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Update from the Canadian Hypertension guidelines

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Disclosures

- Relationships with commercial interests:
  - Grants/Research Support: Bayer, Novartis, Boehringer-Ingelheim, Servier, Idorsia
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  - Consulting Fees: Bayer, Amgen, Servier, Boehringer-Ingelheim, Jansen, Sanofi, Valeant, Novartis, Merck

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Learning Objectives

At the conclusion of this activity, participants will be able to:

- Apply appropriate methods for making a diagnosis of hypertension
- Implement evidence-based threshold and target BPs
- Integrate new guidelines for hypertension management including:
  - Use of longer-acting over shorter-acting diuretics
  - Use of single pill combinations as a first-line treatment

Stratification of total CV risk by categories of HTN

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

2013 ESH Guidelines, J Hypertension, 31, 2013

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Today's focus:

- Longer acting (thiazide-like) diuretics are preferred vs. shorter acting (thiazides)
- Single pill combinations as a first line treatment (regardless of the extent of BP elevation)

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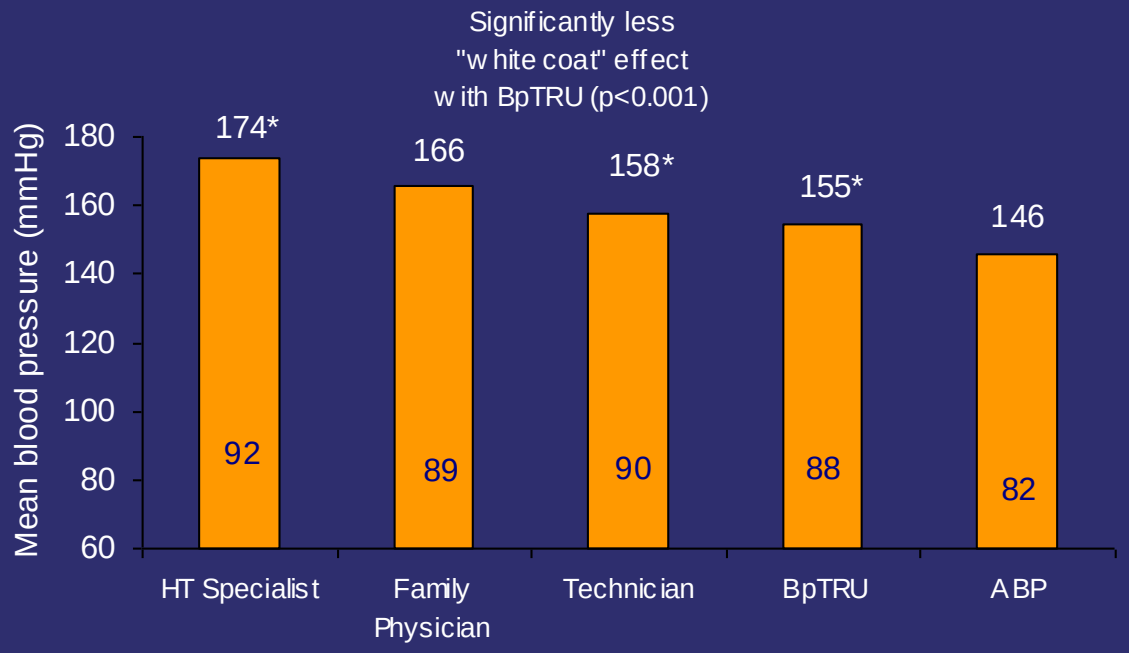
What's still important?

- **The diagnosis of hypertension should be based on out-of-office measurements; in the office, use automated office BP monitoring (AOBP)**
- The threshold and target blood pressures are lower in those at greater risk

BpTRU Significantly Lowered "White-Coat Effect" in Clinical Practice

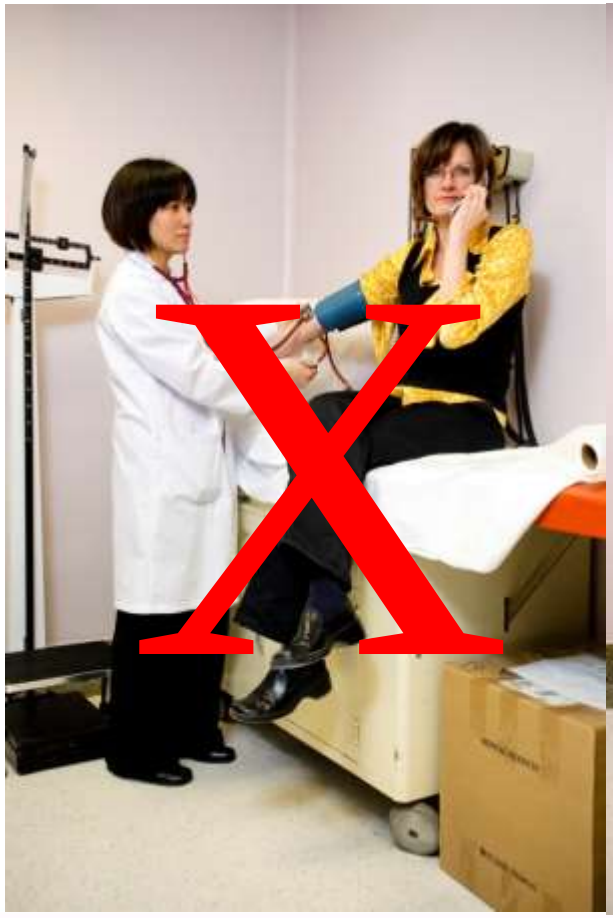
Mean Blood Pressure Values Obtained by Different Evaluations



* Significantly higher than mean awake ambulatory blood pressure (ABP; p<0.01).

Myers MG, *AJH* 2003; 16: 494-7.

Blood Pressure Assessment: Patient position



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Comparisons of blood pressure readings obtained in clinical settings using different methods of blood pressure measurement

	Mean blood pressure* (mmHg)		
	Centre for Studies in Primary Care[1]	ABPM referral unit[2]	CAMBO trial[3]
Routine manual office BP	151/83	152/87	150/81
Automated office BP	140/80	132/75	135/77
Awake ambulatory BP	142/80	134/77	133/74

***** *The automated office blood pressure (BP) and awake ambulatory BP were similar, and both were lower than the routine manual BP obtained in community practice.*

1. *Beckett L et al , BMC Cardiovasc. Disord. 2005; 5: 18.* ***2.*** *Myers MG et al, J. Hypertens. 2009; 27: 280.* ***3.*** *Myers MG, et al. BMJ 2011; 342: d286.*

Auscultatory OBPM is inaccurate

- In the real world, the accuracy of auscultatory OBPM can be adversely affected by provider, patient and device factors such as:
  - too rapid deflation of the cuff
  - digit preference with rounding off of readings to 0 or 5
  - also, mercury sphygmomanometers are being phased out and aneroid devices are less likely to remain calibrated

- Consequence: Routine auscultatory OBPMs are **9/6** mm Hg higher than standardized research BPs (primarily using oscillometric devices)

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Myers MG, et al. *Can Fam Physician* 2014;60:127-32.

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2015

Automated Office BP Measurement Preferred

- Automated office blood pressure (AOBP) is the preferred method of performing in-office BP measurement

(3 – 5 readings)

Automated Office (unattended, AOBP)

Oscillometric (electronic)

Studies comparing AOBP measurement with Awake ABPM

AOBPs Equivalent to Awake ABPs

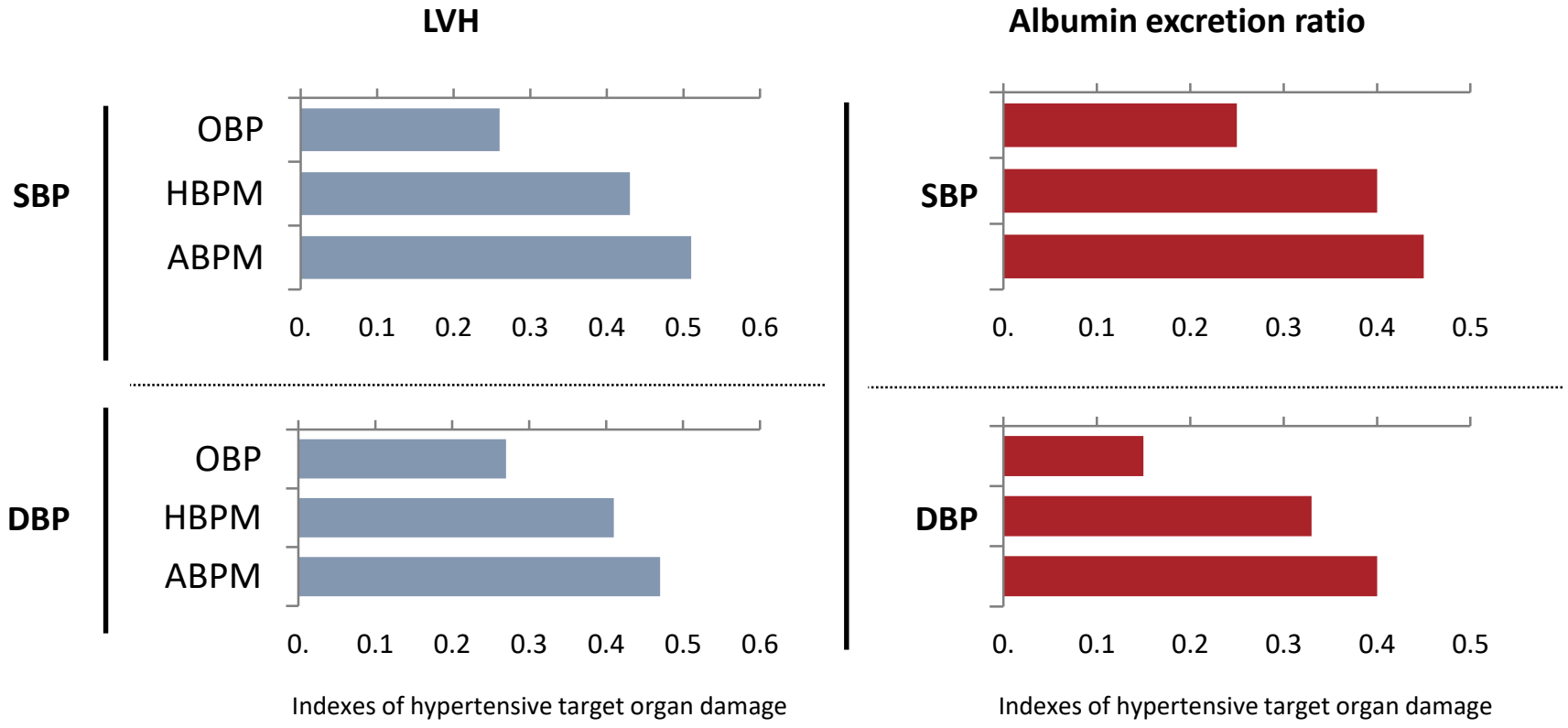
Table 2. Studies comparing AOBP measurement with AABP measurement: *Mean overall AOBP was 137/79 mm Hg, and mean overall AABP was 137/79 mm Hg.*

STUDY	NO. OF PATIENTS	POPULATION	AOBP, mm Hg	AABP, mm Hg
Myers et al,[5] 2009	309	ABPM unit	132/75	134/77
Myers et al,[21] 2008	200	ABPM unit	133/72	135/76
	200	ABPM unit	132/76	134/77
Myers et al,[22] 2010	139	ABPM unit	141/82	142/81
Beckett and Godwin,[25] 2005	481	Family practice	140/80	142/80
Myers et al,[26] 2009	62	Hypertension clinic	140/77	141/77
Myers,[27] 2010	254	ABPM unit	133/80	135/81
Godwin et al,[28] 2011	654	Family practice	139/80	141/80
Myers et al,[29] 2011	303	Family practice	135/77	133/74
Andreadis et al,[30] 2011	90	Research unit	140/88	136/87

AABP—awake ambulatory BP, ABPM—24-hour ambulatory BP monitoring, AOBP—automated office BP, BP—blood pressure.

Myers MG, et al. Can Fam Physician 2014;60:127-32; Myers MG. J Clin Hypertens 2014;16:83-6; Myers MG. J Hypertens 2012;30:1894-8; Myers MG, et al. Family Practice 2012;29:376-82; Myers MG, et al. BMJ 2011;342:d286; Myers MG. J Hypertens 2010;28:703-8; Myers MG, et al. J Hypertens 2009;27:280-6; Myers MG, et al. Blood Press Monit 2009;14:108-11; Myers MG, Godwin M. J Clin Hypertens 2007;9:267-70

Out-of-Office BP Measurements are More Highly Correlated With BP-Related Risk



Mulè G, et al. *J Cardiovasc Risk* 2002;9:123-9.

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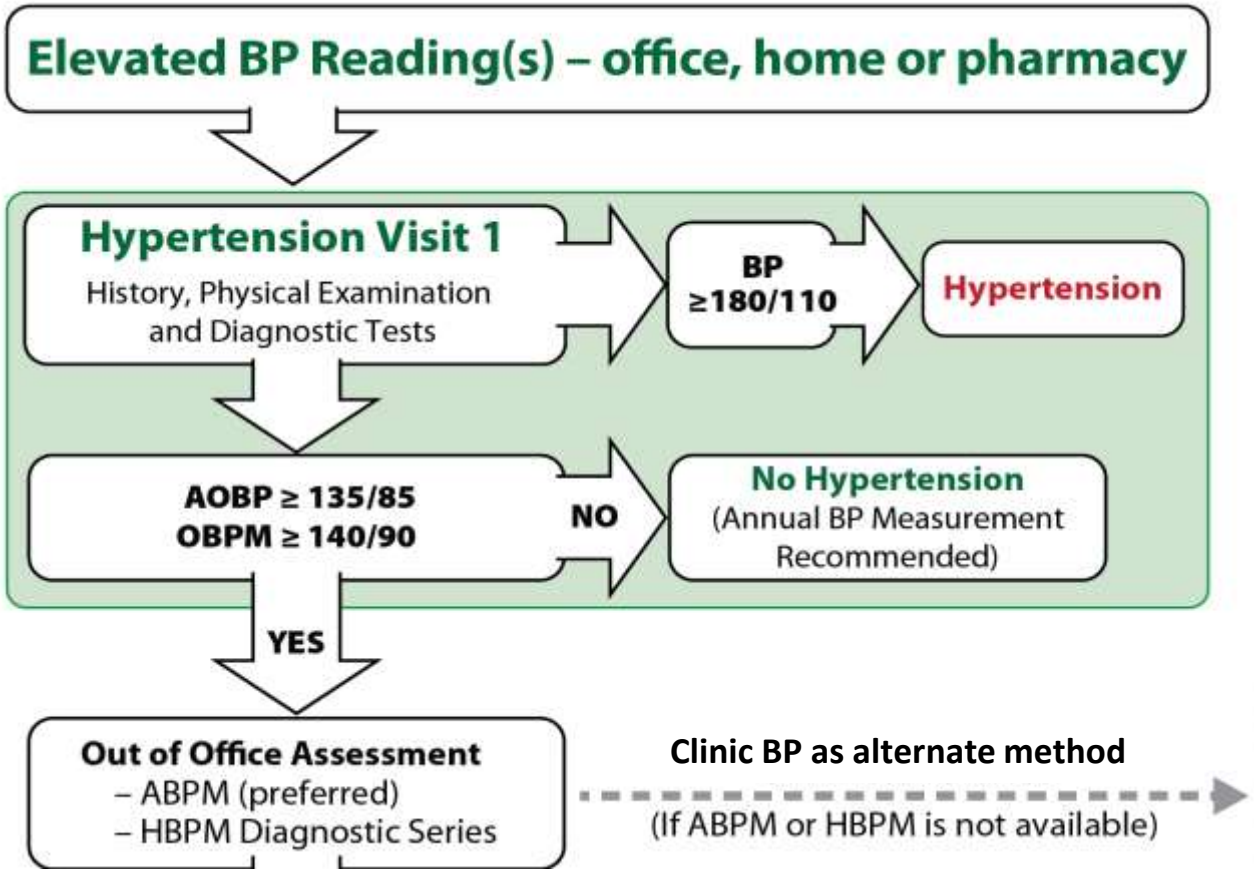
Automated Office BP Measurement

- More closely approximates ABPM than routine office BPs (mitigates white coat effect)[1-3]
- Is more predictive of end organ damage (LVMI, proteinuria and cIMT), similar to ABPM[4-6]

ABPM = ambulatory blood pressure measurement
LVMI = left ventricular mass index
cIMT = carotid intima media thickness

1. Beckett L, et al. *BMC Cardiovasc Disord* 2005;5:18; 2. Myers MG, et al. *J Hypertens* 2009;27:280-6; 3. Myers MG, et al. *BMJ* 2011;342;d286;4. Campbell NRC, et al. *J Hum Hypertens* 2007;21:588-90; 5. Andreadis EA, et al. *Am J Hypertens* 2011;24:661-6; 6. Andreadis EA, et al. *Am J Hypertens* 2012;25:969-73.

Out-of-Office Assessment is the Preferred Means of Diagnosing Hypertension



AOBP = automated office blood pressure
OBPM = office BP measurement

ABPM = ambulatory BP measurement
HBPM = home BP measurement

Out-of-Office BP Measurements

- Out-of-office measurement identifies white coat hypertension and masked hypertension
- ABPM has better predictive ability than OBPM and is the recommended out-of-office measurement method
- HBPM has better predictive ability than OBPM and is recommended if ABPM is not tolerated, not readily available or due to patient preference

ABPM = ambulatory blood pressure measurement
HBPM = home BP measurement
OBPM = office BP measurement

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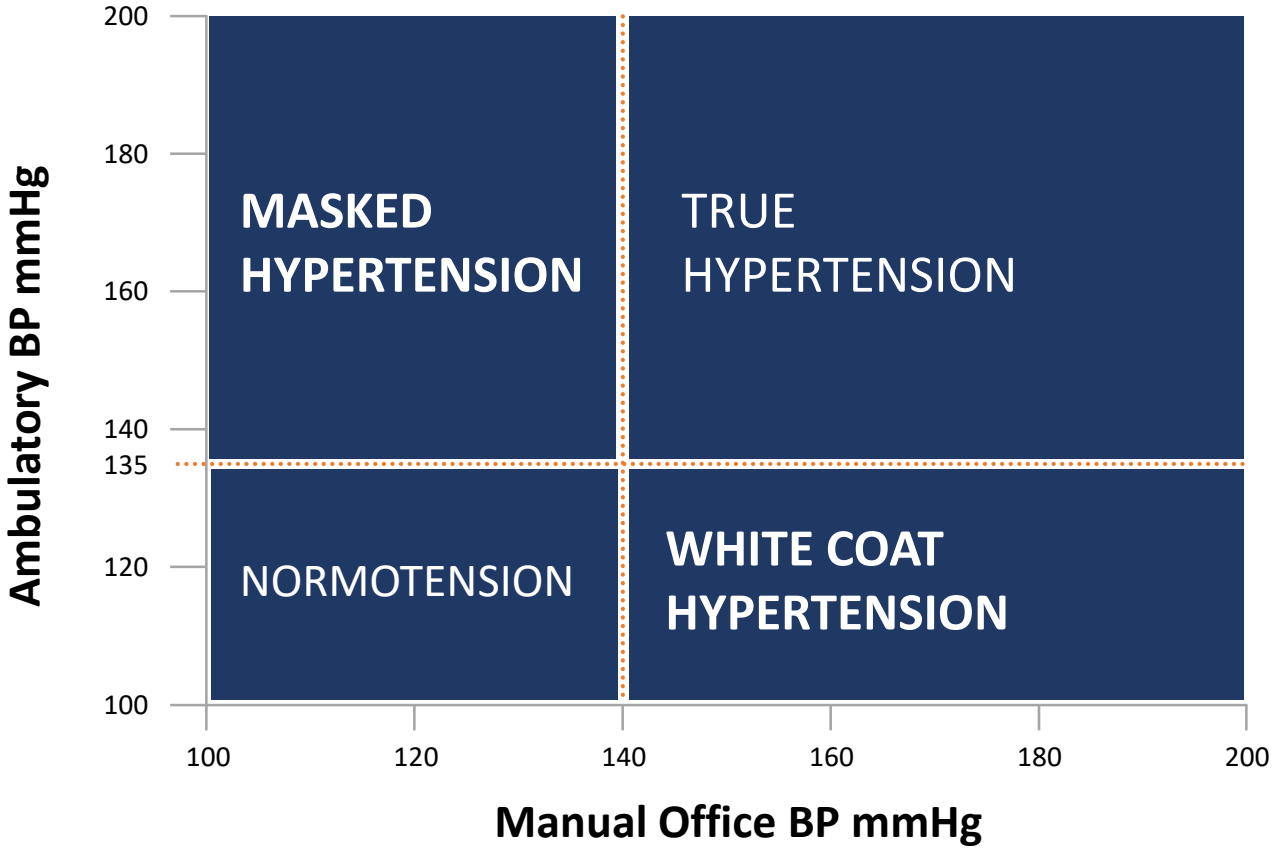
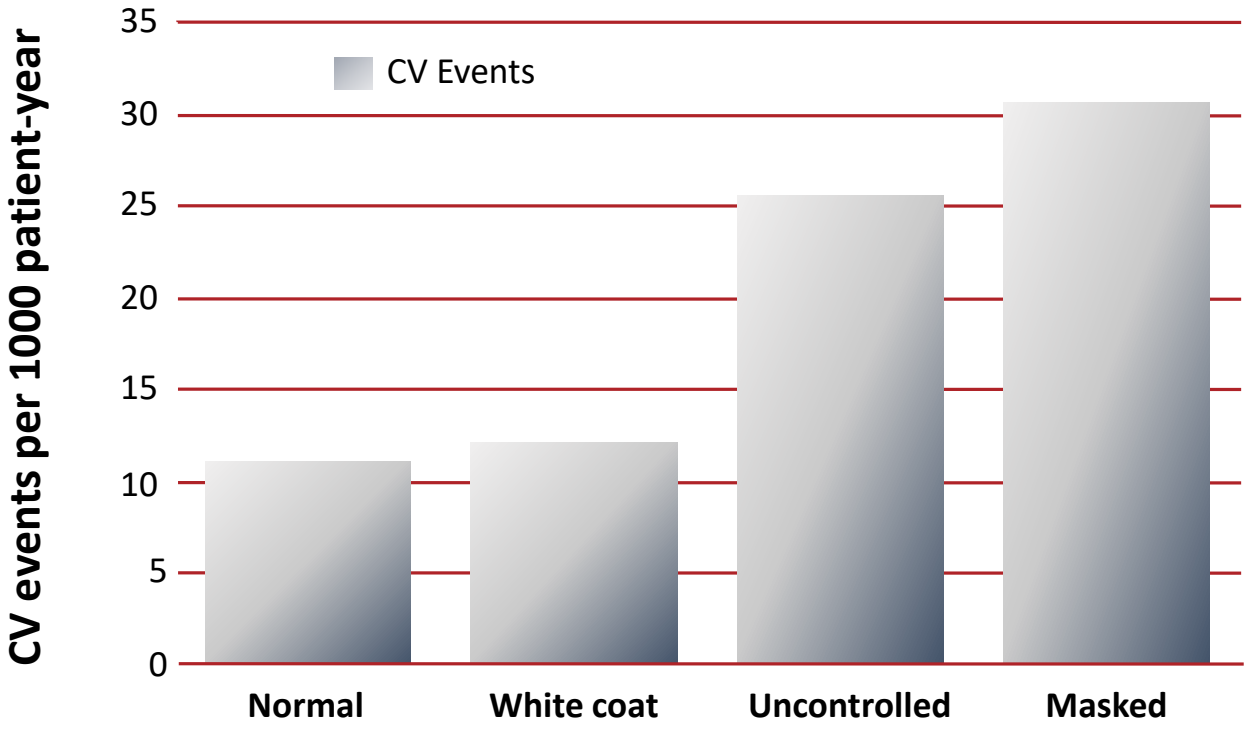
White Coat and *Masked* Hypertension



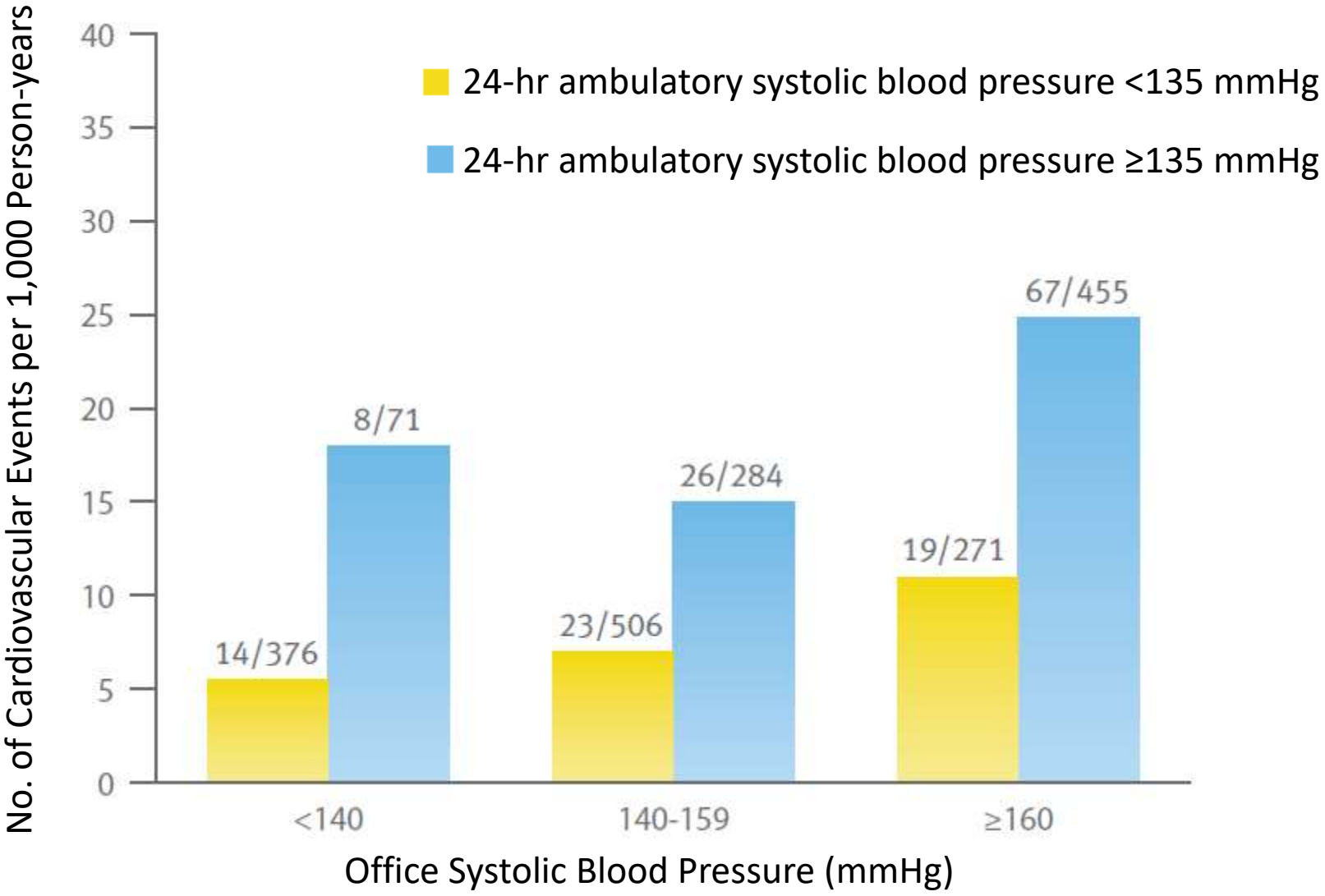
Derived from Pickering TG, et al. *Hypertension* 2002:40:795-6.

The Prognosis of *White Coat* and *Masked* Hypertension



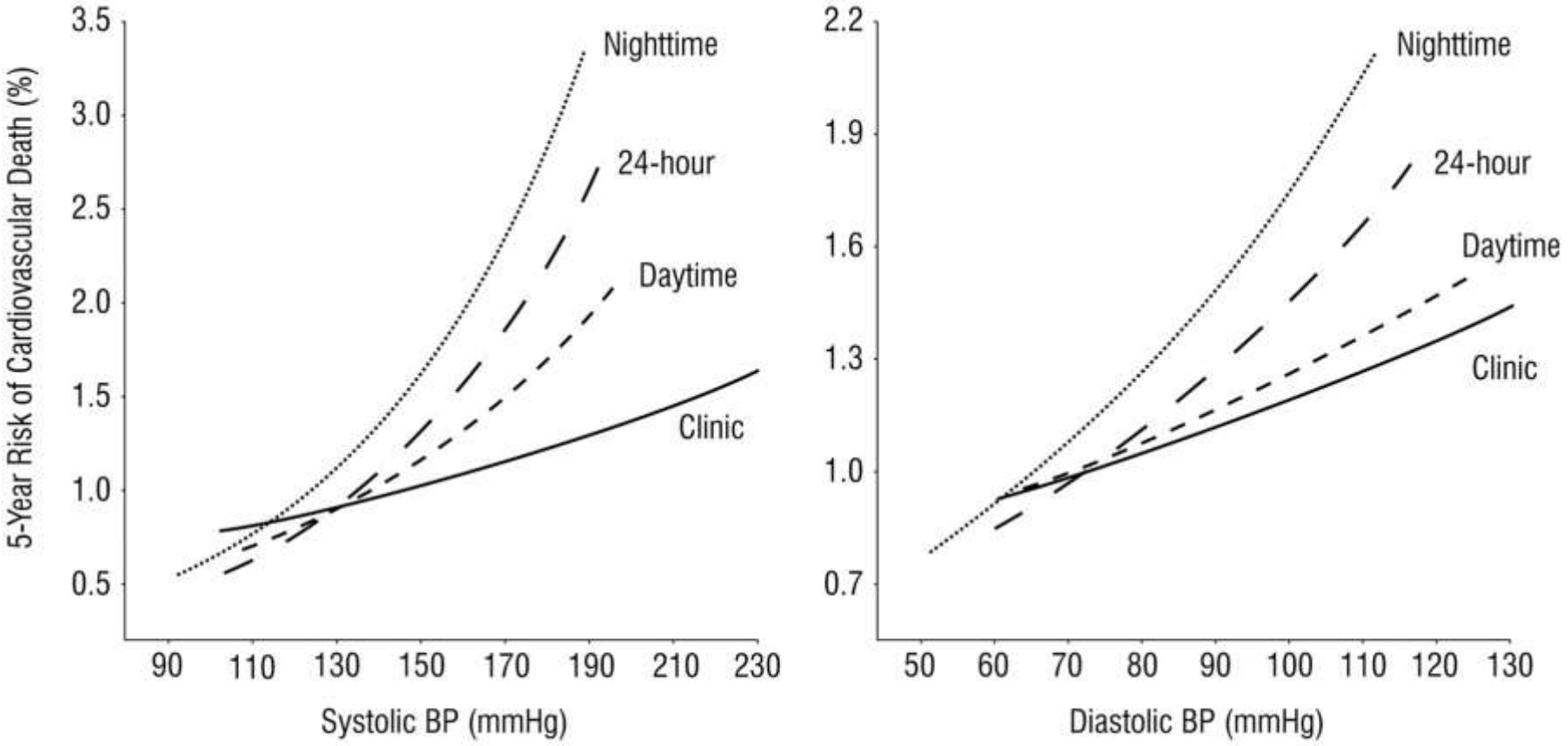
Okhubo T, et al. *J Am Coll Cardiol* 2005;46;508-15

Incidence of CV Events According to SBP



Adapted from Clement DL, et al. *N Engl J Med. 2003;348:2407-2415.*

Superiority of the predictive value of nocturnal BP average for CV mortality



Eamon Dolan et al. Hypertension. 2005;46:156-161

American Heart Association.

Ambulatory BP Monitoring

Beyond the diagnosis of hypertension, ABPM measurement may also be considered for selected patients for the management of HTN

Which patients?

- **Untreated**
  - Mild (Grade 1) to moderate (Grade 2) clinic BP elevation and without target organ damage.
- **Treated patients**
  - Blood pressure that is not below target values despite receiving appropriate antihypertensive therapy.
  - Symptoms suggestive of hypotension.
  - Fluctuating office blood pressure readings.

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What's still important?

- The diagnosis of hypertension should be based on out-of-office measurements; in the office, use automatic office BP monitoring (AOBP)
- The threshold and target blood pressures are lower in those at greater risk

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Usual Office BP **Threshold Values** for Initiation of Pharmacological Treatment

Population	SBP	DBP
High Risk (SPRINT population) #	≥ 130	NA
Diabetes	≥ 130	≥ 80
Moderate *	≥ 140	≥ 90
Low risk (no TOD or CV risk factors)	≥ 160	≥ 100

AOBP = automated office blood pressure
TOD = target organ damage
SBP = systolic blood pressure
DBP = diastolic blood pressure

Based on AOBP

*AOBP threshold ≥ 135/85 mmHg

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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

Based on AOBP
*AOBP threshold ≥ 135/85 mmHg

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New Guideline Post-SPRINT

- For high-risk patients, aged ≥ 50 years, with systolic BP levels ≥130 mm Hg, intensive management to target a systolic BP ≤120 mm Hg should be considered
- Intensive management should be guided by automated office BP measurements
- Patient selection for intensive management is recommended and caution should be taken in certain high-risk groups

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

- There was an increased risk of renal deterioration, potassium abnormalities and hypotension with intensified therapy
- Patients with one or more clinical indications should consent to intensive management

[*] Four variable MDRD equation

[†] Framingham Risk Score, D'Agastino, Circulation 2008

New Thresholds/Targets for the High-Risk Patient Post-SPRINT: *Who does this NOT apply to?*

Limited or No Evidence:

- Heart failure (EF <35%) or recent MI (within last 3 months)
- Indication for, but not currently receiving, a beta-blocker
- Institutionalized elderly

Inconclusive Evidence:

- Diabetes mellitus
- Prior stroke
- eGFR < 20 ml/min/1.73m^2

Contraindications:

- Patient unwilling or unable to adhere to multiple medications
- Standing SBP <110 mmHg
- Inability to measure SBP accurately
- Known secondary cause(s) of hypertension

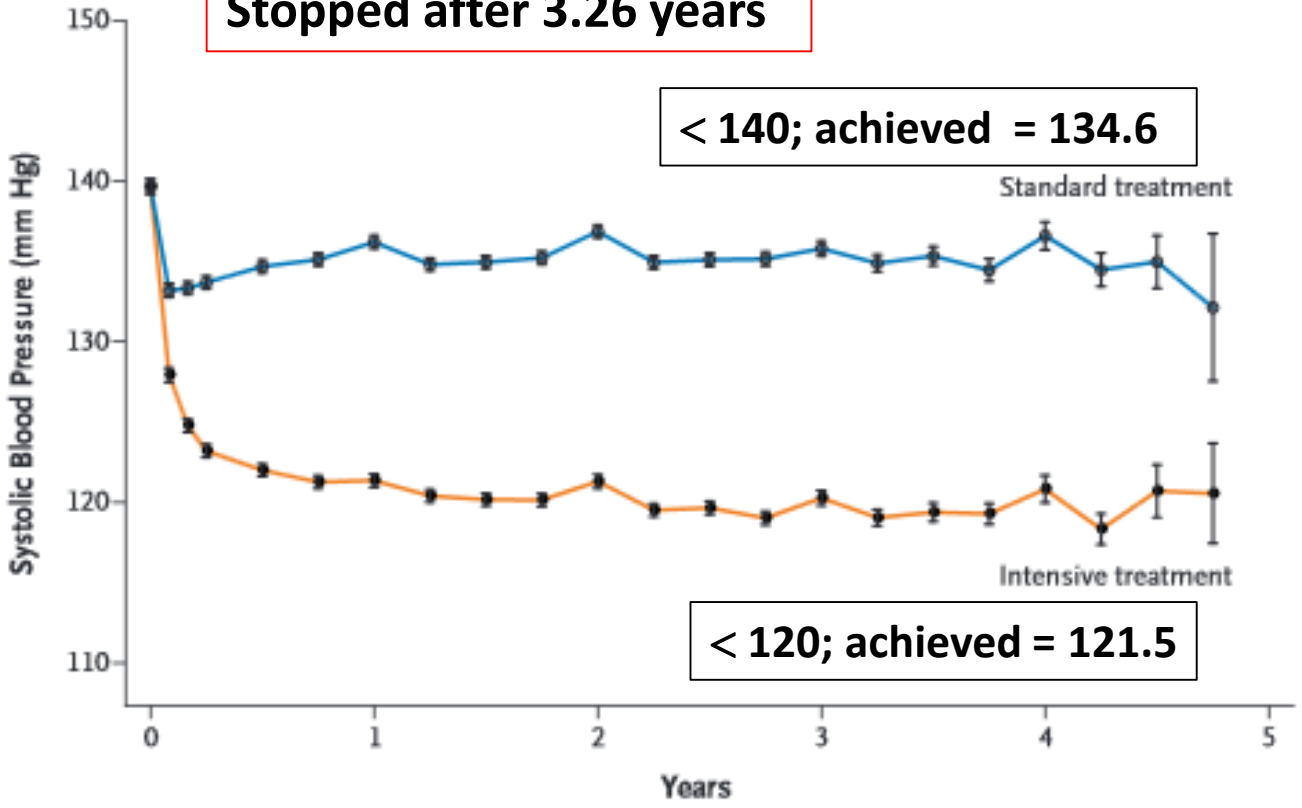
A Randomized Trial of Intensive versus Standard Blood-Pressure Control: the SPRINT study

- N = 9361
- SBP ≥ 130
- ↑ CV risk
- No DM
- No CVA
- 3 readings (unattended)

Stopped after 3.26 years

< 140; achieved = 134.6

< 120; achieved = 121.5



No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286

Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

NEJM, November 9, 2015

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m^2§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	110/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

NNT=61

NEJM, November 9, 2015

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Today's focus:

- Longer acting (thiazide-like) diuretics are preferred vs. shorter acting (thiazides)
- Single pill combinations should be used as a first line treatment (regardless of the extent of BP elevation)

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Longer-acting Diuretics Should be Preferred

(i.e., thiazide-like are preferred to thiazides)

Longer-acting (thiazide-like): chlorthalidone, indapamide

Shorter-acting (thiazides): hydrochlorothiazide

Diuretics in Hypertension

		BA (%)	T½ (h)	Duration (hrs)
Thiazide and Thiazide-like Diuretics	HTCZ	65 – 75	3.0 – 10.0	6 – 12
	Chlorothiazide	30 – 50	15.0 – 25.0	6 – 12
	CLD	65	24.0 – 55.0	24 – 72
	Bendroflumethiazide	90	2.5 – 5.0	18 – 24
	Indapamide	90	6.0 – 15.0	24 – 36
	Metolazone	65	14	12 – 24
Loop Diuretics	Bumetanide	80 – 90	0.3 – 1.5	4 – 6
	Furosemide	10 – 100	0.3 – 3.4	6 – 8
	Torsemide	80 – 100	3.0 – 4.0	6 – 8
Potassium-Sparing Diuretics	Amiloride	15 – 20	17.0 – 26.0	24
	Triamterene	83 (55)*	3.0 (3.0)*	7 – 9
	Spironolactone	> 90	1.5 – 15.0†	48 – 72
	Eplerenone	69	2.2 – 9.4	NA

*Parentheses denote active metabolite. †The half-life of one active metabolite, potassium canrenoate, is 15 h.
BA = bioavailability; T½ = half-life; DOA = duration of action; NA = unknown.

Reprinted from Brater DC. In: Principles of Pharmacology: Based Concepts and Clinical Applications. 1995:657-672, with permission from Springer Science and Business Media; Delyani JA, et al. *Cardiovasc Drug Rev* 2001; 19:185-200; Rosenberg J, et al. *Cardiovasc Drug Ther* 2005; 19:301-306; Sica DA. *Congest Heart Fail* 2003; 9:100-105.

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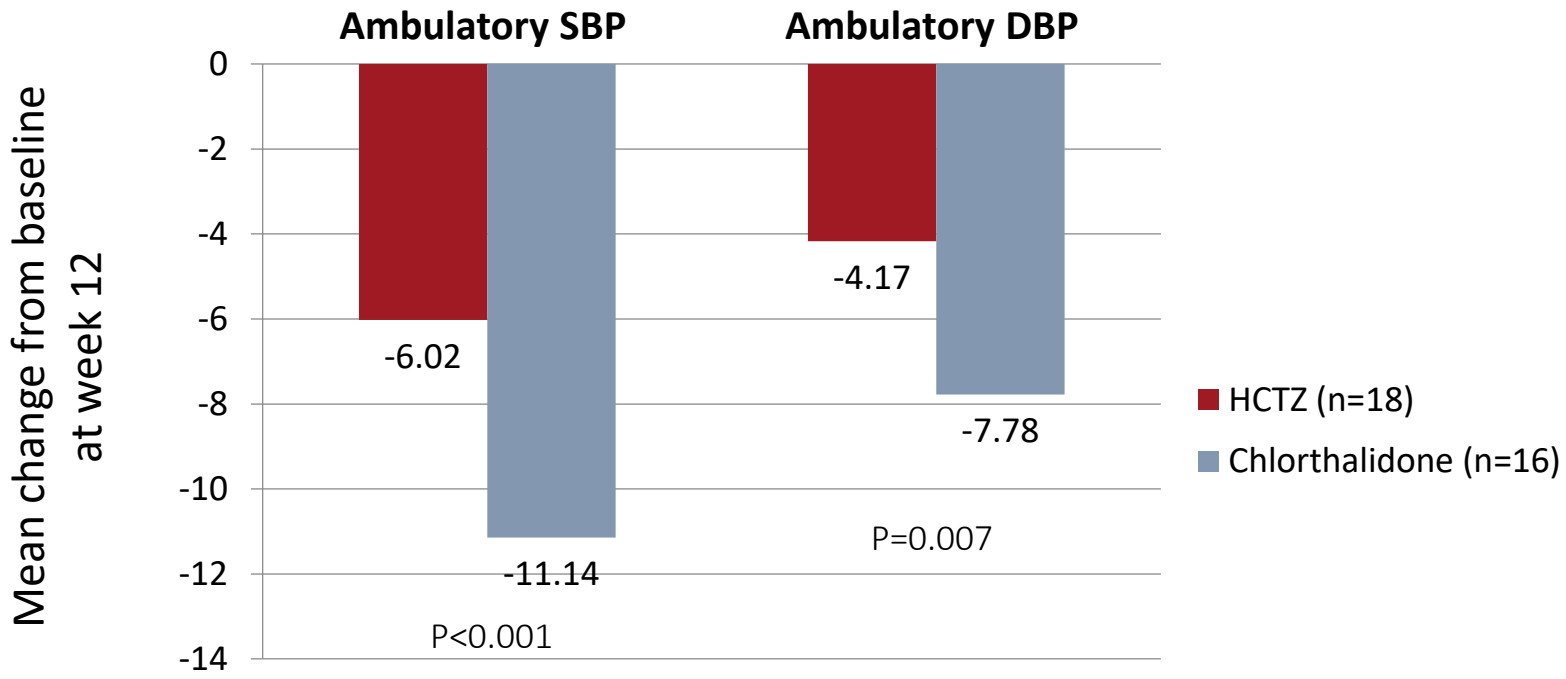
Diuretic Type Meta-Analysis vs. Placebo

- **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;65(5):1033-40

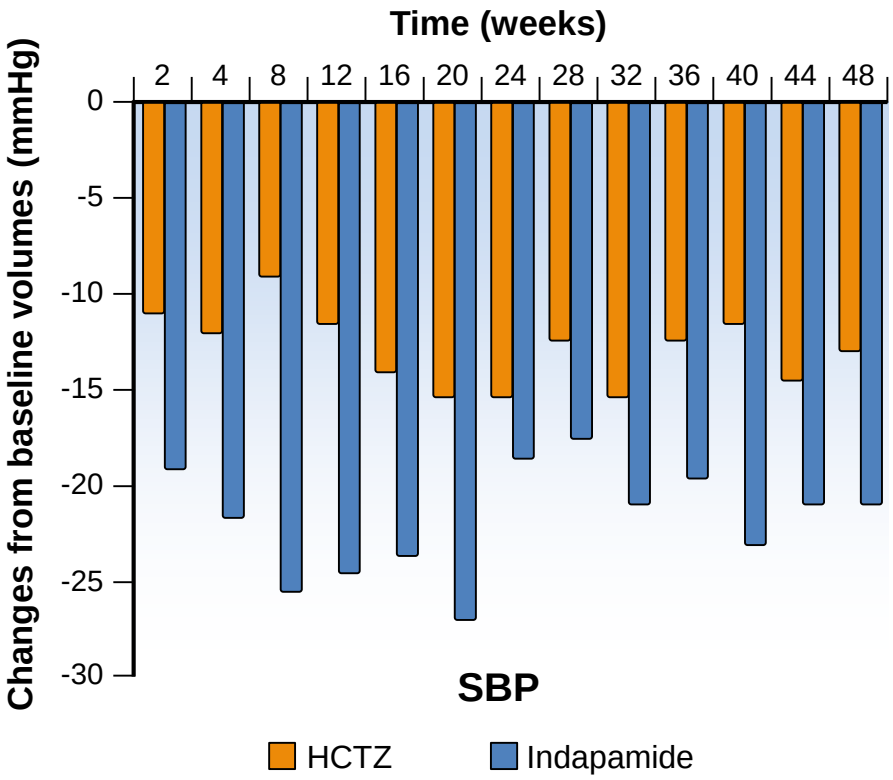
Chlorthalidone More Effective Than Hydrochlorothiazide in BP Reduction

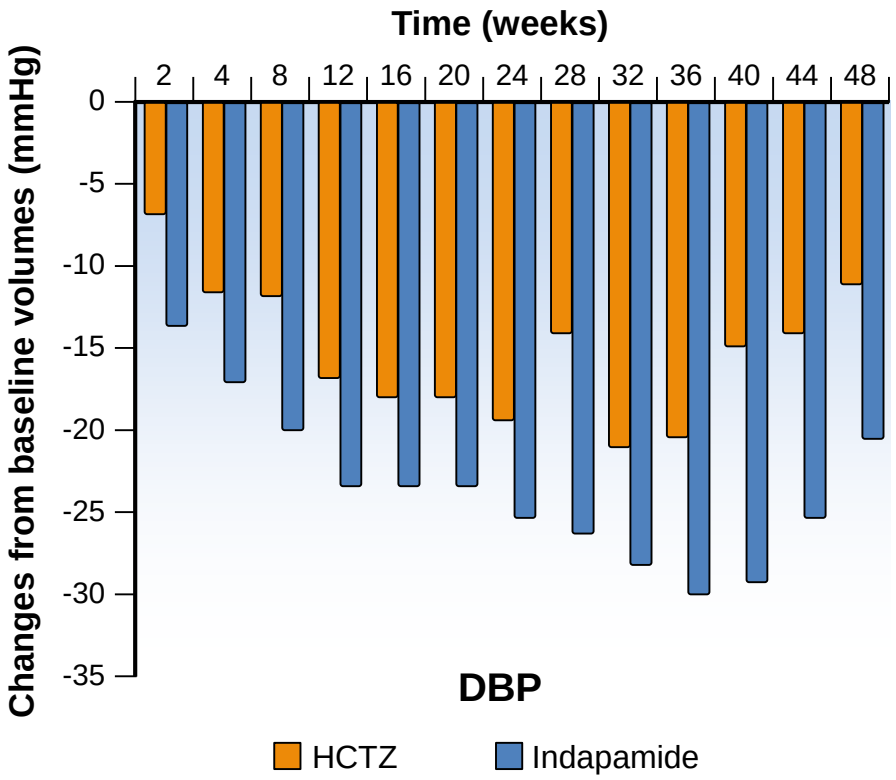


Kruskal-Wallis test used with Dunn's test for multiple comparisons; comparison between baseline and Wilcoxon signed rank test results. Mean 24h SBP was significantly lower for the chlorthalidone group than for the HCTZ group at week 4 (125.52 vs. 139.71 mmHg, respectively, P=0.019) and week 12 (121.87 vs. 136.64 mmHg, respectively, P=0.013). Intent-to-treat population.

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

Indapamide vs. HCTZ: Blood Pressure

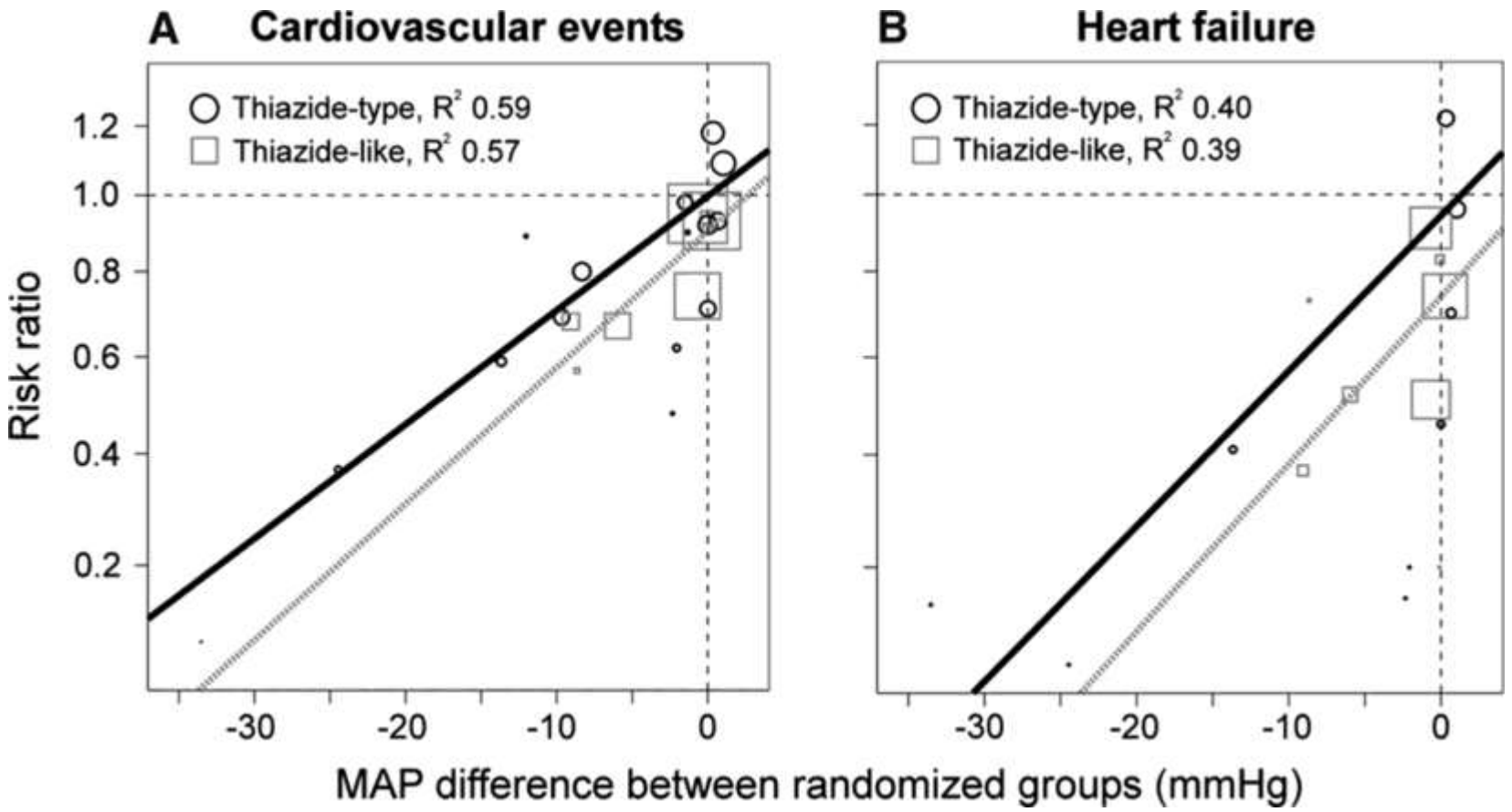




Reduction in systolic and diastolic pressure values from baseline in patients treated with HCTZ or indapamide.

Plante, et al. *Amer J Med* 1988; 82:98-103.

Blood pressure (BP) adjusted analysis.



Rik H.G. Olde Engberink et al. Hypertension. 2015;65:1033-1040

American Heart Association.

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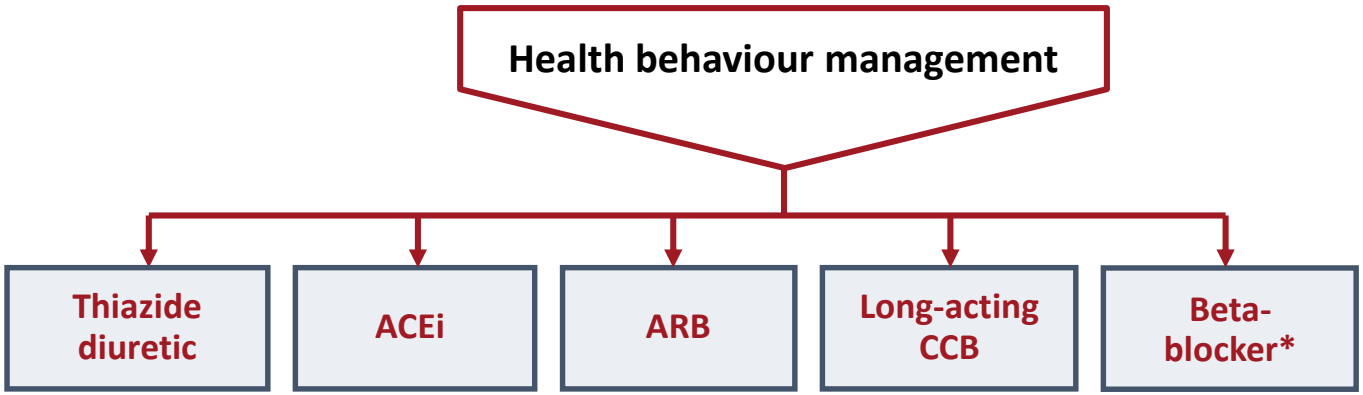
Today's focus:

- Longer acting (thiazide-like) diuretics are preferred vs. shorter acting (thiazide)
- Single pill combinations should be used as a first line treatment (regardless of the extent of BP elevation)

First Line Recommendations Circa 1999-2016

TARGET < 140 mmHg systolic AND < 90 mmHg diastolic



A combination of 2 first line drugs may be considered as initial therapy if the blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target

*Not indicated as first line therapy for patients over 60 yrs.

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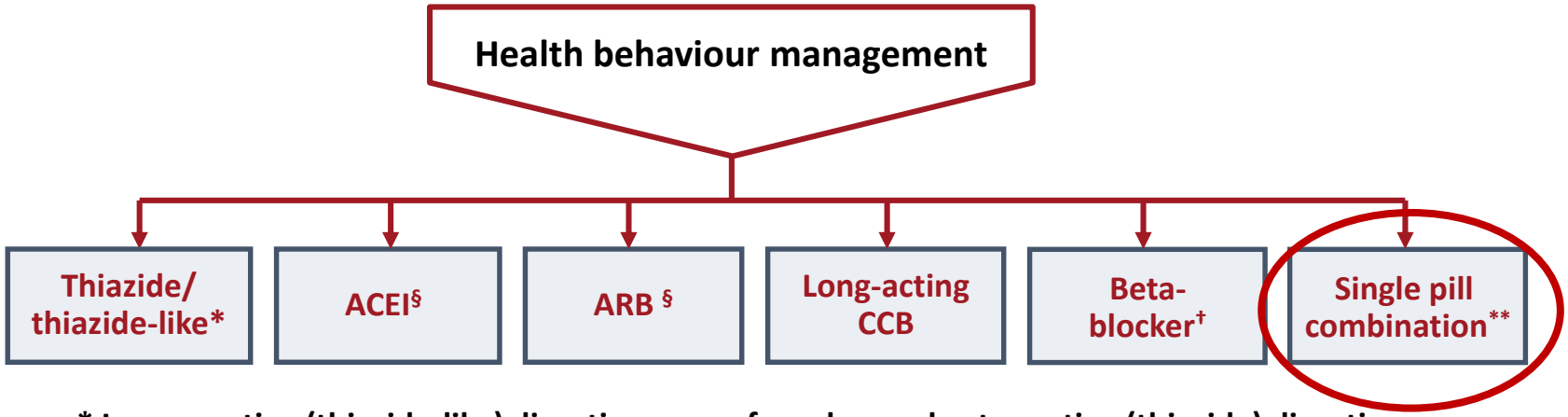
First Line Treatment of Adults with Systolic/Diastolic Hypertension Without Other Compelling Indications

New

TARGET <135/85 mmHg (automated measurement method)

INITIAL TREATMENT



*** Longer-acting (thiazide-like) diuretics are preferred over shorter-acting (thiazide) diuretics**

† BBs are not indicated as first line therapy for age 60 and above

§Renin angiotensin system (RAS) inhibitors are contraindicated in pregnancy and caution is required in prescribing to women of child bearing potential

****Recommended SPC choices are those in which an ACE-I is combined with a CCB, an ARB with a CCB, or an ACE-I or ARB with a diuretic**

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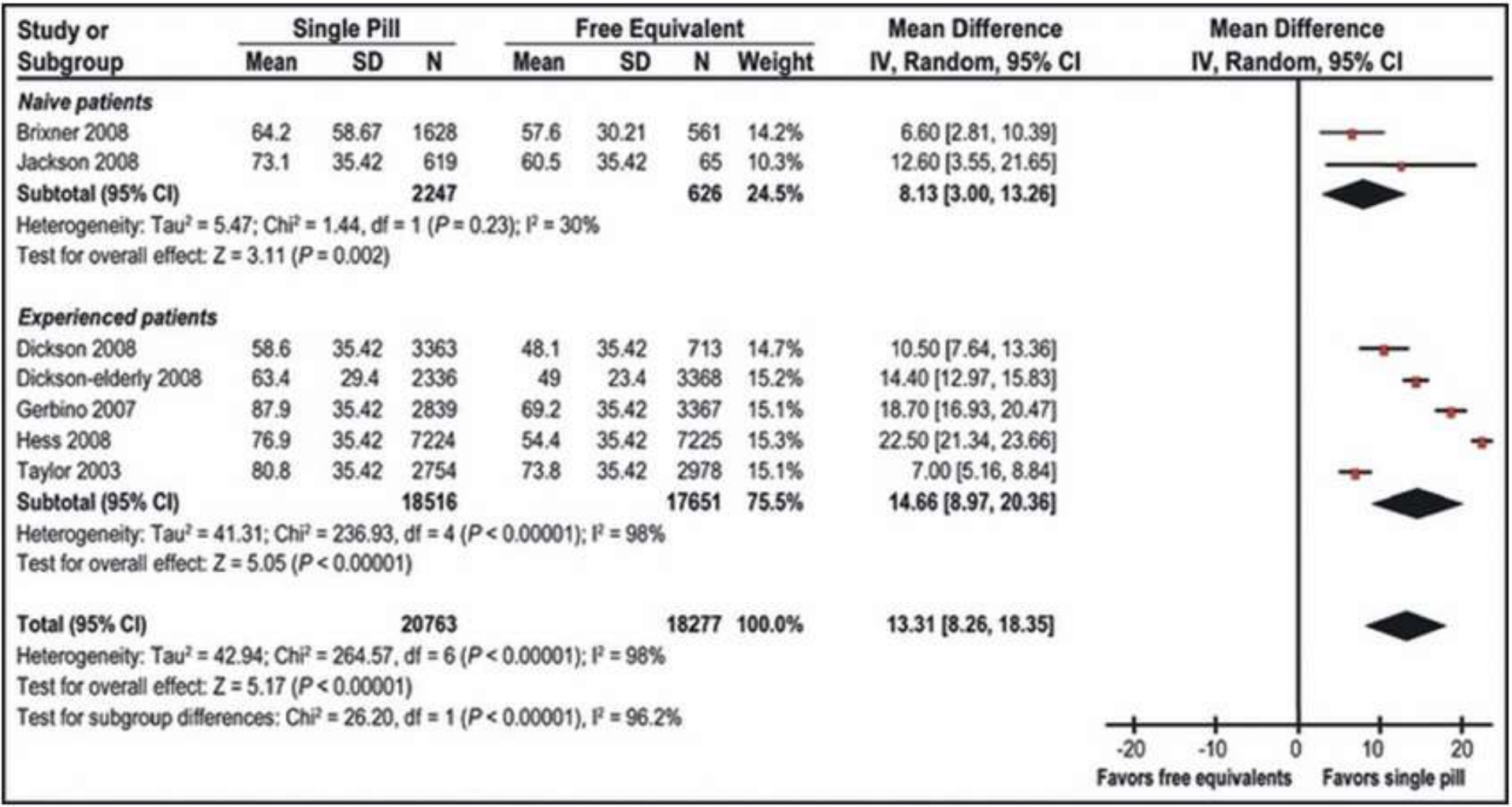
Advantages of Single Pill Combinations (SPCs)

- SPC therapy is associated with better adherence vs. free combinations[1]
- A regimen featuring initial prescription of SPC leads to better BP control[2]
- Initial combination therapy is associated with ↓ risk of CV events than monotherapy[3,4]

1. Sherrill B, et al. *J Clin Hypertens* 2011;13:898-909;
2. Feldman RD, et al. *Hypertension* 2009;53:646-53;
3. Corrao G, et al. *Hypertension* 2011;58:566-72;
4. Gradman AH, et al. *Hypertension* 2013;61(2):309-18.

Meta-analysis: SPCs and adherence

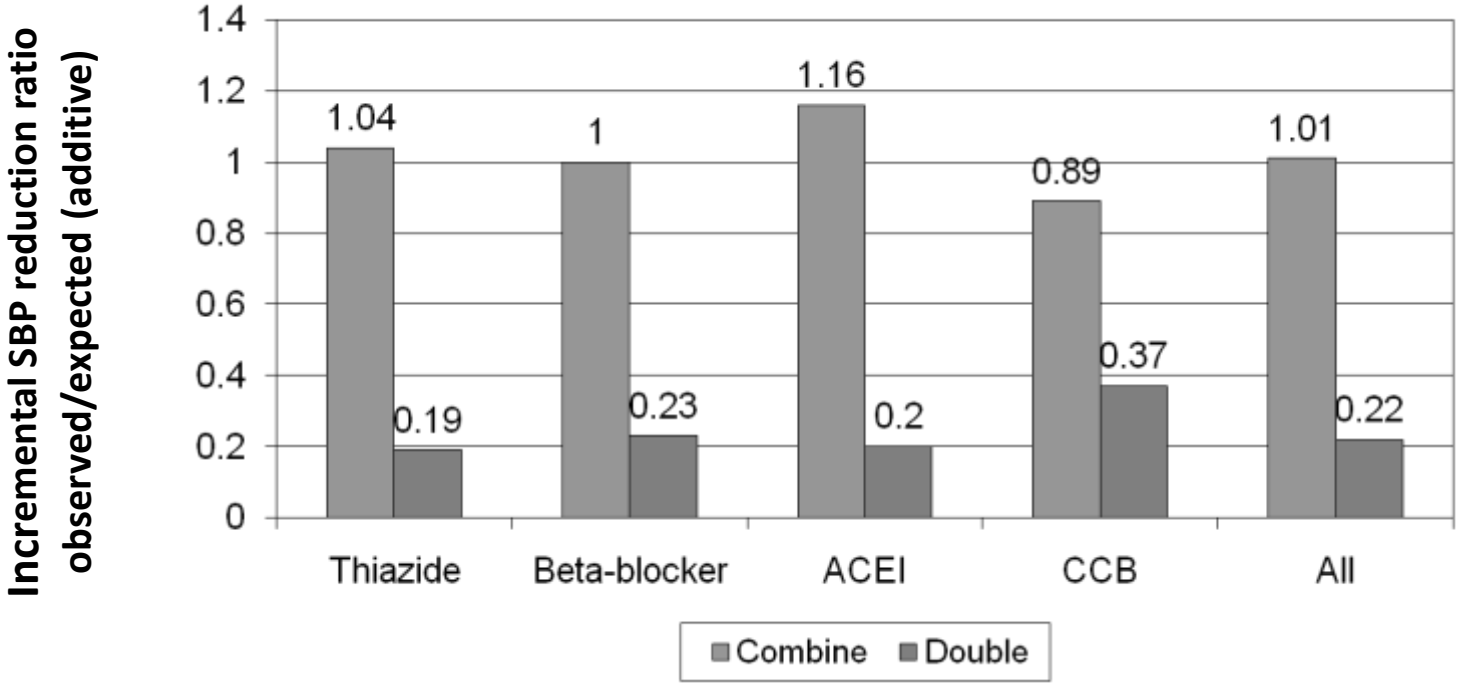


1. Sherrill B, et al. *J Clin Hypertens.* 2011;13(12):898-909.

Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials

David S. Wald, MD, Malcolm Law, FRCP, Joan K. Morris, PhD, Jonathan P. Bestwick, MSc, Nicholas J. Wald, FRS

- **Design:** Meta-analysis of 42 RCTs factorial design (n=10 968)
  - Comparing ΔSBP from <u>combining any 2 drug classes</u> (thiazides, beta-blockers, ACEIs, CCBs) vs. <u>doubling dose of 1 drug alone</u>



- BP reduction from combining 2 drugs is additive—and is 5 times greater than doubling the dose of 1 drug

Wald DS, et al. Am J Med. 2009 Mar;122(3):290-300.

A Simplified Approach to the Treatment of Uncomplicated Hypertension

A Cluster Randomized, Controlled Trial

Ross D. Feldman, Guang Y. Zou, Margaret K. Vandervoort, Cindy J. Wong, Sigrid A.E. Nelson, Brian G. Feagan

- **Design:** cluster randomized trial
- **Population:** 45 family practices in SW Ontario (n=2111 patients with uncontrolled hypertension)
- **Intervention:** STITCH care (i.e., initial treatment with fixed-dose combination ACEI/diuretic or ARB/diuretic; up-titration if needed +/- CCB) vs. CHEP 2007 CPG care (i.e., initial monotherapy; up-titration if needed)
- **1° outcome:** Proportion of patients achieving target control at 6 m higher with STITCH (64.7% vs. 52.7%; absolute diff., 12.0%; p = 0.03) with ↓ BP (absolute diff: 5.2/2.2 mmHg)

STITCH. Hypertension. 2009 Apr;53(4):646-53.

Cardiovascular Protection by Initial and Subsequent Combination of Antihypertensive Drugs in Daily Life Practice

Giovanni Corrao, Federica Nicotra, Andrea Parodi, Antonella Zambon, Franca Heiman, Luca Merlino, Ida Fortino, Giancarlo Cesana, Giuseppe Mancia

- **Design:** case-control study (1:3 matching for age, sex, and date of enrollment) nested in population-based cohort using administrative databases from Lombardy, Italy
- **Population:** 40 to 79-year old with **new** antihypertensive drug Rx with up to 8 years of follow-up
- **Exposure:** defined by index prescription, monotherapy vs. combination therapy
- **Cases:** anyone that was admitted for a CV event (identified by hospital discharge data)
- **Controls:** anyone in cohort still at risk of developing outcome

Corrao G, et al. Hypertension. 2011 Oct;58(4):566-72.

- **Cohort Characteristics:** pool of 209 650 people; mean age 59.9 years; 55.6% women; 82% with initial monotherapy; approx. 6 years of observation per patient
  - **Cases:** n=10 688
  - **Controls:** n=32 064
- **Results:** Initial combination therapy (vs. monotherapy) associated with ↓ CV events (-11%; 95% CI, 5-16%)

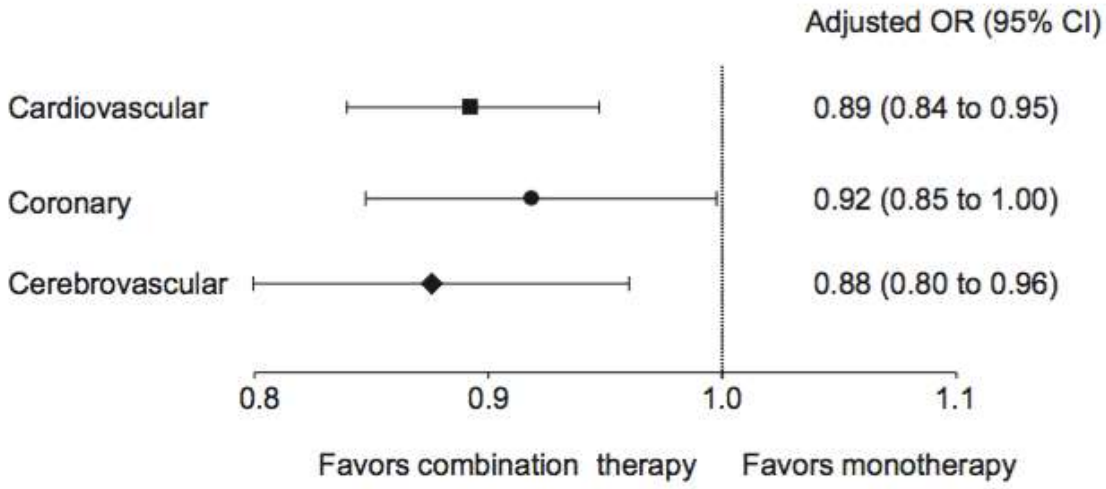
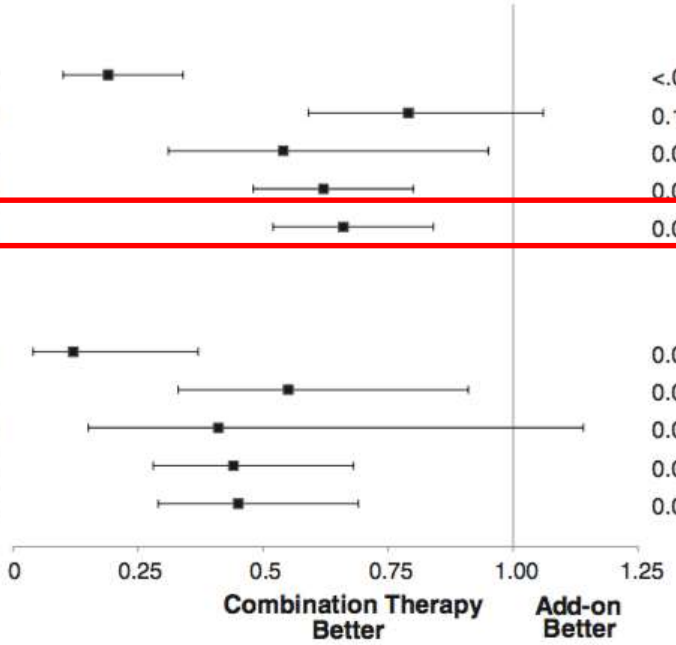


Figure 2. Forest plot comparing odds ratios (and corresponding 95% CIs) of nonfatal cardiovascular (CV) outcomes as a whole, coronary heart disease, or cerebrovascular events associated with an initial combination of blood pressure–lowering agents, with respect to initial monotherapy. Data show the estimates obtained by fitting a conditional logistic model and adjusted for the number of blood pressure–lowering drug classes used during follow-up and the concomitant use of drugs for the treatment of heart failure, coronary heart disease, diabetes mellitus, and other CV disease.

- **Cohort Characteristics:** balanced on all measured variables (age, sex, BP, etc.)
- **Results:** Initial combination therapy (vs. monotherapy) associated with ↓ incidence of CV events (RR, 0.66; p=0.0002), shorter median time to target BP (9.7 vs. 11.9 m; p=0.004), and ↓ rates of healthcare use (RR, 0.91; p<0.001)

	Incidence Rate* (Combination Therapy vs. Add-on)	IRR (95% CI)†	*P*-Value†
All Patients			
(1762 Patients in Each Cohort)			
Acute Myocardial Infarction	0.45 vs. 0.99	0.19 (0.10 - 0.34)	<.0001
Stroke/TIA	2.57 vs. 2.84	0.79 (0.59 - 1.06)	0.1172
Hospitalization for Heart Failure	0.55 vs. 0.78	0.54 (0.31 - 0.95)	0.0311
Overall	3.34 vs. 4.10	0.62 (0.48 - 0.80)	0.0002
Overall (With Death)	3.58 vs. 4.28	0.66 (0.52 - 0.84)	0.0008
Excluding Patients with Diabetes or CKD			
(803 Patients in Each Cohort)			
Acute Myocardial Infarction	0.24 vs. 0.68	0.12 (0.04 - 0.37)	0.0002
Stroke/TIA	1.89 vs. 2.58	0.55 (0.33 - 0.91)	0.0200
Hospitalization for Heart Failure	0.34 vs. 0.63	0.41 (0.15 - 1.14)	0.0875
Overall	2.39 vs. 3.55	0.44 (0.28 - 0.68)	0.0002
Overall (With Death)	2.49 vs. 3.68	0.45 (0.29 - 0.69)	0.0002



Thank you !