Module 5:

Management of Hypertension in Non-diabetes Patients with Chronic Kidney Disease

Case Development & Disclosures

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Conflict Disclosure Information

- Presenter 1:
  - Grants/Research Support: _____
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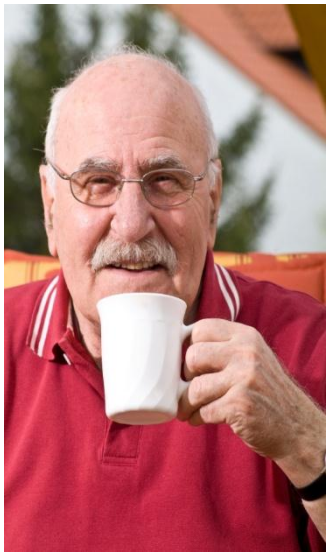
  - Consulting Fees:_____
  - Other: _____

Outline of Today's Activity

- Introduction
- Case Presentation
- Key Learnings & Questions
- Wrap Up

Module 5:

Management of Hypertension in Non-diabetes Patients with Chronic Kidney Disease



Gerald

An 78-year-old man with a 20 year history of hypertension is found to have a creatinine of 140 umol/L on his most recent blood tests

Learning Objectives

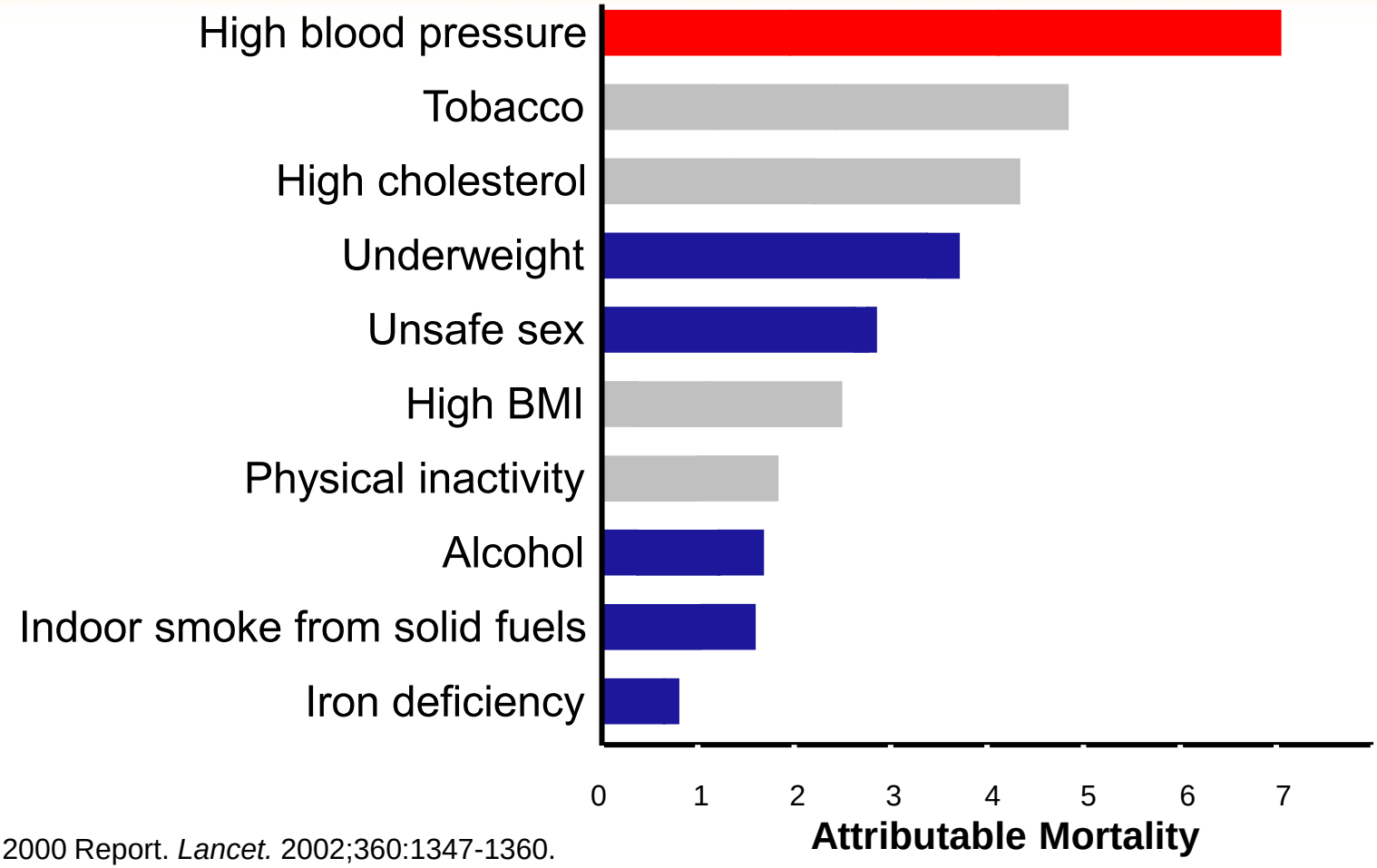
Upon completion of this activity, participants will be able to:

- State the new BP target for patients with non-DM CKD and understand the rationale for this change
- Identify the risk of developing CKD from HTN is graded based on race and comorbidities
- Understand that presence of non-DM CKD in hypertensive patients increases risk for cardiovascular outcomes

Statement of Need

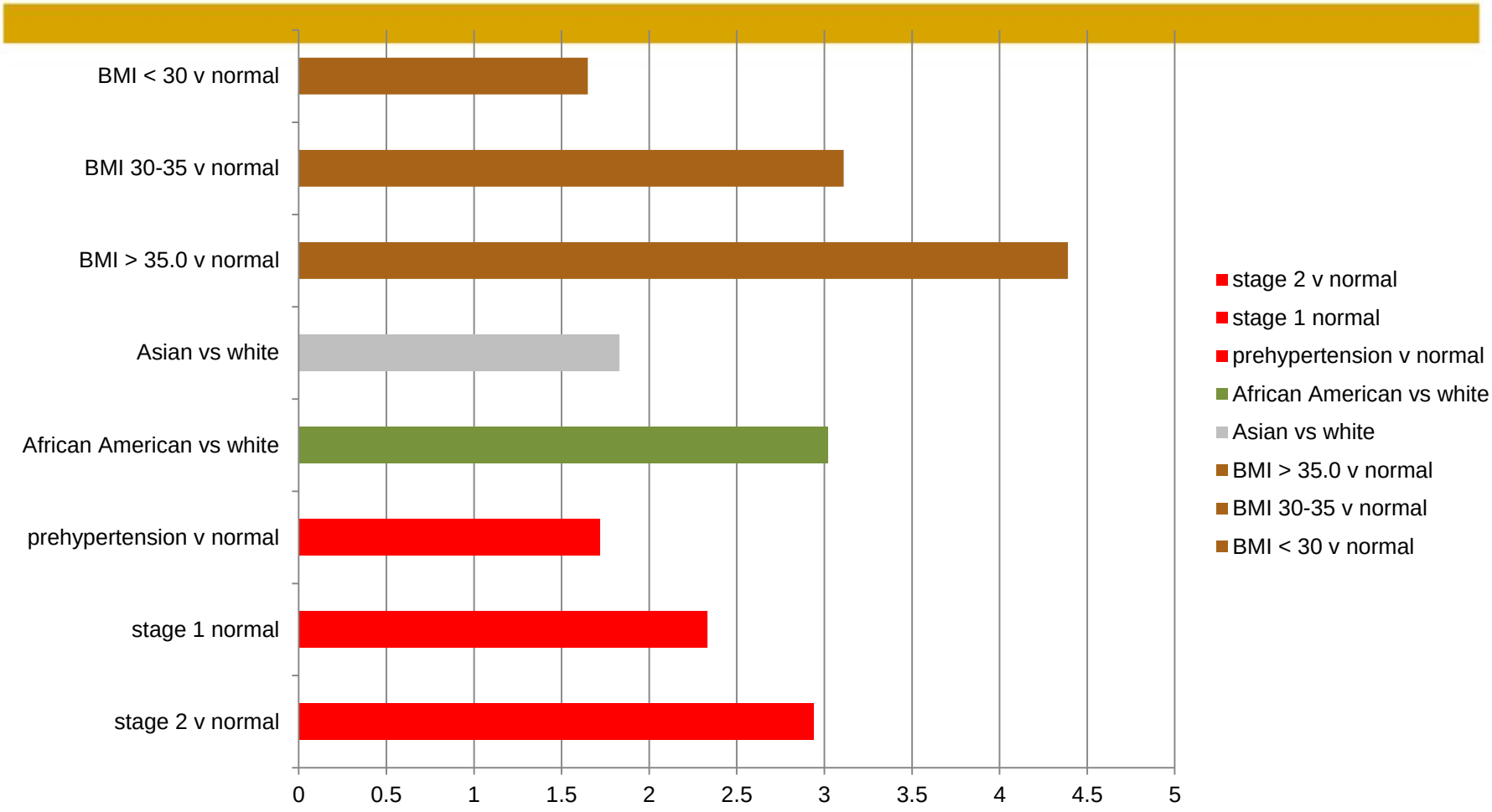
"My greatest challenge as a health care provider in the management of patients with hypertension is _____"

Proportion of Deaths Attributable to Leading Risk Factors Worldwide (2000)



WHO 2000 Report. *Lancet.* 2002;360:1347-1360.

Hazard Ratios For ESRD Among Independent Risk Factors



Kaiser Data set, 5,275,957 person years

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Hsu CY Arch Int Med 2009:169(4)342-350

Hypertension CANADA

Hypertension as a Risk Factor

Hypertension is a significant risk factor for:

- cerebrovascular disease
- coronary artery disease
- congestive heart failure
- renal failure
- peripheral vascular disease
- dementia
- atrial fibrillation

Hypertension Detection and Follow-up Program
Impact of BP on Risk for Declining GFR by CKD

- Renal function was followed as a secondary end point
- Found to be a strong outcome predictor
- **Better blood pressure control was found to be renal protective**
- Renal protection through blood pressure lowering was more marked among those with renal insufficiency at baseline

Incidence of decline in GFR over 5 years per 1000 patient-years	**Intensive Group**	**Usual Care**
BL creatinine 135-150 umol/L	**113.3**	**226.6**
Whole cohort	21.7	24.6

Shulman. *Hypertension*. 1989;13:I80-I93; Hypertension Detection and Follow-up Program Cooperative Group. *JAMA*. 1979;242:2562-2571.

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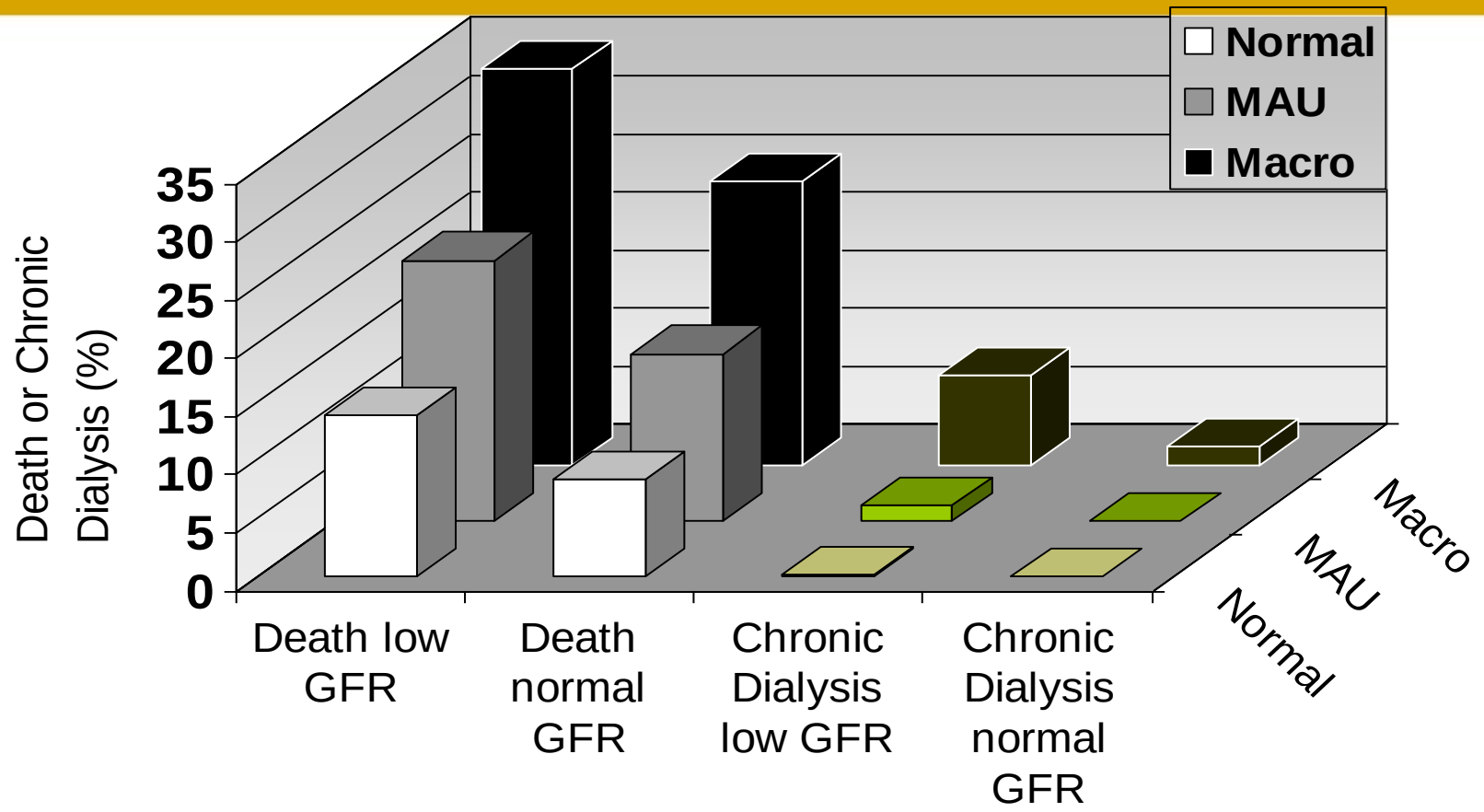
Hypertension CANADA

ONTARGET: CV and Renal Outcomes
Impact of GFR x Albuminuria



1. Dialysis << death for all but macroalbuminuria
2. Both low GFR and albuminuria significantly increase the risk of death

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Tobe, SW, Circulation 2011: 123:1098-1107

Online supplement:
http://circ.ahajournals.org/content/suppl/2011/02/24/CIRCULATIONAHA.110.964171.DC1

Hypertension CANADA

History of Present Illness

- Gerald is an 78-year-old with a 20 year history of hypertension is found to have a creatinine of 140 umol/L on his most recent blood tests
- Present lifestyle
  - Former-smoker (40 pack year history)
  - Active walking 45 minutes, 4 days per week
  - Alcohol – 1 scotch daily or less
  - Married; no children

History of Present Illness

- He has been stable in your clinic for 10 years
  - Blood work over the last 10 years shows a slowly rising creatinine level

	Current	One year ago	Two years ago	Three years ago	Four years ago	Five years ago
Urea	10.5	10	12.6	10.7	8.4	10.4
Creat	140	112	96	98	102	95
eGFR*	42	53	62	61	58	62

*eGFR by Cockcroft and Gault (140-age)x Wt (kg)/Creat (umol/L) x 1.2 (for male)

Cockcroft DW, Nephron 1976, 16(1) 31-41

Past History

- Hypertension
  - diagnosed and treated for 20 years
- Stable coronary artery disease
  - coronary stent in 2004
- No history of peripheral vascular disease
- No history of diabetes

Family History

- Mother
  - history of hypertension
- Father
  - history of hypertension
- Sister
  - 1 sister has hypertension
- Brothers
  - 2 younger brothers also hypertensive

Current Medications

- HCTZ 25 mg OD
- Amlodipine 10 mg OD
- ECASA 81 mg OD
- Atorvastatin 40 mg OD
- Ramipril 10 mg OD

Physical Examination

- Height: 183 cm
- Weight: 85 kg
- BMI: 25.4 kg/m^2
- BP (left arm, seated):
  136/72 mmHg using an automated device
- Pulse: 78 regular
- No murmurs, no gallops
- No bruits
- No edema
- Lungs clear on chest exam
- Peripheral pulses reduced

What additional lab information do you want?

Lab Tests

- Electrocardiogram (ECG)
- Fasting glucose and lipids
- Electrolytes, urea, and creatinine
- Complete blood count (CBC)
- Calcium, Phosphate, Parathyroid Hormone Test (PTH)
- Urinalysis and urine, albumin/creatinine ratio (ACR)
- Abdominal ultra-sound

Laboratory Investigations

Test	Results	Normal Values
Glucose	5.5 mmol/L	4.0-8.0 mmol/L
Urea	7.8 mmol/L	3.0-7.0 mmol/L
Creatinine	144 µmol/L eGFR 41 ml/min	44-106 umol/L
K	4.4 mmol/L	3.5-5.0 mmol/L
Hb	114 g/L	115-165 g/L
ACR	19 mg/mmol	< 2.0 mg/mmol

Laboratory Investigations

Test	Results	Normal Values
LDL	2.2 mmol/L	<2.50 mmol/L
Total Chol	3.8 mmol/L	<5.20 mmol/L
TG	2.2 mmol/L	<1.70 mmol/L
HDL	1.1 mmol/L	>0.99 mmol/L
TC:HDL	3.75	High risk target: <4.0 Mod risk target: <5.0 Low risk target: <6.0

Ultrasound Abdomen

- Right kidney is 8.4 cm
- Left kidney is 8.7 cm
- Both show cortical thinning consistent with medical-renal disease.
- No hydronephrosis
- No stones

Discussion Question 1

What is the blood pressure target for Gerald?

Discussion Question 1)
What is the blood pressure target (mmHg) for Gerald?

a) < 120/80

b) < 130/80

c) < 135/85

d) < 140/90

Note: Discussion questions do not necessarily have only one correct answer

a) < 120/80

- **<120/80 mmHg**
- **Correct**

Treatment Targets: Hypertension and CKD

- The SPRINT study included a renal subgroup demonstrating that the lower BP target resulted in improved CV outcomes
- Renal outcomes were not improved and there were more people with rises in creatinine and in acute kidney injury

b) < 130/80

- Incorrect in this case
- < 130/80 mmHg is the BP target for people with diabetes with or without CKD

C) < 135/85

- Incorrect
- This is the correct answer if you use home BP readings or an automated device in your office, such as BpTRU

d) < 140/90

- No longer Correct
- This was the BP target for people with chronic kidney disease and no diabetes before the SPRINT study

In 2012, CHEP revisited the CKD BP targets following publication of significant new data

CHEP 2011	*CHEP 2012*
For patients with nondiabetic chronic kidney disease, target BP is <130/80 mm Hg (Grade C).	**For patients with nondiabetic chronic kidney disease, target blood pressure is <140/90 mm Hg (Grade B).**

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Hypertension CANADA

The ups and downs of BP targets in CKD

✓1999: ADDED new recommendation lowering BP targets in CKD based on the MDRD study

- For patients with proteinuria that is greater than 1 g/day, target blood pressure is lower than 125/75 mm Hg (MAP 92) (GRADE C)

x 2006: REMOVED recommendation based on REIN-2.

- Target of 130/80 still supported based on AASK and MDRD studies

? 2010: Revisiting the AASK follow-up data, little support for lower targets except (maybe) for those with proteinuria….

Triggering revisiting of overall recommendation

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Hypertension CANADA

Studies of BP targets in CKD patients

Upadhyay , Ann Intern Med. 2011;154:541-548

	MDRD	AASK	REIN-2
n	840	1094	334
Target BP	~125/75 vs.~140/90	~125/75 vs.~140/90	130/80 vs. x/90
1º outcome	change in GFR	composite	ESRD
Mortality	ND	ND	ND
CVD events	ND	ND	x
GFR decline	ND	ND	ND
ESRD	ND	ND	ND

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Hypertension CANADA

New thresholds/targets for the high risk patient post-SPRINT: *who does this apply to??*

- Clinical or sub-clinical cardiovascular disease

  OR

- **Chronic kidney disease (non-diabetic nephropathy, proteinuria <1 g/d, *estimated glomerular filtration rate 20-59 mL/min/1.73m^2**)

  OR

- †Estimated 10-year global cardiovascular risk ≥15%

  OR

- Age ≥ 75 years

Patients with one or more clinical indications should consent to intensive management.

* Four variable MDRD equation

† Framingham Risk Score, D'Agastino, Circulation 2008

Sprint Study, NEJM, November 9 2015

Demographic & baseline characteristics

	Total (N = 9,361)	Intensive (N = 4,678)	Standard (N = 4,683)	Targeted
Mean (SD) age, years	67.9 (9.4)	67.9 (9.4)	67.9 (9.5)	
% ≥ 75 years	28.2%	28.2%	28.2%	**35%**
Female, %	35.6%	36.0%	35.2%	**50%**
White, %	57.5%	57.7%	57.7%	**60%**
African-American, %	29.9%	29.5%	30.4%	
Hispanic, %	10.5%	10.8%	10.3%	
Prior CVD, %	20.1%	20.1%	20.0%	
Mean 10y Framingham CVD risk, %	20.1%	20.1%	20.1%	
Taking antihypertensive meds, %	90.6%	90.8%	90.4%	
Mean (SD) number of antihypertensive meds	1.8 (1.0)	1.8 (1.0)	1.8 (1.0)	
CKD (> REIN, ASK, MDRD together)	**28%(2697)**	**28%**	**28%**	**46%**
Mean (SD) BL BP, mm Hg Systolic	139.7 (15.6)	139.7 (15.8)	139.7 (15.4)	
Diastolic	78.1 (11.9)	78.1 (11.9)	78.0 (12.0)	

Recommended Office BP Treatment Targets

Treatment consists of health behaviour ± pharmacological management

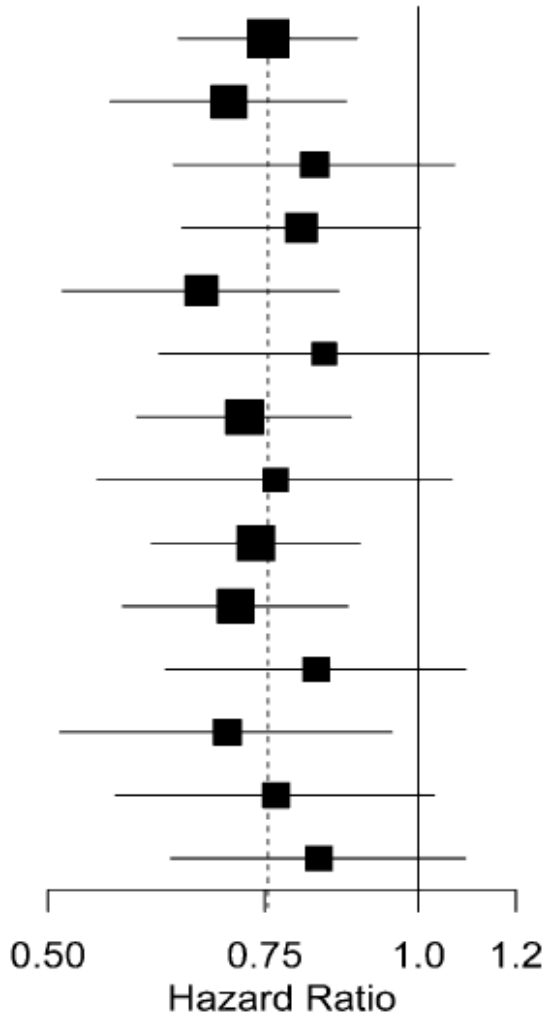
Population	SBP	DBP
High Risk	≤120	NA
Diabetes	< 130	< 80
All others*	< 140	< 90

* Target BP with AOBP < 135/85

SPRINT Primary outcomes in pre-specified subgroups of interest

Subgroup	HR	P*
Overall	0.75 (0.64,0.89)	
No Prior CKD	0.70 (0.56,0.87)	0.36
Prior CKD	0.82 (0.63,1.07)	
Age < 75	0.80 (0.64,1.00)	0.32
Age ≥ 75	0.67 (0.51,0.86)	
Female	0.84 (0.62,1.14)	0.45
Male	0.72 (0.59,0.88)	
African−American	0.77 (0.55,1.06)	0.83
Non African−American	0.74 (0.61,0.90)	
No Prior CVD	0.71 (0.57,0.88)	0.39
Prior CVD	0.83 (0.62,1.09)	
SBP ≤ 132	0.70 (0.51,0.95)	0.77
132 < SBP < 145	0.77 (0.57,1.03)	
SBP ≥ 145	0.83 (0.63,1.09)	

*Treatment by subgroup interaction
*Unadjusted for multiplicity



SPRINT
Systolic Blood Pressure Intervention Trial

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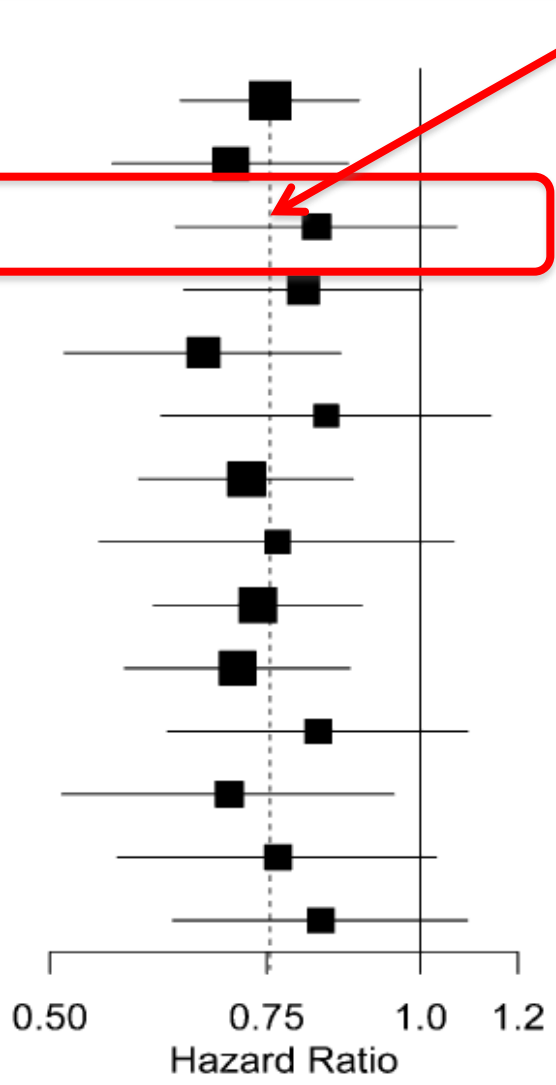

SPRINT
Systolic Blood Pressure Intervention Trial

Discussion Question 2

In addition to his medications what other factors should we consider in his BP management?

In addition to his medications what other factors should we consider in his BP management?

a) RAAS blockade
b) 24-hr ABPM
c) Low sodium diet
d) Avoid NSAIDS/Aminoglycosides/nephrotoxic drugs

Note: Discussion questions do not necessarily have only one correct answer

a) RAAS blockade

- The patient is taking ramipril 10 mg/day

b) 24-hr ABPM

- Determine whether patient has masked HTN (prevalence 20%)
- Determine whether nocturnal HTN – consider longer acting ACE inhibitor

c) Low sodium diet

- High dietary sodium is an key contributor to high blood pressure.
- To decrease blood pressure, consider reducing sodium intake towards 2,000 mg (5g of salt or 87mmol of sodium) per day.

d) Avoid NSAIDS/Aminoglycosides/nephrotoxic drugs

- Nephrotoxic drugs can cause hemodynamic compromise of kidney in patients with CKD
- Examples of nephrotoxic drugs
  - Aminoglycosides
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Acyclovir
  - Amphotericin B
  - Lithium
  - Phenytoin
  - Sulfonamides
  - Vancomycin
  - Zoledronic acid

Baumgarten, Gehr. *Am Fam Physician* 2011;84:1138-48

Discussion Question 3
How would you control Gerald's BP?

Current BP 136/72

Meds

- HCTZ 25 mg OD
- Amlodipine 10 mg OD
- ECASA 81 mg OD
- Atorvastatin 40 mg OD
- Ramipril 10 mg OD

How would you control Gerald's BP?

a) A long acting diuretic
b) Changing to a fixed dose combination (FDC)?
c) Consider Sprironolactone or other Mineralocorticoid Receptor Antagonist?
d) Assess for OSA and Tx if present

Note: Discussion questions do not necessarily have only one correct answer

a) A long acting diuretic

- Longer acting diuretics are preferred
  – eg. Chlorthalidone, indapamide
  vs shorter acting HCTZ

Thiazide-type (shorter acting) vs Thiazide-like Diuretics: CV events and Mortality Meta-analysis

- **Design:** Meta-analysis of 21 RCTs of BP lowering comparing thiazide-type or thiazide-like diuretics vs. placebo or another antihypertensive on CV events and mortality
- >500,000 person years of observation combined
- Thiazide-type:
  - HCTZ
  - Bendrofluazide
  - Chlorothiazide
- Thiazide-like:
  - Indapamide
    - Chlorthalidone

Olde Engberink RH. Hypertension. 2015 May;65(5):1033-40

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Hypertension CANADA

Diuretic Type Meta-Analysis vs Placebo

- **Both** types of diuretics reduced CV events, cerebrovascular events, and HF;
- **Only thiazide-like diuretics** additionally reduced coronary events and all-cause mortality

Event	Thiazide-Type	Thiazide-Like
CV	**0.67 (.56-.81)**	**0.67 (0.60-0.75)**
Coronary	0.81 (0.63-1.05)	**0.76 (0.61-0.96)**
Cerebrovascular	**0.52 (0.38-0.69)**	**0.68 (0.57-0.80)**
Heart Failure	**0.36 (0.16-0.84)**	**0.47 (0.36-0.61)**
All-cause Mortality	0.86 (0.75-1.00)	**0.84 (0.74-0.96)**

Olde Engberink RH. Hypertension. 2015 May;65(5):1033-40

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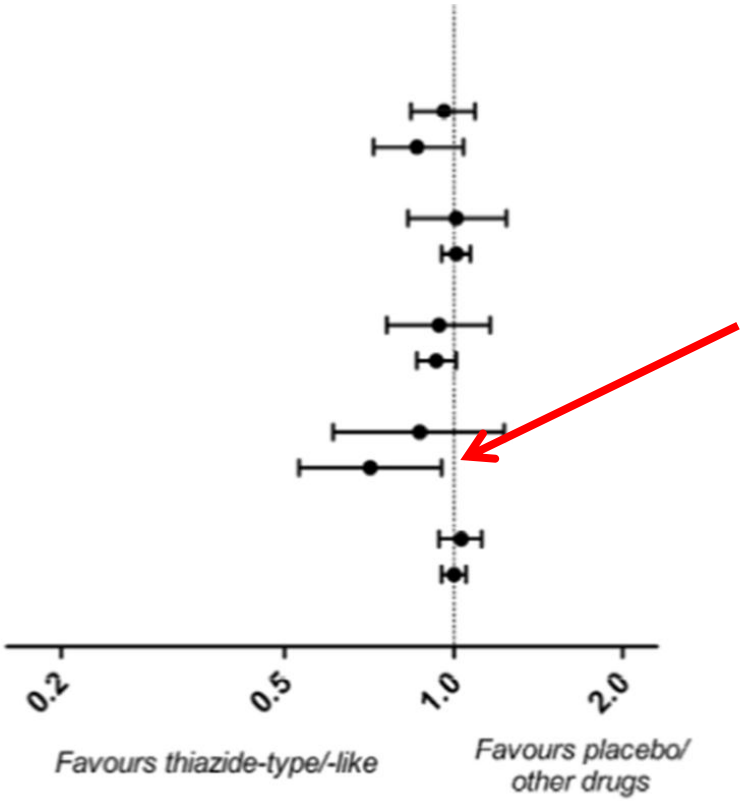
Hypertension CANADA

Diuretic Type Meta-Analysis vs Other Therapy

- **<u>Only</u> thiazide-like diuretics additionally** reduced risk of HF, no additional difference for the other outcomes

Other drug comparisons		
Cardiovascular events		
Thiazide-type	0.96 (0.84-1.09)	59%
Thiazide-like	0.86 (0.72-1.04)	88%
Coronary events		
Thiazide-type	1.01 (0.83-1.24)	62%
Thiazide-like	1.01 (0.95-1.07)	0%
Cerebrovascular events		
Thiazide-type	0.94 (0.76-1.16)	56%
Thiazide-like	0.93 (0.86-1.01)	0%
Heart failure		
Thiazide-type	0.87 (0.61-1.23)	53%
Thiazide-like	0.71 (0.53-0.95)	91%
All-cause mortality		
Thiazide-type	1.03 (0.94-1.12)	0%
Thiazide-like	1.00 (0.95-1.05)	0%



Olde Engberink RH. Hypertension. 2015 May;65(5):1033-40

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Hypertension CANADA

Head to Head: HCTZ vs Chlorthalidone vs Indapamide

- Meta-analysis
- Used 3 dose levels to try to standardize dosing
  - HCTZ (12.5/25/50)
  - Chlorthalidone (6.25/12.5/25)
  - Indapamide (1.5/2.0/2.5)
  - Outcomes:
    - BP lowering
    - Metabolic
    - CV events

Roush GC: Hypertension 2015, 65, 1041-1046

Head to Head: HCTZ vs Chlorthalidone vs Indapamide

- Meta-analysis
- Used 3 dose levels to try to standardize dosing
  - HCTZ (12.5/25/50)
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  - Indapamide (1.5/2.0/2.5)

Studies

BP Lowering	Metabolic effect
HCTZ vs Indap (10)	HCTZ vs Indap (7)
HCTZ vs chlor (3)	

Roush GC: Hypertension 2015, 65, 1041-1046

Head to Head: HCTZ vs Chlorthalidone vs Indapamide

- **SBP reduction:**
  - Indapamide vs. HCTZ: −5.1 mmHg (p=0.004)
  - Chlorthalidone vs. HCTZ: −3.6 mmHg (p=0.052)
- **Metabolic effects:**
  - No differences between HCTZ vs. indapamide in adverse effects (K+, Na+, Cr, BG, cholesterol, uric acid);
  - no data for HCTZ vs. chlorthalidone

Roush GC: Hypertension 2015, 65, 1041-1046

Chlorthalidone vs HCTZ for BP Lowering (ABPM)

- **Design:** 12-week RCTs (double-blind)
- **Population:** stage 1 hypertension (140 -159/ 90-99 mmHg), India (n=54)
- **Intervention:** chlorthalidone 6.25 vs HCTZ 12.5 vs HCTZ (ER) 12.5
- **1˚ outcomes:** 24 h ABPM baseline to weeks 4 & 12
  - ↓ SBP & DBP with chlorthalidone and HCTZ CR ($p < 0.01$), but not conventional HCTZ

Pareek AK, et al. J Am Coll Cardiol. 2016 Feb 2;67(4):379-89.

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Hypertension CANADA

Summary: Long-acting diuretics preferred

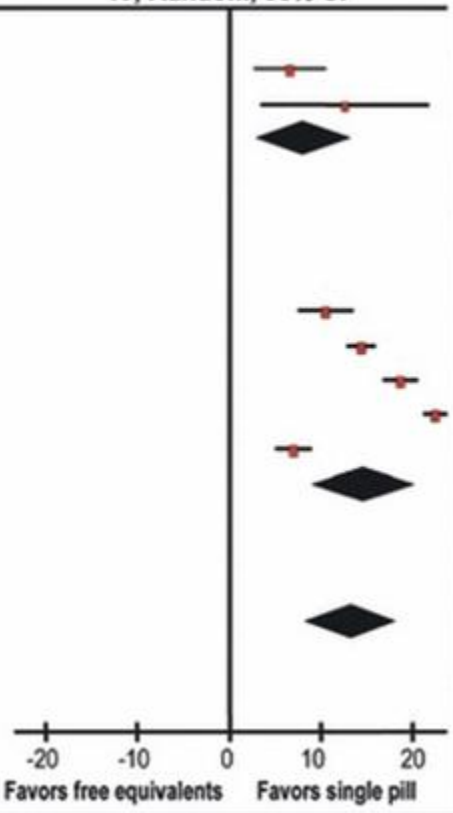
Long-acting (thiazide-like) diuretics appear more effective at reducing CV events and SBP & DBP

b) Change to Fixed Dose Combination

- Single pill combination therapy is associated with better adherence vs. free combinations
- A regimen featuring initial prescription of SPC leads to better blood pressure control
- Initial combination therapy is associated with ↓ risk of cardiovascular events than monotherapy.

SPCs improve adherence

Study or Subgroup	Single Pill Mean	SD	N	Free Equivalent Mean	SD	N	Weight	Mean Difference IV, Random, 95% CI
Naive patients								
Brixner 2008	64.2	58.67	1628	57.6	30.21	561	14.2%	6.60 [2.81, 10.39]
Jackson 2008	73.1	35.42	619	60.5	35.42	65	10.3%	12.60 [3.55, 21.65]
Subtotal (95% CI)			**2247**			**626**	**24.5%**	**8.13 [3.00, 13.26]**
Heterogeneity: $Tau^2 = 5.47$; $Chi^2 = 1.44$, df = 1 ($P = 0.23$); $I^2 = 30\%$								
Test for overall effect: Z = 3.11 ($P = 0.002$)								
Experienced patients								
Dickson 2008	58.6	35.42	3363	48.1	35.42	713	14.7%	10.50 [7.64, 13.36]
Dickson-elderly 2008	63.4	29.4	2336	49	23.4	3368	15.2%	14.40 [12.97, 15.83]
Gerbino 2007	87.9	35.42	2839	69.2	35.42	3367	15.1%	18.70 [16.93, 20.47]
Hess 2008	76.9	35.42	7224	54.4	35.42	7225	15.3%	22.50 [21.34, 23.66]
Taylor 2003	80.8	35.42	2754	73.8	35.42	2978	15.1%	7.00 [5.16, 8.84]
Subtotal (95% CI)			**18516**			**17651**	**75.5%**	**14.66 [8.97, 20.36]**
Heterogeneity: $Tau^2 = 41.31$; $Chi^2 = 236.93$, df = 4 ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: Z = 5.05 ($P < 0.00001$)								
Total (95% CI)			**20763**			**18277**	**100.0%**	**13.31 [8.26, 18.35]**
Heterogeneity: $Tau^2 = 42.94$; $Chi^2 = 264.57$, df = 6 ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: Z = 5.17 ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 26.20$, df = 1 ($P < 0.00001$), $I^2 = 96.2\%$								



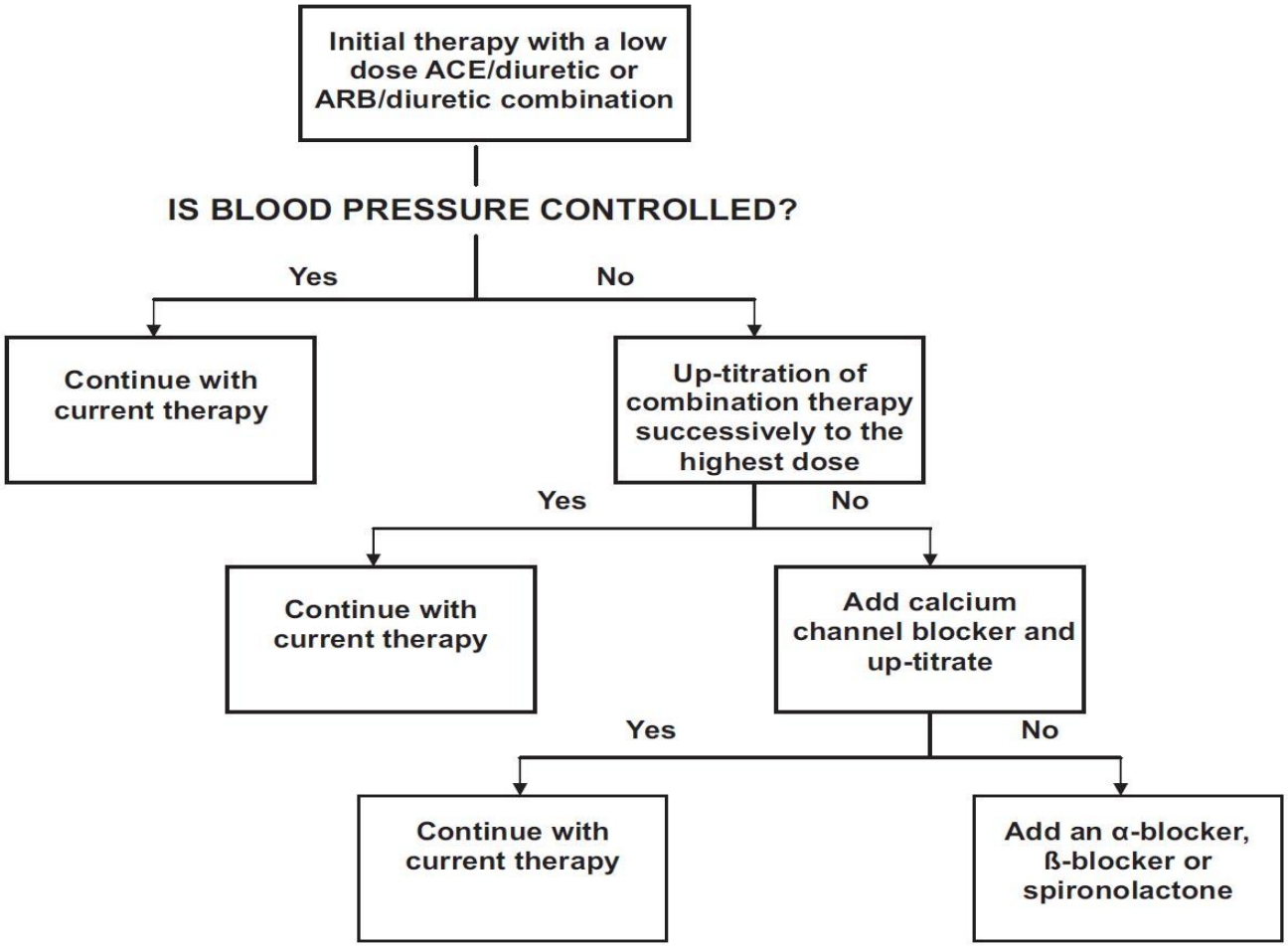
In Favor of ACEI/ARB with CCB/diuretic

3 studies identified:

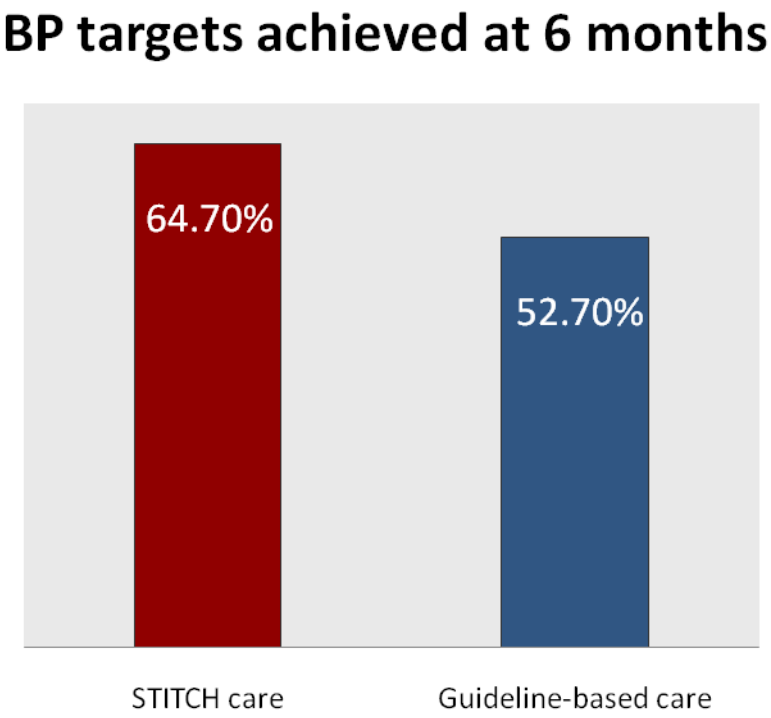
1. Feldman RD. Hypertension. 2009;53:646-53.
2. HOPE-3. N Engl J Med. 2016 26;374(21):2009-20.
3. ACCOMPLISH. N Engl J Med. 2008;359(23):2417-28.

STITCH algorithm: initiating RX with a low dose SPC

(Simplified Treatment Intervention To Control Hypertension)



STITCH study: Results



Absolute difference: 12.0%
95% CI 1.5-22.4%
P = 0.026
Relative difference: 23%

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Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D.,

- **Design:** 2x2 factorial RCT (double-blind)
- **Population:** intermediate-risk (no CVD); 22% had BP Rx at baseline; n=12 705
- **Intervention:** candesartan 16 mg/d plus HCTZ 12.5 mg/d vs. candesartan 16 mg/d plus placebo
- **1° outcomes:** overall, no significant differences in first (p=0.40) or the second coprimary outcomes (p=0.51)
  - coprimary #1: CV death, nonfatal MI, or nonfatal stroke
  - coprimary #2: #1 plus resuscitated cardiac arrest, HF, revascularization

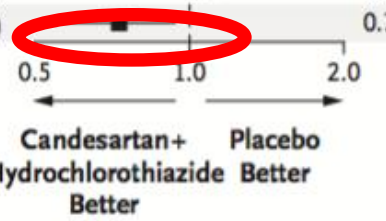
BP Change in HOPE - 3 BP

	Active	Placebo
SBP BL	138.2 +- 14.7	137.9 +- 14.8
Change from BL	10.0 +- 13.1	4.0 +- 12.9
DBP BL	82 +- 9.4	81.8 +- 9.3
Change from BL	5.7 +- 8.2	2.7 +- 7.9

- 1/3 at baseline had a history of hypertension and 22% were on antihypertensives at baseline.
- Annual event rates were 0.8% vs 2.1% in ACCORD and 2.2% in SPRINT.

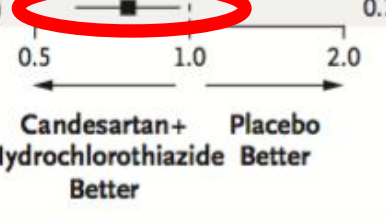
A First Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	260/6356 (4.1)	279/6349 (4.4)	0.93 (0.79–1.10)	—
Systolic blood pressure						0.02
≤131.5 mm Hg	122.2	6.1/3.1	70/2080 (3.4)	62/2122 (2.9)	1.16 (0.82–1.63)	
131.6–143.5 mm Hg	137.6	5.6/2.7	87/2120 (4.1)	81/2141 (3.8)	1.08 (0.80–1.46)	
>143.5 mm Hg	154.1	5.8/3.0	103/2156 (4.8)	136/2084 (6.5)	0.73 (0.56–0.94)	



B Second Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	312/6356 (4.9)	328/6349 (5.2)	0.95 (0.81–1.11)	—
Systolic blood pressure						0.009
≤131.5 mm Hg	122.2	6.1/3.1	90/2080 (4.3)	74/2122 (3.5)	1.25 (0.92–1.70)	
131.6–143.5 mm Hg	137.6	5.6/2.7	99/2120 (4.7)	98/2141 (4.6)	1.02 (0.77–1.34)	
>143.5 mm Hg	154.1	5.8/3.0	123/2156 (5.7)	156/2084 (7.5)	0.76 (0.60–0.96)	



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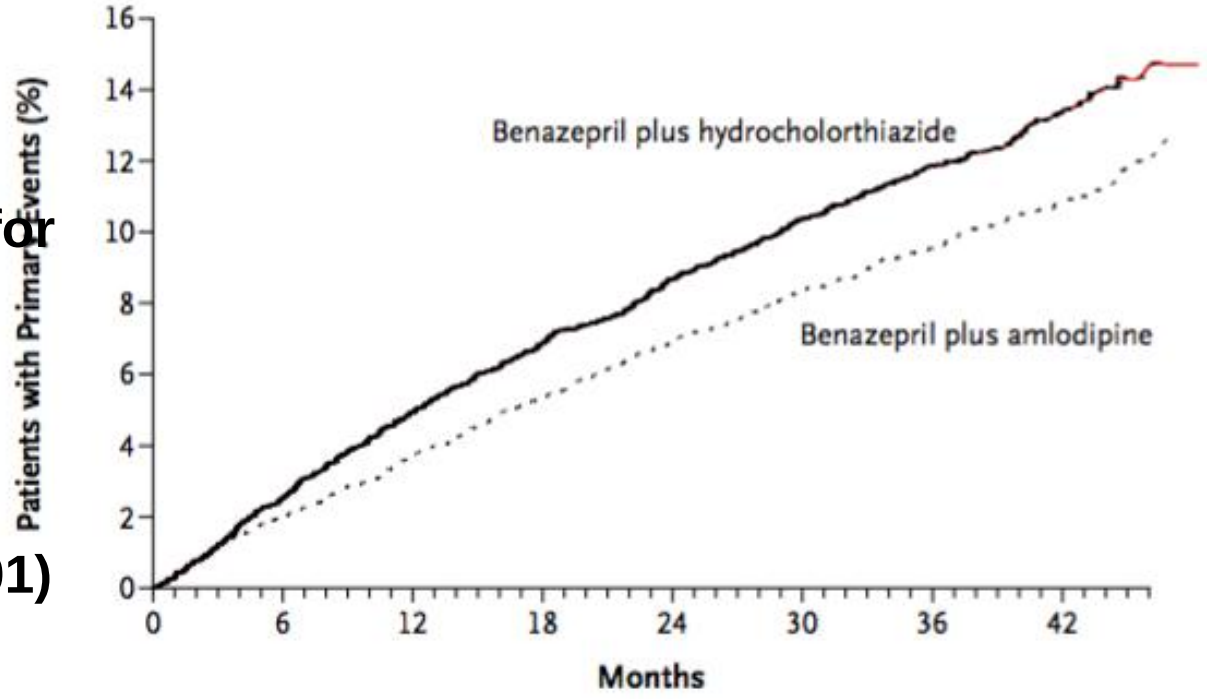
Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

Kenneth Jamerson, M.D., Michael A. Weber, M.D., George L. Bakris, M.D., Björn Dahlöf, M.D., Bertram Pitt, M.D.,

- **Design:** RCT (double-blind)
- **Population:** high-risk; 97% had BP Rx at baseline; n=11 506
- **Intervention:** benazepril plus amlodipine vs. benazepril plus HCTZ
- **1° outcome:** CV death, nonfatal MI, nonfatal stroke, hosp. for angina, resuscitation after cardiac arrest, and coronary revasc.
  - Terminated early after mean follow-up of 36 m

ARR = 2.2%
(11.8% vs. 9.6% for ACEI-HCTZ vs. ACEI-CCB)

RRR = 19.6%
(HR, 0.80; p<0.001)



No. at Risk							
Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

Figure 2. Kaplan–Meier Curves for Time to First Primary Composite End Point.

There were 552 patients with events (9.6%) in the benazepril–amlodipine group, as compared with 679 patients with events (11.8%) in the benazepril–hydrochlorothiazide group. The relative risk reduction was 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90; P<0.001).

- Benazepril–amlodipine superior to benazepril-HCTZ in reducing MACE

c) Consider Spironolactone or other MRA

- Drug resistant hypertension
  - Uncontrolled BP despite three drugs, one of which is a diuretic

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

Summary

Background Optimal drug treatment for patients with resistant hypertension is undefined. We aimed to test the hypotheses that resistant hypertension is most often caused by excessive sodium retention, and that spironolactone would therefore be superior to non-diuretic add-on drugs at lowering blood pressure.

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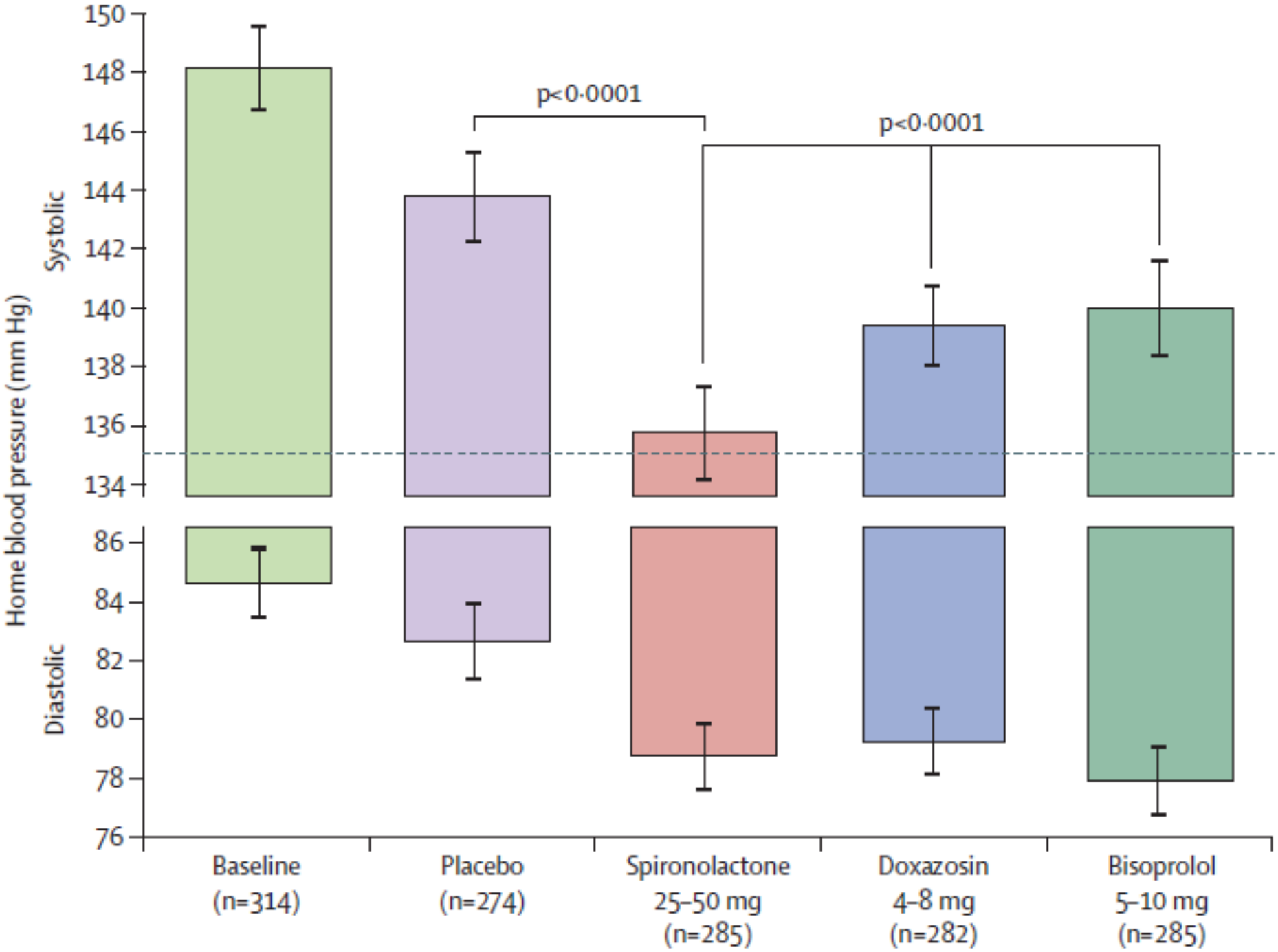
September 21, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00257-3

Methods

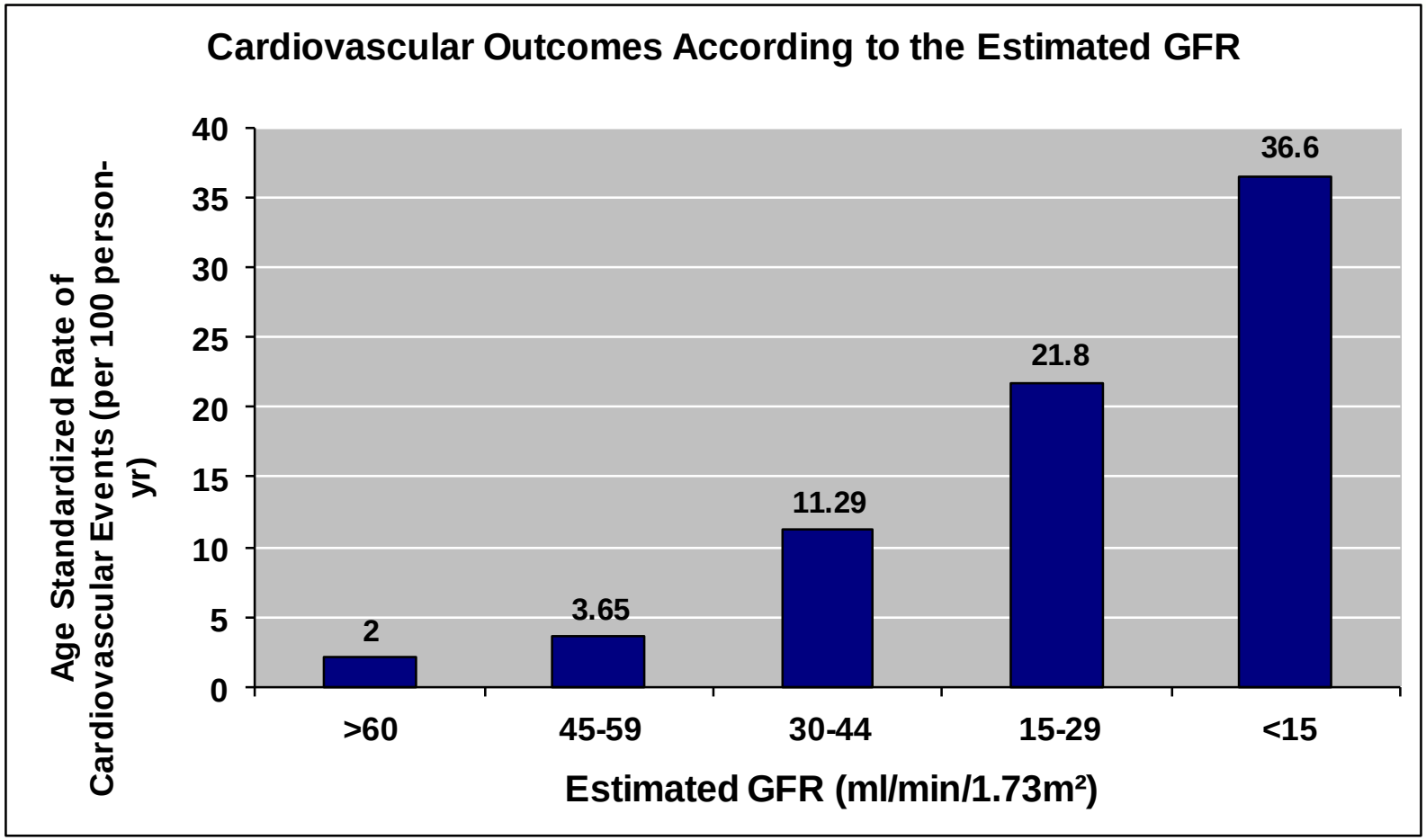
- RCT Double blind placebo controlled
- Age 18-79 on 3 or more antihypertensives
- BP
  - 140 + in office
  - 135 + in office for DM
  - 130 + on HBPM
- Each patient gets 12 weeks of in addition to their meds:
  - Spironolactone 25-50
  - Bisoprolol 5-10
  - Doxazosin 4-8
  - Placebo
- Outcome:
  - Difference in HBPM between
    - Spironolactone and placebo
    - Spironolactone and Bis and Dox


Home blood pressure (mm Hg)
Systolic
Diastolic
150
148
146
144
142
140
138
136
134
86
84
82
80
78
76
p<0·0001
p<0·0001
Baseline
(n=314)
Placebo
(n=274)
Spironolactone
25–50 mg
(n=285)
Doxazosin
4–8 mg
(n=282)
Bisoprolol
5–10 mg
(n=285)

d) Sleep Apnoea

- Consider OSA
- Sleep study
- CPAP

Presence of CKD Increases Risk for CVD Events



Go Alan, et al. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. NEJM 2004; 351:1296-305.

Case Progression

- Gerald was started on doxazosin 1 mg at hs, then titrated to 4 mg at hs
- Gerald's BP is now controlled, < 120 systolic
- You also discuss the need for ongoing global cardiovascular risk reduction strategies and give him positive feedback for achieving optimal medical therapy including:
  - ✓ being on a RAAS blocker and BP at target
  - ✓ regular exercise
  - ✓ careful diet
  - ✓ good LDL control with a statin
  - ✓ maintaining a smoke free lifestyle

Key Learnings

- ✓ For patients with nondiabetic chronic kidney disease (eGFR 20-60), target systolic blood pressure should be **<120 mmHg**
- ✓ Reduce CV risk

The full slide set of the

2015 CHEP Recommendations

is available at

www.hypertension.ca