comments	- We are not aware of comments from CDA however CHEP has not changed recommendations based on ACCORD.	- Supports SBP target of <130 (Grade C) - No statistical correction for multiple comparisons - Results of some outcomes based on small numbers
Academic Detailing comments	- Supports a SBP goal of <140 mmHg in the populations studied - Does not support a SBP goal of < 130 mmHg	- Questionable support for any target since primary outcome negative and benefits in secondary outcomes inconsistent with ABCD HT. - Part of benefit may come from enalapril.



### Various Interpretations and Recommendations for Patients with Diabetes

- The current CHEP has made no change to recommendations since the publication of ACCORD BP.<sup>1</sup>
- The CDA has not released an update since the publication of ACCORD BP.<sup>2</sup>
- The 2011 American Diabetes Association states that a SBP level of <130 mmHg is appropriate for most patients with diabetes (Grade C).<sup>45</sup>
  - Higher or lower targets may be appropriate based on patient characteristic, medication tolerance, and response to therapy (Grade B).
  - The ADA notes that most analyses have suggested that outcomes are worse if the SBP is >140mmHg.

### Effect of Chronic Kidney Disease in Patients with Diabetes

- Diabetes, hypertension, and CKD often coexist. Together, diabetes and hypertension, account for more than two-thirds of CV risk.<sup>46</sup>
- Other risk factors such as dyslipidemia and CKD, particularly in the presence of albuminuria, contribute to the remainder of CV risk.
- **Chronic kidney disease** is defined as either eGFR <60 ml/min/1.73 m<sup>2</sup> for > 3 months **or** kidney damage.
  - **Kidney damage** is defined as pathological abnormalities or markers of damage, including
    1. Persistent albumin/proteinuria
    2. Abnormalities in urine tests sediment (persistent presence of erythrocytes, erythrocyte casts, leukocytes or leukocyte casts)
    3. Abnormal results in imaging studies (evidence of scarring or small kidneys on ultrasound or bilateral cystic changes consistent with polycystic kidney disease)
- **Albuminuria** allows detection of kidney disease in its **early** stages and is a powerful predictor of progression of kidney disease. (eGFR can detect only moderate to advanced CKD.)
  - The presence of albuminuria is best determined by calculating the urine albumin to creatinine ratio (ACR) in a random urine specimen.
  - ACR is equivalent to doing a 24-hour urine for albumin but is easier for the patient.<sup>5</sup>
    - The first morning sample correlates best with the 24-hour urine.
    - There is a 40% daily variation in ACR. Therefore CDA recommends that 3 tests be done in a 3-month period.
    - It is recommended that patients with diabetes have this test annually to detect CKD. The regional laboratory sites in each District Health Authority in Nova Scotia offer ACR testing.
      - ACR should be ordered as a request test and the specimen will automatically be sent to the regional laboratory site in your district.





- An ACR value of  $\geq 2$  mg/mmol in men and  $\geq 2.8$  mg/mmol in women indicates kidney **damage**. However it is important to **confirm** the persistence of albuminuria with repeat tests. (See box page 38).
  - ACR levels above 20.0 mg/mmol for males and 28.0 mg/mmol for females correspond to a urine albumin level in excess of 300 mg/day (i.e. macroalbuminuria) and indicate **overt** diabetic nephropathy.
- Albuminuria has been shown to decrease with
  - Monotherapy with ACEIs or ARBs.<sup>47-49</sup>
  - Decreasing sodium intake<sup>50, 51</sup>
- Current evidence does **not** address whether lowering BP to  $<130/80$  in patients with **diabetes and CKD** will result in improved cardiovascular or renal outcomes.
  - ACCORD BP did include ~30% of patients with microalbuminuria (ACR 2 – 20 mg/mmol for males and 2 - 28 mg/mmol for females) but the majority of patients did **not** have substantive CKD.
    - The authors did not report outcomes for patients with and without CKD.
  - There are 3 RCTs involving patients with **non-diabetic** kidney disease assigned to different BP targets (MDRD,<sup>52, 53</sup> AASK,<sup>54</sup> REIN-2.<sup>55</sup>
    - In all of these RCTs the **overall** results showed **no** statistically significant **difference** in **renal** outcomes between the usual BP target group ( $<140/90$  mmHg) and the low BP target group (125/75 to 130/80 mmHg).
      - However, in two of the studies<sup>54,56</sup> sub-group analyses by baseline proteinuria level suggest lower rates of GFR decline in the group with lower BP targets in patients with proteinuria  $> 300$  mg/day<sup>54</sup> or  $> 1$  g/day.<sup>56</sup>
      - These subgroup analyses were not prespecified. “Exploratory subgroup analyses, although important in generating hypothesis for future research, are often underpowered, susceptible to spurious results because of multiple testing, and vulnerable to reporting and publication biases.”<sup>57</sup>
      - Participants in the low BP target groups needed more antihypertensive medications and had a slightly higher rate of adverse events.
      - Cardiovascular outcomes were not evaluated.
  - A recently published systematic review<sup>57</sup> of the 3 RCTs involving patients with **non-diabetic** kidney disease concluded that
    - “Available evidence is inconclusive but does not prove that a lower BP target of  $<130/80$  mmHg improves clinical outcomes more than a target of  $<140/90$  mmHg in adults with CKD. A lower BP target **may** be beneficial in patients with proteinuria  $>300$  to 1000 mg/d.”
  - **Extrapolating** from post hoc subgroup analyses of patients **without diabetes** and with albuminuria in AASK and MDRD, **expert opinion** suggests it may be reasonable to aim for lower BP targets in patients **with diabetes** and albuminuria. An approach adapted from KDOQI<sup>5</sup> is in the box.



### Monitoring CKD in Patients with Diabetes: Relevance to BP Targets

- Do annual random urine albumin to creatinine ratio (ACR).
  - You may have to write this request on the lab requisition.
- If ACR <2 mg/mmol in men or <2.8 mg/mmol in women, result indicates no kidney damage, repeat in one year.
  - There is no need for prescribing an ACEI or ARB unless the patient has hypertension.
  - BP threshold and target uncertain but based on ACCORD BP may be <140/90 rather than <130/80.<sup>36</sup>
- If ACR ≥2 mg/mmol in men or 2.8 mg/mmol in women, result indicates presence of kidney damage.
  - If there are indicators of **overt** nephropathy, there is no need to repeat the test. The patient has kidney damage. Indicators of overt nephropathy include
    - Positive urine dipstick for protein
    - ACR levels above 20.0 mg/mmol for males and 28.0 mg/mmol for females
    - Urine albumin level > 300mg/day
  - If there are **no** indicators of overt nephropathy repeat ACR twice at 1 to 8 week intervals.
  - If 2 of the 3 tests are positive, the patient has kidney damage.
    - Start ACEI or ARB regardless of BP to delay progression of CKD(Grade A)<sup>2</sup>
    - **BP target** is SBP <130 mmHg (Grade C); DBP <80 (Grade B)

### Considerations in Achieving SBP of <130 mmHg

- There is some evidence that achieving a SBP of <130 mmHg can be difficult to achieve without excessive lowering of DBP.<sup>58</sup>
  - Osher et al titrated 257 patients with type 2 diabetes to a BP of <130/85, in accordance with the Joint National Committee VI guidelines, the recommendations in place at the time of the study.
  - Initial mean BP was 159/86 reflecting that most were already receiving medications.
  - The SBP of 130 mmHg was reached in only **33%** of patients.
  - SBP and DBP targets were reached in only **32%** of patients.
  - While the DBP of ≤85 mmHg was reached in **90%** of patients, attempts to reach both SBP and DBP targets resulted in lowering DBP to
    - ≤70 mmHg in 57% of patients      mean DBP in this group was 66
    - <70 mmHg in 21% of patients      mean DBP in this group was 60
  - Lower DBP levels in these patients with diabetes were associated with
    - Advancing age
    - Higher initial SBP levels
    - Pre-existing coronary artery disease



- The decline in DBP was not associated with any drug class or combination of drugs.
- Authors' conclusions
  - Attempted lowering of BP to SBP <130 mmHg is associated with inordinate lowering of DBP in a significant number of patients.
  - Whether the benefits of tight SBP control to <130 mmHg outweigh the risks of excessive diastolic reduction, especially in older diabetes persons or diabetes persons with coronary artery disease, remains unresolved.
- The implications of excessive lowering of DBP were explored in a **secondary observational analysis** of the INVEST trial.
  - The original INVEST trial randomized patients with hypertension and coronary heart disease to antihypertensive therapy based on either a calcium channel blocker or  $\beta$ -blocker.<sup>38</sup>
    - N = 22,576; Duration 2.7 years
    - There was no statistically significant difference in the primary outcome of all-cause death, non-fatal MI, and non-fatal stroke between the 2 drug treatment groups.
  - The **secondary analysis** explored the relation between achieved SBP and DBP and the primary outcome and its components.<sup>59</sup>
    - There was J-shaped curve of outcomes in relation to both SBP and DBP, but more pronounced for the latter.
    - The primary outcome, total MI, and total stroke occurred more frequently with a DBP  $\leq$ 70 mmHg than with a DBP of 70 to 90 mmHg. The association was stronger for MI than for stroke (Table 12).

**Table 12 Association between achieved DBP and outcomes in INVEST reanalysis<sup>59</sup>**

Efficacy outcomes	Event Rates Achieved DBP		ARI	RR	NNH for 2.7 yrs	
	$\leq$ 70	70-90			NNH	95% CI
All-cause death, non-fatal MI, non-fatal stroke	18%	8.6%	9.9%	2.1	10	9 to 12
Fatal and non-fatal MI	6.5%	3.4%	3.1%	1.9	32	24 to 48
Fatal and non-fatal stroke	2.2%	1.4%	0.8%	1.6	126	71 to 542

DBP, diastolic blood pressure; ARI, absolute risk reduction; RR, relative risk; NNH, number needed to harm; CI, confidence interval.



**Academic detailing comments**

- The study by Osher indicates there may be difficulty achieving a SBP of <130 mmHg and doing so may lead to excessive lowering of DBP.
- This INVEST secondary analysis is an observational study and results should be interpreted with **caution** because of the limitations of post-hoc observational analyses.
  - However taken with the ACCF/AHA Consensus recommendation not to decrease DBP to <65 mmHg in the elderly (see page 23) the finding suggests a cautious approach to excessive lowering of DBP in the elderly and people with coronary heart disease and/or with type 2 diabetes.

**Question 3: What is the role of adhering to a low sodium diet and assuring good compliance with medications in managing hypertension?**

**SUMMARY**

- Epidemiological studies have consistently shown an association between salt intake and cardiovascular disease.
- We found no RCTs that examined the effect of lowering dietary sodium and hard clinical outcomes like stroke and cardiovascular disease.
- Based on a Cochrane review, decreasing sodium intake by approximately 2400 mg could reduce SBP by 7.2 mmHg and DBP by 3.8 mmHg in hypertensive patients.
- A local study indicates that following a low-sodium diet and taking medications as prescribed are the two factors most strongly associated with achieving BP targets in patients with diabetes.
  - Frequent self-monitoring of BP was not associated with better BP control.

- Epidemiological studies have consistently shown an association between salt intake and cardiovascular disease.<sup>60</sup>
- A meta-analysis of prospective studies published between 1966-2008 assessed the relation between the levels of habitual salt intake and stroke or total CVD outcome.<sup>60</sup>
  - 13 studies N=177,025 Duration 3.5 to 19 years
  - Higher daily salt intake (~2000 mg Na = 5000 mg of salt) was associated with increased risk of
    - Stroke – relative risk increase 23% (95% CI: 6% to 43%)
    - Cardiovascular disease – relative risk increase 17% (95% CI: 2% to 32%)
- We found no RCTs that examined the effect of lowering dietary sodium and clinical outcomes like stroke and cardiovascular disease.



- However a recent Cochrane review conducted a meta-analysis of RCTs that studied the effects of salt reduction on BP in people with and without hypertension.<sup>8</sup> Inclusion criteria for studies in the review were
  - RCTs or crossover trials
  - No concomitant pharmacological or non-pharmacological interventions
  - Duration of salt reduction of  $\geq 4$  weeks
  - Urinary sodium excretion decreased by  $\geq 1000$  mg per 24 hours
- In **hypertensive** patients (20 studies, N = 802)
  - Reduction in urinary excretion of  $\sim 1840$  mg sodium per 24 hours was associated with decrease of SBP of 5.1 mmHg and DBP of 2.7 mmHg.
  - A reduction of 2400 mg of sodium per day predicted a fall in SBP of 7.2 mmHg and DBP of 3.8 mmHg.
- In **normotensive** patients (11 studies, N = 2220)
  - Reduction in urinary excretion of  $\sim 1760$  mg sodium per 24 hours was associated with decrease of SBP of 2.0 mmHg and DBP of 1.0 mmHg.
  - A reduction of 2400 mg of sodium per day predicted a fall in SBP of 3.6 mmHg and DBP of 1.7 mmHg (Table 13).

**Table 13 Effects of sodium reduction on systolic and diastolic BP<sup>8</sup>**

Patient characteristics	Decrease in urinary Na mg/24 hrs	Decrease in SBP mmHg	Decrease in DBP mmHg	Predicted change with reduction of 2400 mg Na	
				SBP mmHg	DBP mmHg
<b>Hypertensive</b>	1840	5.1	2.7	7.2	3.8
<b>Normotensive</b>	1760	2.0	1.0	3.6	1.7

- The **economic benefits of sodium reduction** have been estimated for the Canadian population based on the established cause and effect between sodium intake and BP and the correlation between BP and CVD.
  - It has been estimated that a decrease in the average sodium intake of 1840 mg/day would
    - Decrease prevalence of hypertension by 30%<sup>61</sup>
    - Result in  $\sim 1$  million fewer hypertension patients
    - Result in a direct annual savings of \$430 million (decreased physician visits, lab tests, and drug use)
    - Decrease prevalence of CVD event by 13%
    - Prevent 23,500 CVD events/year
    - Result in a direct annual savings of \$949 million<sup>61</sup> to 1.38 billion<sup>62</sup> and a total of 2.99 billion/year if indirect costs are included.<sup>62</sup>



- A study conducted by Dalhousie and other local researchers surveyed 570 patients with type 2 diabetes and analyzed their medical records.<sup>63</sup>
  - Patients were from Maritime family practices in rural and urban locations.
  - 54% of patients were at target for SBP and DBP.
  - 62% of patients were at target for SBP.
  - 79% of patients were at target for DBP.
- Factors associated with **decreased** odds of reaching SBP and DBP targets were

**Odds Ratio 95% CI**

- |  |      |              |
|--|------|--------------|
| • Overt nephropathy. . . . .                   | 0.48 | 0.33 to 0.69 |
| • Frequent self-monitoring of BP . . . . .     | 0.51 | 0.33 to 0.79 |
| • Low adherence to medication regimen. . . . . | 0.29 | 0.09 to 0.86 |
- The factor associated with **increased** odds of reaching SBP and DBP targets was
    - Eating food low in salt . . . . . 1.74 1.25 to 2.41
  - Of these factors, two can be influenced by primary care providers
    - Adherence to study medication
    - Low salt diet.

- **Adherence to medication** is a complicated issue with no one solution. CHEP has provided suggestions and some are listed below.<sup>64</sup>

1. Assist your patient to adhere by:
  - Tailoring pill-taking to fit patients' daily habits (Grade D);
  - Simplifying medication regimens to once-daily dosing (Grade D);
  - Replacing multiple pill antihypertensive combinations with single pill combinations (Grade C);
  - Utilizing unit-of-use packaging (of several medications to be taken together) (Grade D); and
  - Adherence to an antihypertensive prescription can be improved by a multidisciplinary team approach (Grade B).
2. Assist your patient in getting more involved in their treatment by:
  - Educating patients and patients' families about their disease/treatment regimens (Grade C)
3. Improve your management in the office and beyond by:
  - Assessing adherence to pharmacological and non-pharmacological therapy at every visit (Grade D);
  - Encouraging adherence with therapy by out of office contact (either by phone or mail), particularly over the first three months of therapy (Grade D);
  - Coordinating with pharmacists and work-site healthcare givers to improve monitoring of adherence with pharmacological and lifestyle modification prescriptions (Grade D): and
  - Utilizing electronic medication compliance aids (Grade D).



- Clinicians should also advise their patients about the importance of a **low sodium diet**.
  - CHEP recommendations for daily sodium intake are
    - Adults  $\leq$  50 years old      1500 mg
    - Adults 51 to 70 years old    1300 mg
    - Adults > 70 years old        1200 mgThese recommendations are Grade B.  
CHEP defines the tolerable upper intake level for sodium as 2300 mg. This is “the highest average daily level of intake likely to pose no risk of adverse effects, and reflects an intake level that should not be exceeded.”<sup>65</sup>
- CHEP also provides suggestions to help patients reduce their sodium intake.
  - **DO**
    - Buy and eat more fresh foods especially fruits and vegetables.
    - Choose processed foods with low salt labels or brands with the lowest percentage of sodium on the food label.
    - Wash canned foods or other salty foods in water before eating or cooking.
    - If desired, use unsalted spices to make foods taste better.
    - Eat less food at restaurants and fast food outlets and ask for less salt to be added in your food orders.
    - Use less sauce on your food.
    - Eat foods with less than 200 mg of sodium or less than 5% of the daily value per serving.
  - **DON'T**
    - Buy or eat heavily salted foods (e.g., pickled foods, salted crackers or chips, processed meats, etc.).
    - Add salt in cooking and at the table.
    - Eat foods with more than 400 mg of sodium or more than 15% of the daily value per serving.
- **Academic Detailing Comment**
  - Simple measures such as promotion of dietary sodium reduction and medication compliance can have substantial benefits in improving hypertension management.



## Question 4: What is the evidence for the efficacy and safety of aliskiren (Rasilez), a direct renin inhibitor, in hypertension?

### SUMMARY

- Aliskiren is the only direct renin inhibitor currently marketed in Canada.
- We found **no studies** of aliskiren that addressed **hard clinical** outcomes.
- A 2009 Cochrane review found that compared to **placebo**, aliskiren reduced SBP and DBP in a dose-related manner:
  - 150 mg dose decreased SBP by 5.5 mmHg and DBP by 3 mmHg
  - 300 mg dose decreased SBP by 8.7 mmHg and DBP by 5 mmHg
- Aliskiren has been found to be as effective in lowering BP as ACEIs, ARBs, and HCTZ.
- In most studies, aliskiren at doses up to 300 mg daily was as well tolerated as placebo.
- There is no long-term safety data available for aliskiren.
- Aliskiren is more expensive than other drugs which have proven benefit in reducing cardiovascular and cerebrovascular outcomes.

- Dysregulation of the renin-angiotensin-aldosterone system is an important contributor in the pathogenesis of hypertension and its sequelae. Key steps in the system are in Figure 1 and summarized below:<sup>66,67</sup>
  1. Renin is secreted from the kidney and promotes the conversion of angiotensinogen to angiotensin I.
  2. Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE).
  3. Angiotensin II primarily binds to AT1 receptors present in almost all tissues of adults. Activation of this receptor results in
    - Secretion of aldosterone from the adrenal gland
    - Vasoconstriction
    - Activation of the inflammatory cascade, which includes increased formation of reactive oxygen species, cytokine and chemokine production
    - Inflammatory cell activation
    - Cell proliferation and hypertrophy
  4. Angiotensin II activation of LOX-1 receptors in cells of the vascular wall also contributes to lipid accumulation and acceleration of atherosclerosis.
- Aliskiren (**Rasilez®**) is the first of the direct renin inhibitors, a new class of agents that prevents the formation of renin, the enzyme that catalyzes the conversion of angiotensinogen to angiotensin 1 (Step 1).





- (ACE inhibitors and angiotensin receptor blockers inhibit step 2 and step 3 respectively, but neither blocks the renin-angiotensin-aldosterone system completely.)
- It has been **speculated** that the direct renin inhibitors might provide a more effective means of blockade of the renin-angiotensin-aldosterone system than is possible with ACE inhibitors and ARBs.<sup>66</sup>
- The recommended initial dose of aliskiren is 150 mg daily and the recommended maximum dose is 300 mg daily.
- Effects are dose-dependent up to 300 mg daily; 600 mg daily produces little additional BP reduction and is associated with an increased incidence of adverse effects, particularly diarrhea.<sup>66</sup>
- Aliskiren, alone or in combination with other BP lowering agents, has been shown to reduce BP in **short-term** trials (ranging from 6 weeks to 1 year).
  - Monotherapy
    - A 2009 Cochrane review<sup>7</sup> (6 studies N=3694) found that compared to **placebo** aliskiren reduced SBP and DBP in a dose-related manner:
      - 150 mg dose decreased SBP by 5.5 mmHg and DBP by 3 mmHg
      - 300 mg dose decreased SBP by 8.7 mmHg and DBP by 5 mmHg
    - Aliskiren has demonstrated similar BP lowering effects compared to
      - ACEIs (ramipril, lisinopril)<sup>68,69</sup>
      - ARBs (valsartan, irbesartan)<sup>70-72</sup>
      - HCTZ<sup>73</sup>
  - Combination therapy vs placebo or monotherapy
    - Combination therapy of aliskiren with either ARBs or HCTZ provides a significant reduction in BP compared to **placebo**.<sup>70-73</sup>

	<b>Decrease vs Placebo (mmHg)</b>	
	<b>SBP</b>	<b>DBP</b>
• Aliskiren 150 mg + HCTZ 25 mg	12	5.8 <sup>73</sup>
• Aliskiren 300 mg + HCTZ 25 mg	13.7	7.4 <sup>73</sup>
• Aliskiren 150 mg + valsartan 320 mg	7.7	3.3 <sup>71</sup>
• Aliskiren 300 mg + valsartan 320 mg	11.1	6.4 <sup>70, 71</sup>



- In general, combination therapy of aliskiren with ARBs, ACEIs or HCTZ<sup>68, 70, 71, 73</sup> provides a significant reduction in BP compared to the drugs given as monotherapy.

**Average decrease vs monotherapy (68) (mmHg)**

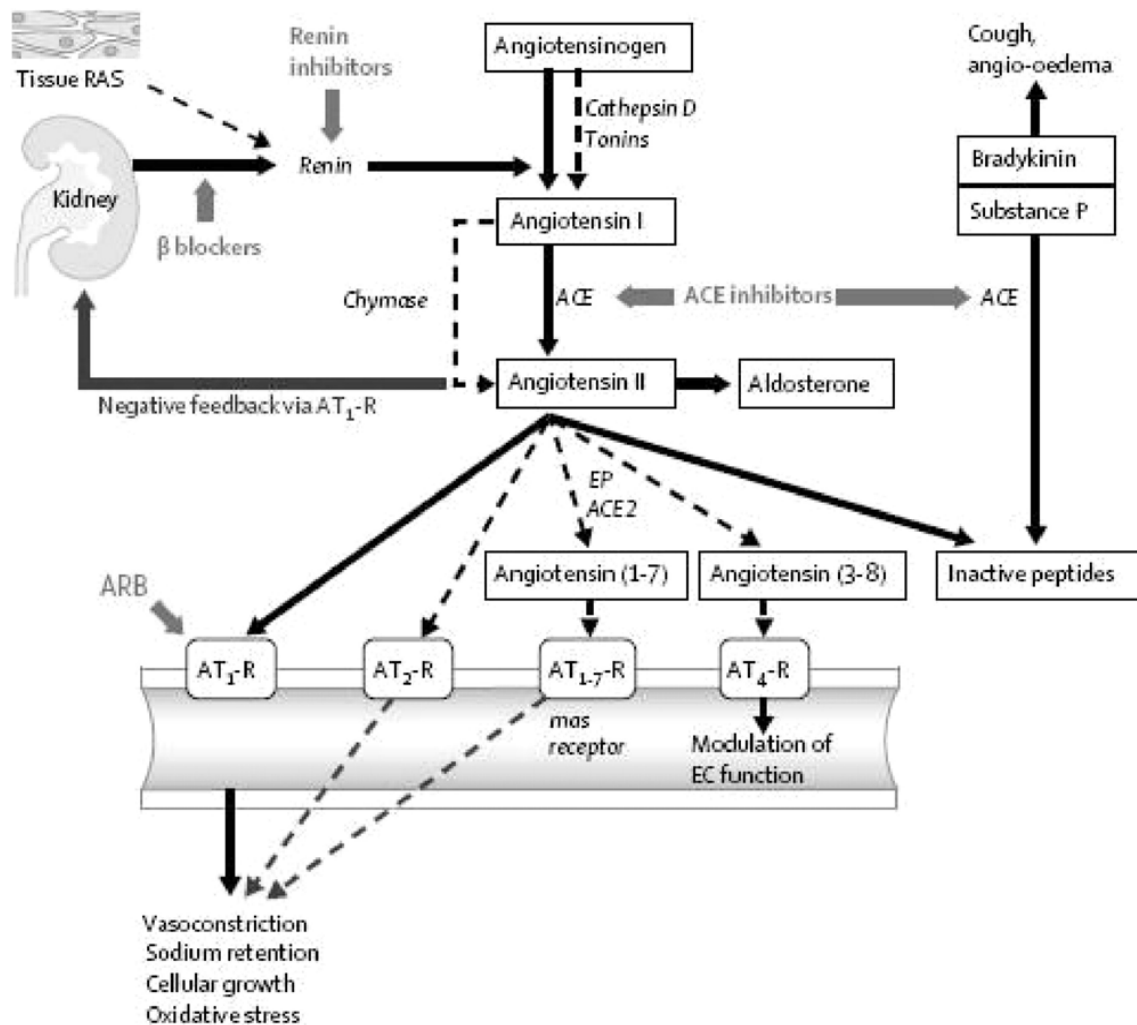
	<b>SBP</b>	<b>DBP</b>
• Aliskiren 150 mg + HCTZ 25 mg	6.3	3.6 <sup>73</sup>
• Aliskiren 300 mg + HCTZ 25 mg	6.2	4.5 <sup>73</sup>
• Aliskiren 150 mg + valsartan 320 mg	3.8	1.7 <sup>71</sup>
• Aliskiren 300 mg + valsartan 320 mg	4.5	2.6 <sup>70,71</sup>
• Aliskiren 300 mg + ramipril 10 mg	3.3	1.8 <sup>68</sup>

- In most studies, aliskiren at doses up to 300 mg daily was as well tolerated as placebo.<sup>7,72</sup>
- The **Canadian Expert Drug Advisory Committee (CEDAC)** reviewed aliskiren in 2008. CEDAC provides formulary listing recommendations to publicly funded drug plans.
  - The committee recommended that aliskiren not be listed based on the following reasons:
    - “While aliskiren, alone and in combination with other antihypertensive agents, has been shown to reduce BP in short term trials, no long-term randomized trials have investigated if this translates into improvements in clinically important cardiovascular, cerebrovascular or renal outcomes.”
    - “There is insufficient evidence from clinical trials that aliskiren is effective and safe in patients with refractory hypertension, and there are multiple classes and types of antihypertensive agents currently funded by drug plans.”
    - “There are many other antihypertensive agents, lower or similar in cost compared to aliskiren (*\$1.29 for 150mg or 300mg*), which have been demonstrated to improve clinically important cardiovascular and cerebrovascular outcomes (e.g. thiazide diuretics, ACEIs, ARBs).”
  - The committee recommended that the status of aliskiren be reviewed when the results of ongoing clinical trials evaluating the effect of aliskiren on clinically important cardiovascular and cerebrovascular outcomes are available
- One **content expert** considers there is a possible role for this drug as a 4th or 5th line agent in select patients.
- Academic detailing Comments:**
  - Studies have shown that combining aliskiren with an ACEI or an ARB reduces BP compared to monotherapy however, the clinical relevance of this BP reduction is uncertain.
    - Also, there was increased hyperkalemia and decreased GFR with combination therapy vs monotherapy.



- This is consistent with studies of combination therapy with ACEIs and ARBs<sup>74,75</sup> which have been shown to decrease BP but that dual-agent blockade of the renin–angiotensin–aldosterone system increases hyperkalemia and decreases GFR without clinical benefit.
- Therefore it seems prudent to not use aliskiren in combination with ACEIs or ARBs.

**Figure 1 Sites of action of antihypertensive drugs on the renal-angiotensin-aldosterone system<sup>67</sup>**



Reprinted from The Lancet 368(9545). Staessen JA, Li Y, Richart T. Oral renin inhibitors. Pages No 1449-56. Copyright 2006 with permission from Elsevier.



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**Appendix 1. Summary of HOT, UKPDS 38, ABCD HT, and ABCD NT**

	<b>HOT<sup>a</sup></b>	<b>UKPDS 38</b>	<b>ABCD HT</b>	<b>ABCD NT</b>
<b>Goal/Question</b>	Assess association between major CV events and DBP targets of $\leq 90$ , $\leq 80$ , and $\leq 80$ and between CV events and DBP achieved	Does tight BP control (<150/85) decrease morbidity and mortality in hypertensives with T2DM?	Test effect of moderate vs intensive BP control on CrCl in hypertensive T2DM patients with nephropathy, retinopathy, neuropathy	Is lowering BP in normotensive people (<140/90) with T2DM beneficial?
<b>N</b>	1501	1148	470	480
<b>Duration</b>	3.8 years	8.4 years	5.3 years	5.3 years
<b>Drugs</b>	Felodipine, ACEIs, B-blockers, diuretics	Captopril or atenolol then other drugs	Nisoldopine / enalapril vs nisoldopine / enalapril	Nisoldopine or enalapril vs placebo
<b>Inclusion SBP</b>	"Hypertension"	$\geq 160$ on no meds $\geq 150$ on meds		
<b>Inclusion DBP</b>	100-115	$\geq 90$ on no meds $\geq 85$ on meds	$\geq 90$	80 to 89 on no meds
<b>Target SBP</b>		Tight control <150 vs Less tight control <180		
<b>Target DBP</b>	$\leq 90$ vs $\leq 85$ vs $\leq 80$	Tight control: <85 Less tight control: <105	Intensive: < 75 Moderate: 80 to 89	Intensive: 10 mm lower than on entry Moderate: 80 to 89
<b>Baseline BP</b>	170/105	160/94	155/98	136/84
<b>Achieved SBP</b>	Not reported	144 vs 154	132 vs 138	128 vs 137
<b>Achieved DBP</b>	Not reported	82 vs 87	78 vs 76	75 vs 81
<b>Results</b>	Decrease in primary outcome of major CV events, CV mortality	Decrease in most outcomes including primary composite of diabetes-related complications	- No benefit in primary outcome of CrCl - Benefit in mortality	- No benefit in primary outcome of CrCl - Benefit in stroke, proteinuria, retinopathy
<b>CDA comment</b>	- Supports DBP target of <80 (Grade B)	- Supports DBP target of < 80 (Grade B)	- Not cited	- Supports SBP target of <130 (Grade C) - No statistical correction for multiple comparisons - Results of some outcomes based on small numbers
<b>ADS comment</b>	- No test of heterogeneity reported - Overall results were negative, treat sub-group analysis with caution - No statistical correction for multiple comparisons - Achieved SBP and DBP not reported	- Supports DBP target of approximately 80 but benefit in tight control group may come from use of ACEIs in that group.	Questionable support for any target since primary outcome negative and benefits in secondary outcomes inconsistent with ABCD NT. - Part of benefit may come from enalapril	Questionable support for any target since primary outcome negative and benefits in secondary outcomes inconsistent with ABCD HT. - Part of benefit may come from enalapril

<sup>a</sup> Diabetes subgroup

## Clinical Frailty Scale

1. **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age. 
2. **Well** – People who have no active disease symptoms but are less fit than Category 1. Often, they exercise or are very active occasionally, e.g. seasonally. 
3. **Managing Well** – People whose medical problems are well controlled, but are not regularly active beyond routine walking. 
4. **Vulnerable** – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being “slowed up,” and/or being tired during the day. 
5. **Mildly Frail** – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework. 
6. **Moderately Frail** – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing. 

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7. **Severely Frail** – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).



8. **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.



9. **Terminally Ill** – Approaching the end of life. This category applies to people with a life expectancy < 6 months, who are not otherwise evidently frail.

### Where dementia is present, the degree of frailty usually corresponds to the degree of dementia:

- **Mild dementia** – includes forgetting the details of a recent event, though still remembering the event itself, repeating the same question / story and social withdrawal.
- **Moderate dementia** – recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
- **Severe dementia** – they cannot do personal care without help.

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