

## Hypertension Updates

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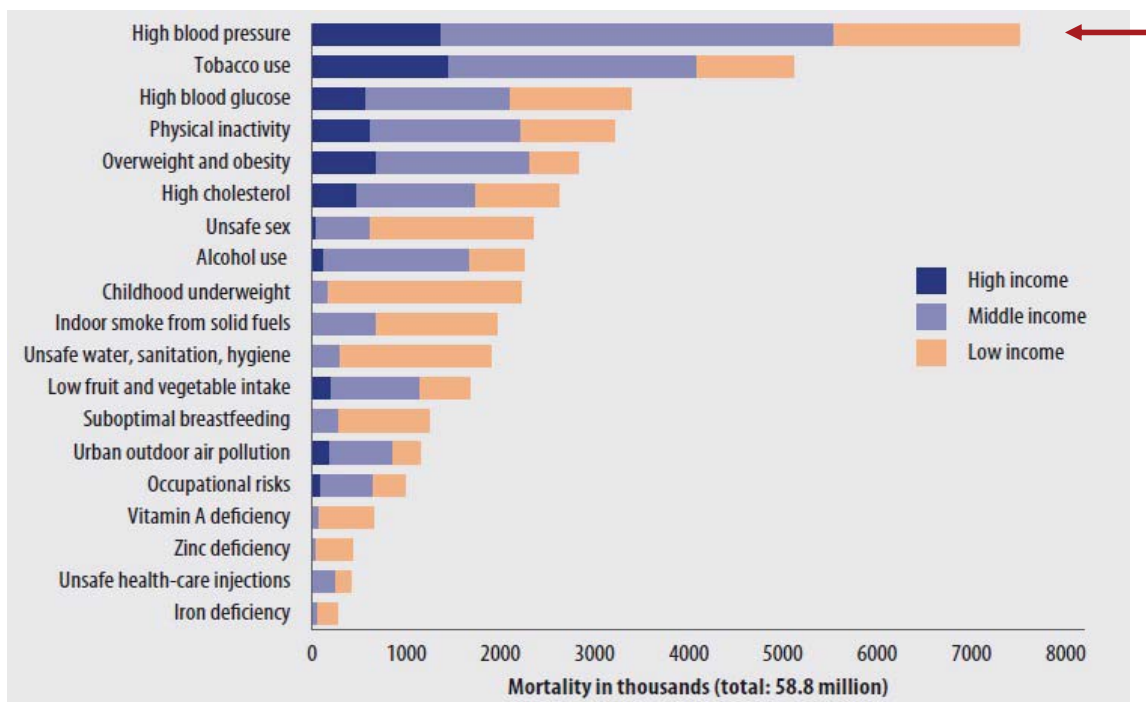


**52<sup>nd</sup> Annual Course in Drug Therapy**  
May 5, 2022

## Learning Objectives

- **Single pill combination** as a first line treatment
- Review the **SPRINT** recommendation
- Hypertension in **women** and in **men**

# Proportion of Deaths Attributable to Leading Risk Factors Worldwide



**\*SBP >115 mmHg**

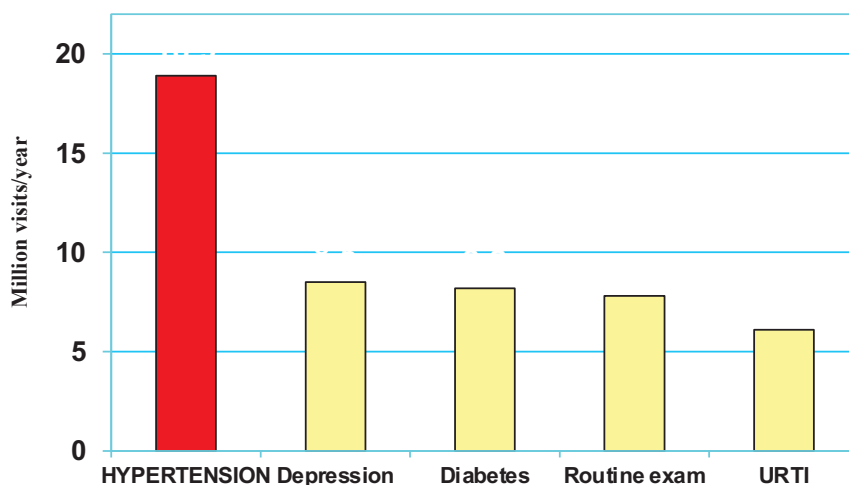
Ezzati M, et al. Lancet 2002;36034:1347-60

[http://www.who.int/healthinfo/global\\_burden\\_disease/GlobalHealthRisks](http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks)

# Visits to Physician Offices in Canada

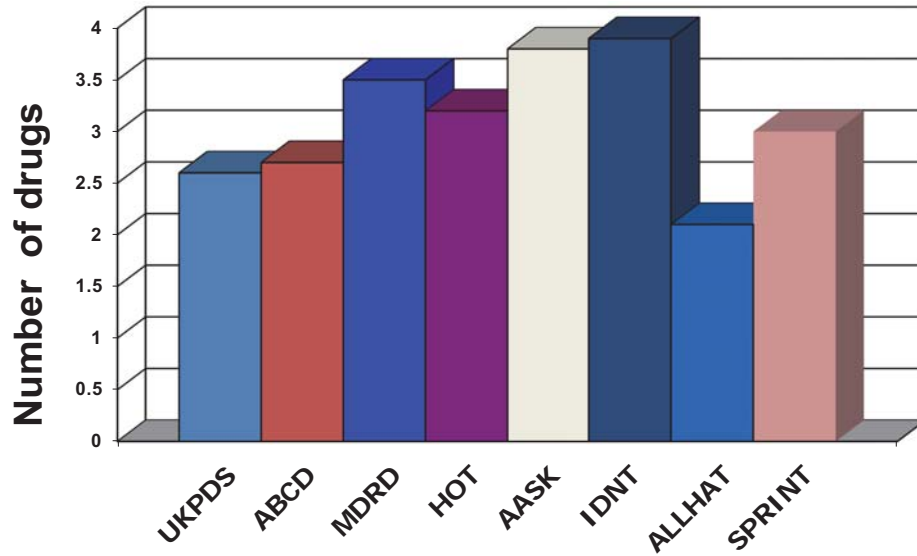


## Leading diagnoses



Source: IMS HEALTH Canada 2002. <http://www.imshealthcanada.com/>

# Most Pts with HTN need more than 1 drug



# Single Pill Combination as a First Line Treatment



# Single Pill Combination-based Treatment Leads To



- Improved adherence (and decreased medical resource utilization)

Taylor AA, Shoheiber O. *Congest Heart Fail.* 2003;9:324-32

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

- Improved BP control

Feldman RD, et al. *Hypertension.* 2009;53:646-53

Egan BM, et al *Hypertension* 2012;59:1124-31

- Faster BP control

Gradman AH, et al. *Hypertension* 2013;61:309-18

- Fewer adverse effects (synergy/dose dependent)

Law, M R et al. *BMJ* 2003;326:1427

- Reduced hypertension-related CV complications

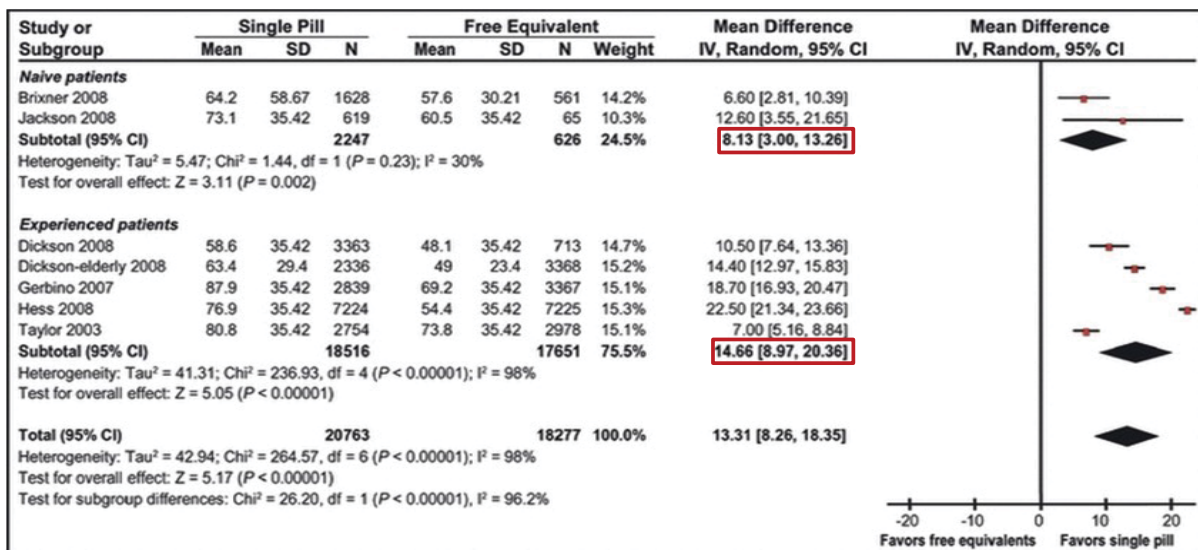
Corrao G, et al. *Hypertension.* 2011;58:566-72

Gradman AH, et al. *Hypertension* 2013;61:309-18

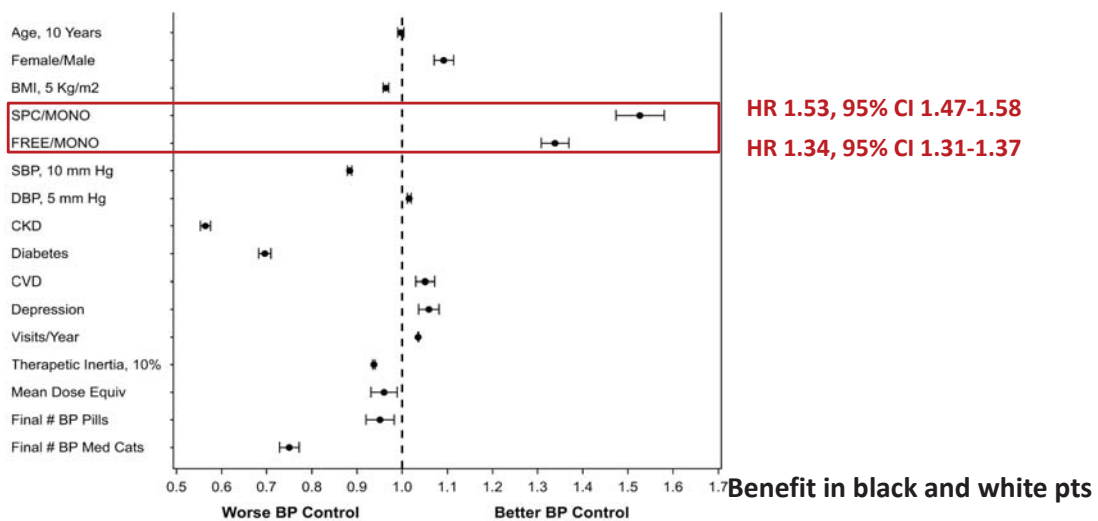
## Improved Adherence



### Meta-analysis: SPCs and Adherence



## BP Control in Previously Untreated Patients with HTN During the Initial Treatment Year



Benefit in black and white pts

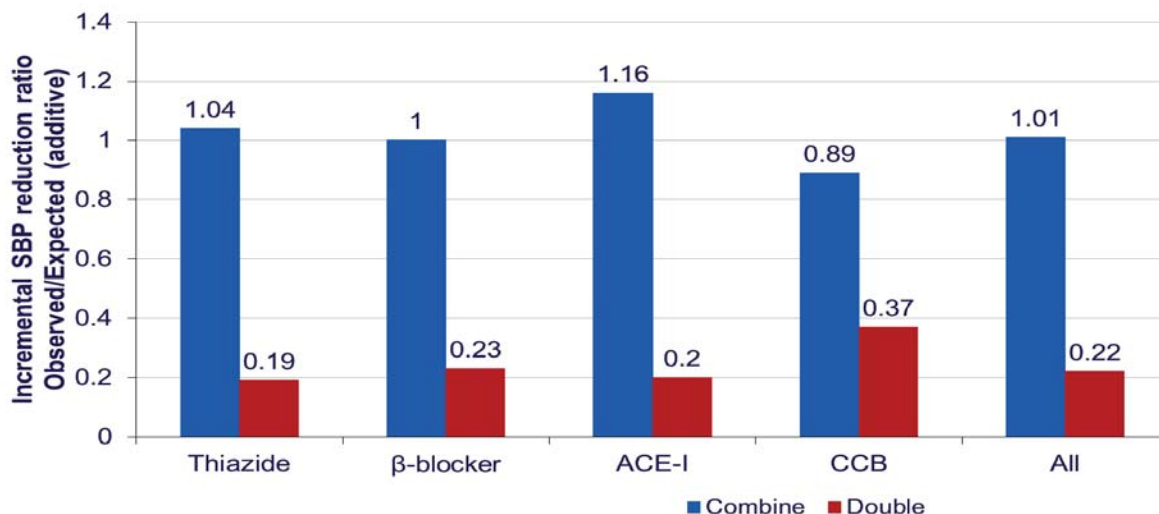
180 practice sites; 106,621 pts with HTN

Egan BM, et al Hypertension 2012;59:1124-31

## 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

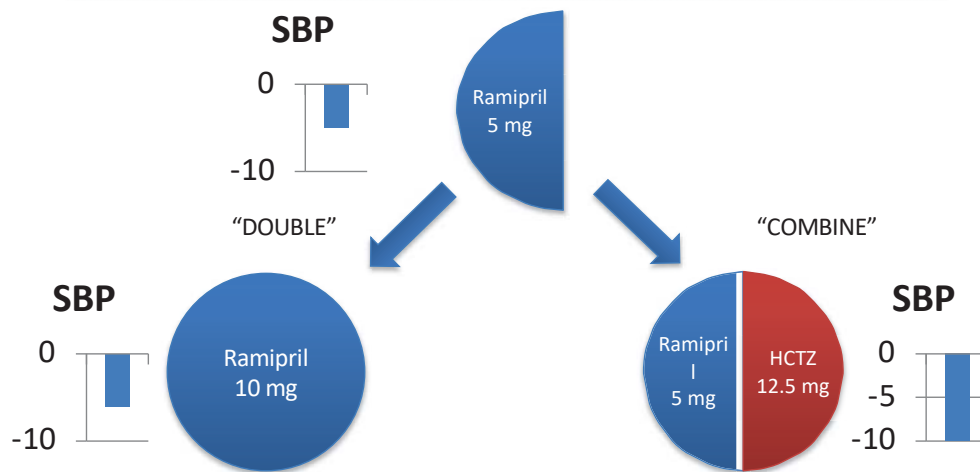
- Comparing  $\Delta$ SBP from combining any 2 drug classes (thiazides,  $\beta$ -blockers, ACEIs, CCBs) vs. doubling dose of 1 drug alone



- 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;122:290-300

## Options to Intensify HTN Pharmacotherapy

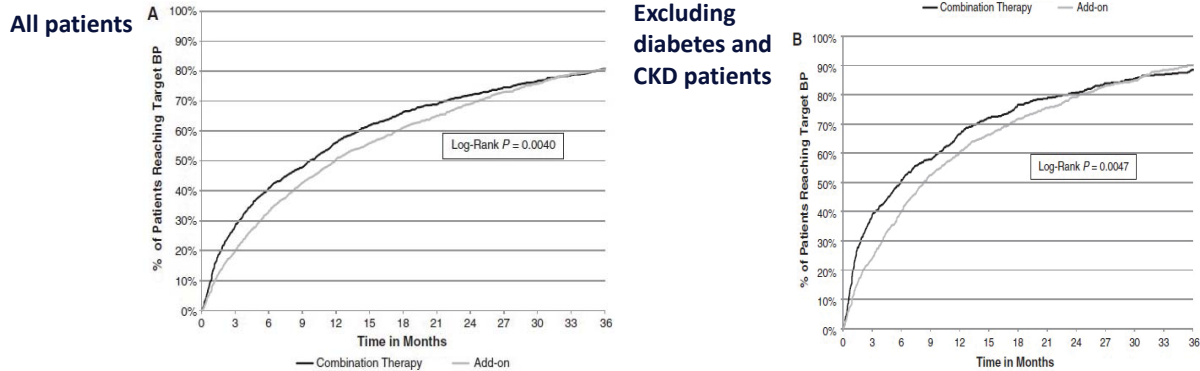


## Low Dose Combination Treatment & BP Lowering

- Dose response curves for efficacy are relatively **flat**
- **80%** of the BP-lowering efficacy is achieved at **half-standard dose**
- Combinations of low doses have **additive** BP-lowering effects and **reduce adverse effects**

## Combination Therapy in First-line was Associated with Faster BP Control

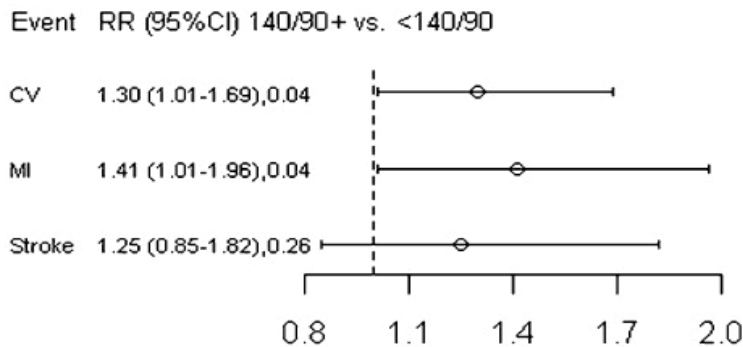
- Newly diagnosed patients initiated on combination therapy vs. standard care
  - Usage of combination therapy in first-line



Gradman AH, et al. Hypertension 2013;61:309-18

# Faster BP control is associated with better prognosis

1 year post HTN diagnosis, patients with BP  $\geq 140/90$  mmHg have more CV events, over 38 months of follow-up, compared to patients with BP  $< 140/90$  mmHg



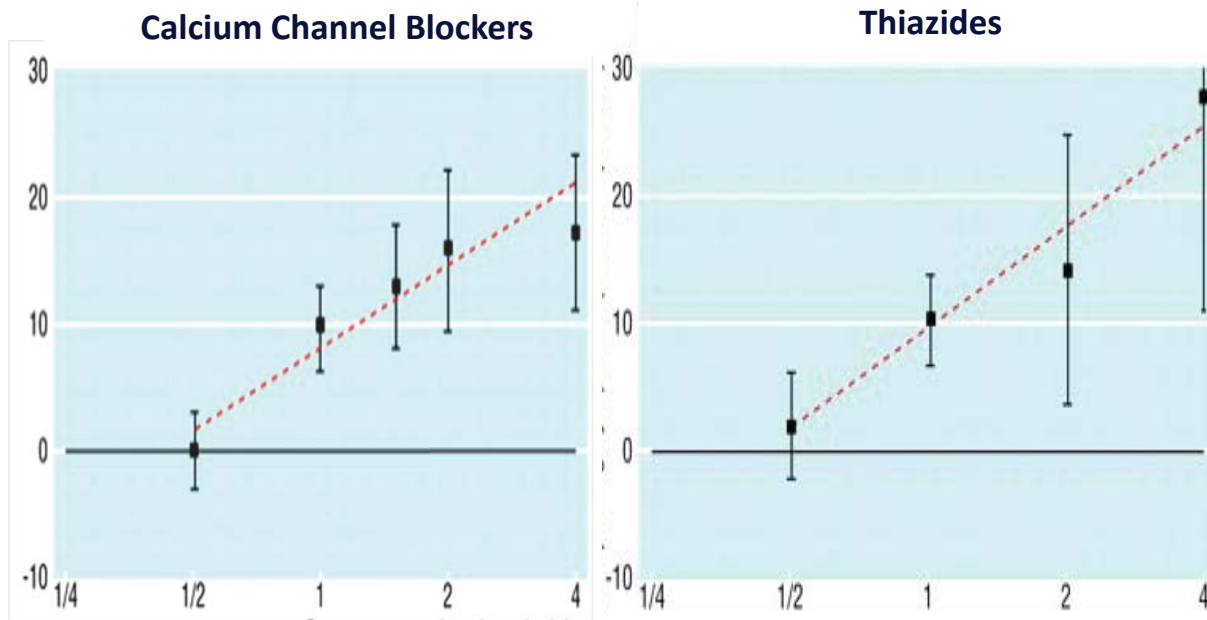
**Adequate BP control within the 1st year after HTN diagnosis is associated with less CV events over 3 years**



# Fewer Adverse Effects



**At low doses the adverse effects of most antihypertensives approach those of placebo**

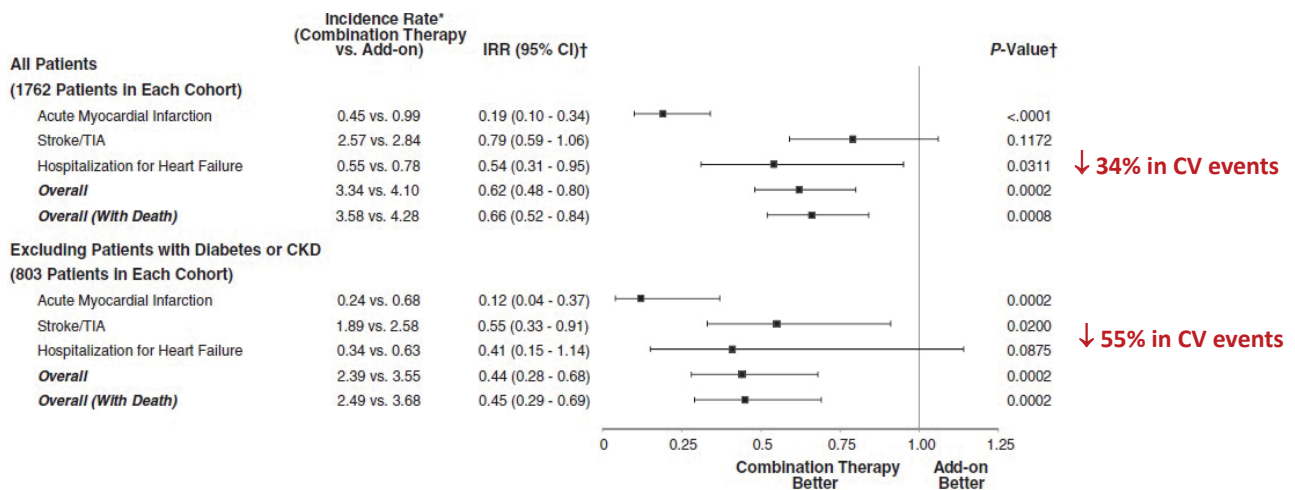


Law, MR et al. BMJ 2003;326:1427

# Reduced HTN-related CV complications



**Combination Therapy in First-line was Associated With CV Protection**



**Initial combination therapy was associated with a significant 34% reduction in CV events**

Gradman AH, et al. Hypertension 2013;61:309-18



- **Improved adherence (and decreased medical resource utilization)**

*Taylor AA, Shoheiber O. Congest Heart Fail. 2003;9:324-32*

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

- **Improved BP control**

*Feldman RD, et al. Hypertension. 2009;53:646-53*

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- **Faster BP control**

*Gradman AH, et al. Hypertension 2013;61:309-18*

- **Fewer adverse effects**

*Law, M R et al. BMJ 2003;326:1427*

- **Reduced hypertension-related CV complications**

*Corrao G, et al. Hypertension. 2011;58:566-72*

*Gradman AH, et al. Hypertension 2013;61:309-18*

- The 2019 WHO added single pill combination to the Essential Medicines List, considering treatment with SPC as the emerging best practice<sup>1</sup>
- The latest 2020 ISH guidelines endorsed the single pill combination as a preferred strategy for initial two-drug combination treatment of hypertension to improve efficiency, speed, and BP control rates<sup>2</sup>

1.WHO/MVP/EMP/IAU/2019.05

2.Unger T et al. J Hypertens. 2020;38(6):982–1004

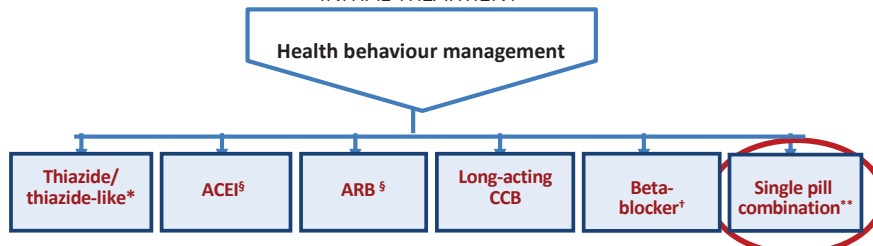


## First-line Treatment of Adults with Systolic/Diastolic Hypertension Without Other Compelling Indications

2017

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

## Review the SPRINT Recommendation





## A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group\*

This trial looked at the effect of **intensive SBP control (<120 mmHg) vs standard control (<140 mmHg)** in 9361 hypertensive patients without DM or previous stroke followed for a mean of 3.26 years in the US (study stopped prematurely)

### Major Inclusion Criteria

- ≥50 years old
- SBP 130 to 180 mmHg (depending on treatment)
- Additional CVD risk
  - Clinical or subclinical CVD
  - CKD (eGFR 20 to <60 ml/min/1.73m<sup>2</sup>)
  - Framingham risk score for 10-year CVD risk ≥ 15%
  - Age ≥ 75 years old

### Major Exclusion Criteria

- Stroke
- Diabetes
- Polycystic kidney disease
- Heart Failure (symptoms or EF < 35%)
- Proteinuria > 1g/d
- CKD with eGFR <20 ml/min/1.73m<sup>2</sup>
- Adherence concerns

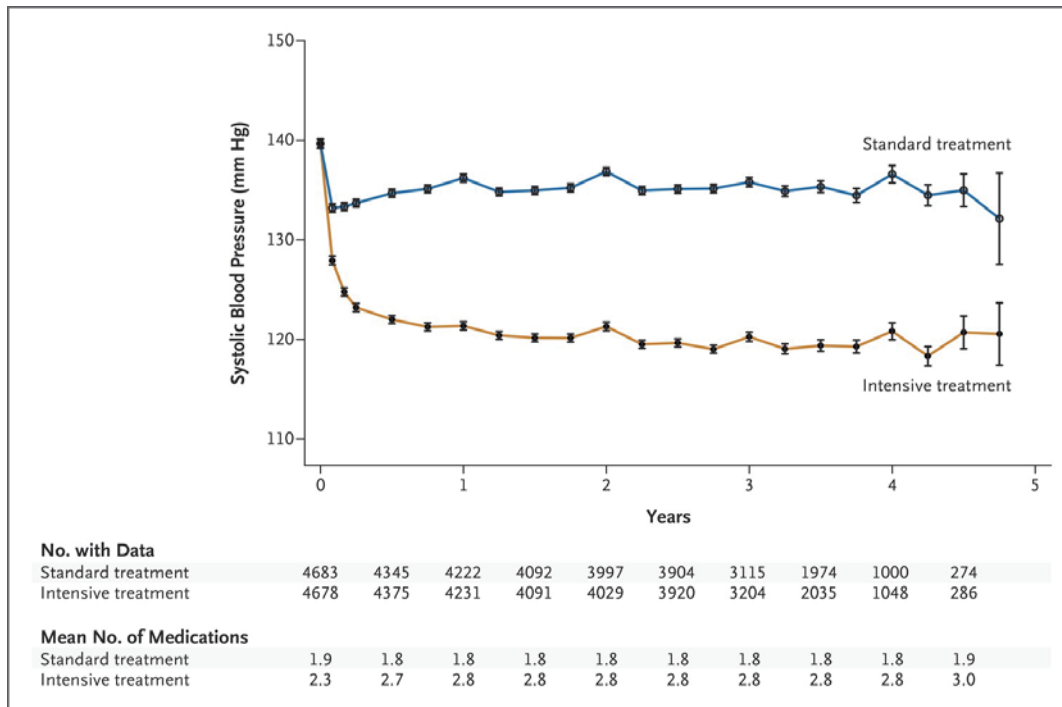
SPRINT Research Group. N Engl J Med. 2015;373:2103-16

## SPRINT Trial Design



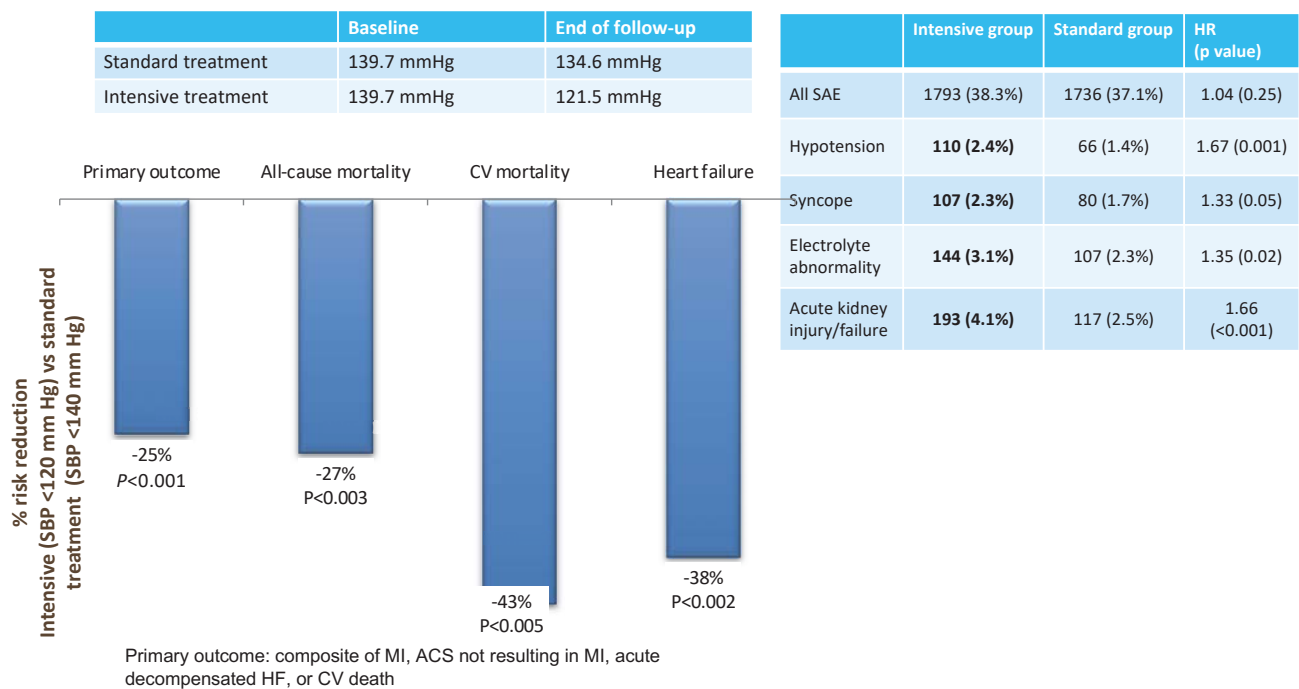
- Patients (n=9361), age ≥50 years, with SBP ≥130 mm Hg and ↑CV risk (but without diabetes) assigned to:
  - SBP target <120 mm Hg (**intensive** treatment),
  - or
  - SBP target <140 mm Hg (**standard** treatment)
- Primary composite outcome: MI, other acute coronary syndromes, stroke, HF, or death from CV causes

# SBP in the 2 Treatment Arms



SPRINT Research Group. N Engl J Med. 2015;373:2103-16

# SPRINT Results



SPRINT Research Group. N Engl J Med. 2015;373:2103-16

- To attain the BP goal in the intensive group, patients were on average on **3 antihypertensive medications**
- Intensive BP control led to
  - **25% reduction in primary endpoint** (HR 0.75, 0.64-0.89) – **NNT 61**
  - **27% reduction in all-cause mortality** (HR 0.73, 0.60-0.90) – **NNT 90**
- **No overall difference in serious adverse events (SAEs)** between treatment groups but SAEs associated with **hypotension, syncope, electrolyte abnormalities** and **acute kidney injury/failure** were more common in the intensive group
- **Overall, benefits of more intensive BP control exceeded the potential harm**

SPRINT Research Group. N Engl J Med. 2015;373:2103-16

## Implications of SPRINT in the *Long Run*

Given the benefit of more intensive treatment, there is an even greater need for tailoring Rx regimes to minimize **clinical inertia** and **nonadherence**

2016

For high-risk patients, aged  $\geq 50$  years, with SBP levels  $\geq 130$  mm Hg, intensive management to target a SBP  $\leq 120$  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

Leung AA, Nerenberg K, Daskalopoulou SS, et al; CHEP Guidelines Task Force. Can J Cardiol. 2016;32:569-88

## BP Pharmacologic Treatment Thresholds & Targets in Subjects with HTN

Population	BP Thresholds (SBP/DBP, mmHg)	BP Targets (SBP/DBP, mmHg)
High-risk (SPRINT population) <sup>#</sup>	$\geq 130/NA$	$\leq 120/NA$
Diabetes mellitus	$\geq 130/80$	$< 130/80$
Moderate-risk <sup>*</sup>	$\geq 140/90$	$< 140/90$
Low-risk (no TOD or CV risk factors)	$\geq 160/100$	$< 140/90$
All others	$\geq 140/90$	$< 140/90$

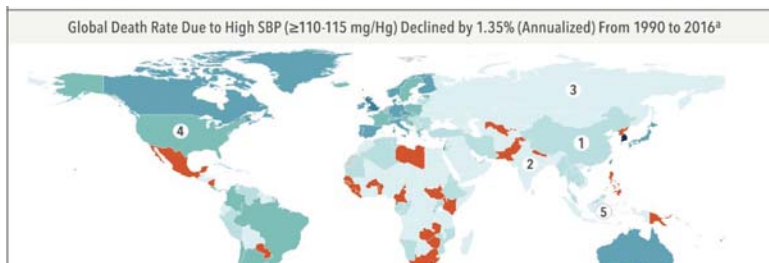
<sup>#</sup> Based on AOBP

<sup>\*</sup>AOBP threshold  $\geq 135/85$  mmHg

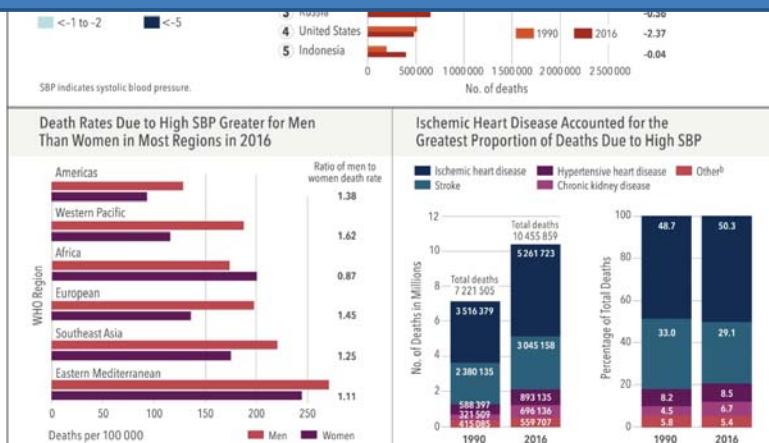
# HTN in Women and in Men



# Global Deaths Attributable to High SBP, 1990-2016



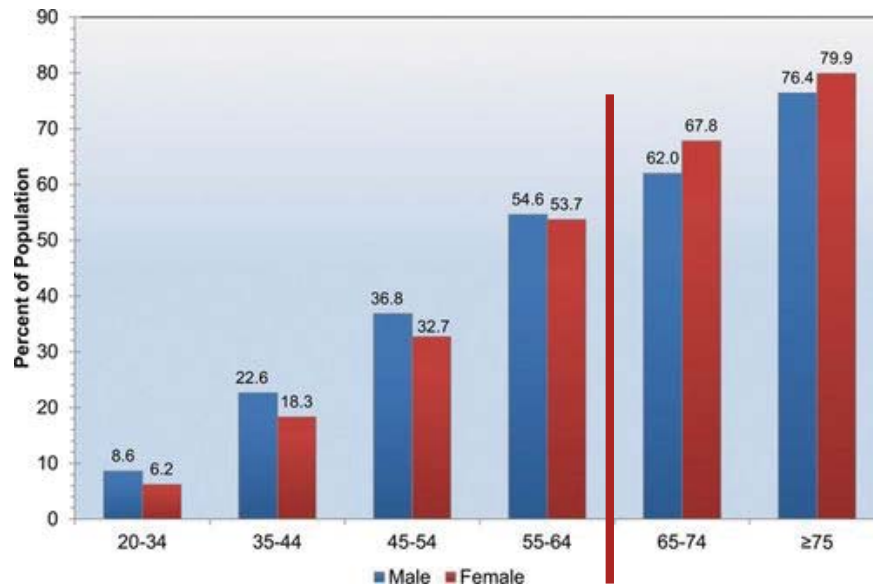
# HTN accounts for about 1 in 5 deaths of women



\*Death rates are age-standardized per 100,000 population for adults 25 years or older. <sup>a</sup>Aortic aneurysm, atrial fibrillation and flutter, cardiomyopathy and myocarditis, endocarditis, peripheral artery disease, rheumatic heart disease, and other cardiovascular and circulatory diseases. WHO, World Health Organization.



# Prevalence of Hypertension in Adults by Age & Sex



- Men have a higher prevalence of HTN compared to women of the same age until the **sixth decade of life**
- Age-adjusted prevalence of HTN (both diagnosed and undiagnosed) is **75%** for older (≥65 y) women and **65%** for older men

Mozaffarian D, et al. Circulation. Heart Disease and Stroke Statistics—Update, 2016;133:e38-e360

# Worsening Hypertension Awareness, Treatment, and Control Rates in Canadian Women (2007-2017)

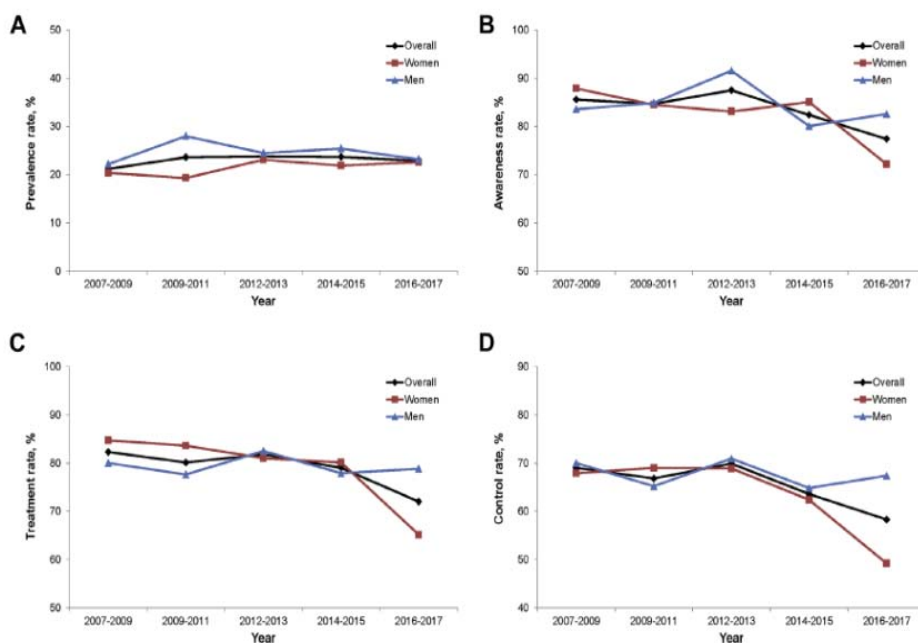
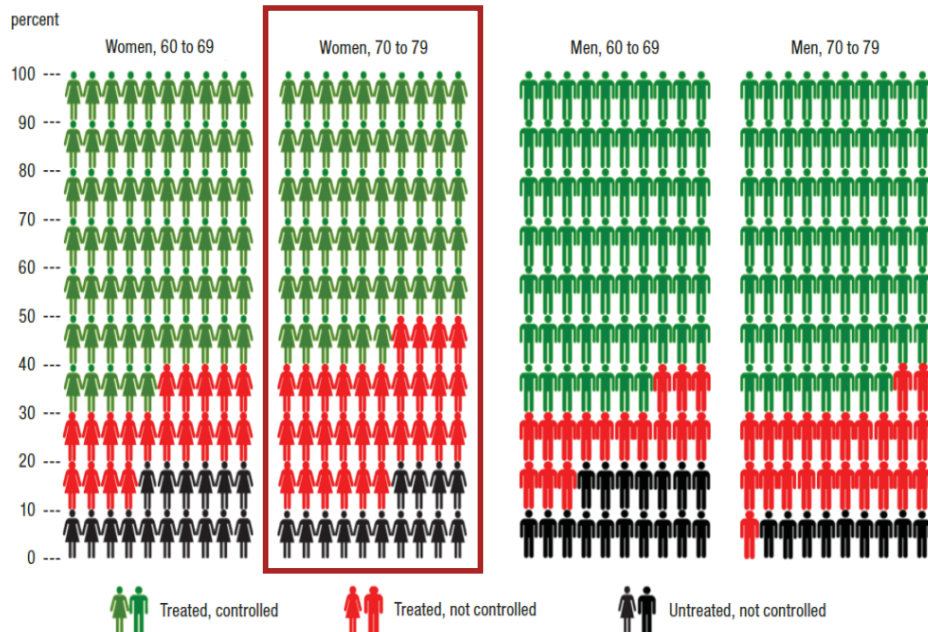


Figure 1. Canadian (A) prevalence, (B) awareness, (C) treatment, and (D) control rates overall and by gender.

# Lowest Prevalence of Hypertension Treatment and Control in Women Aged 70-79



Source: 2007 to 2009, 2009 to 2011, 2012 to 2013, and 2014 to 2015 Canadian Health Measures Survey, combined.

Bushnik T, et al. Health Rep 2018;29:3-10

## Hypertension in Women and Men



### HTN is a greater burden for women than men

- More women than men with HTN develop adverse pathophysiologic consequences, including:
  - LVH
  - diastolic dysfunction
  - HF (HFpEF)
  - increased arterial stiffness
  - diabetes
  - CKD
- For each 10 mmHg increase in SBP, the effect size for increased risk of CVD is **25% for women** and **15% for men** (meta-analysis)

Wenger NK, et al. J Am Coll Cardiol 2018;71:1797-813

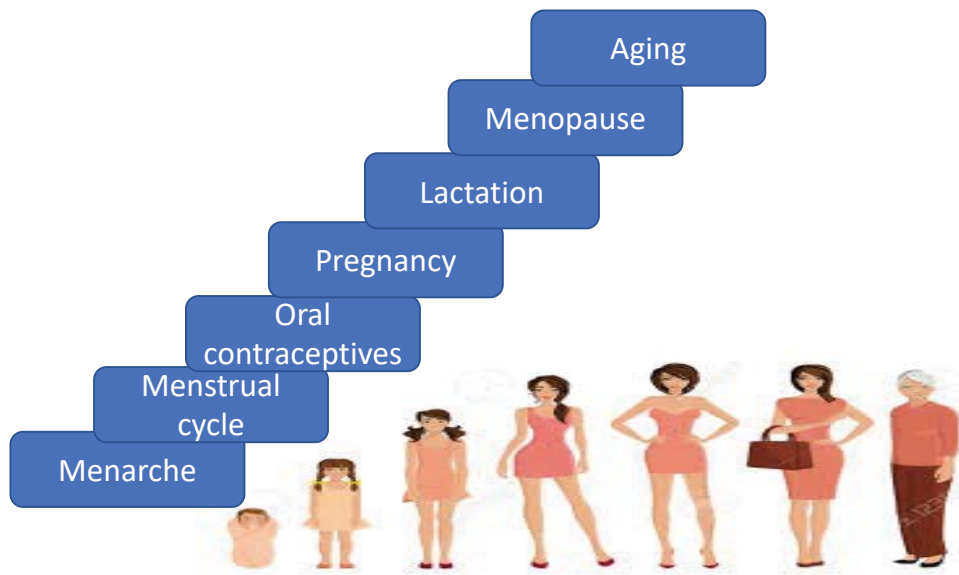
Wei YC, et al. PLoS One 2017;12:e0170218

- **Common risk factors**

- Excess weight
  - 20-30% of HTN is related to overweight/obesity, with 2-6-fold increase in HTN prevalence when overweight
- Physical inactivity
- Increased salt intake
- Diabetes
- Alcohol abuse
- OSA

- **Sex-specific processes**

Wenger NK, et al. J Am Coll Cardiol 2018;71:1797-813

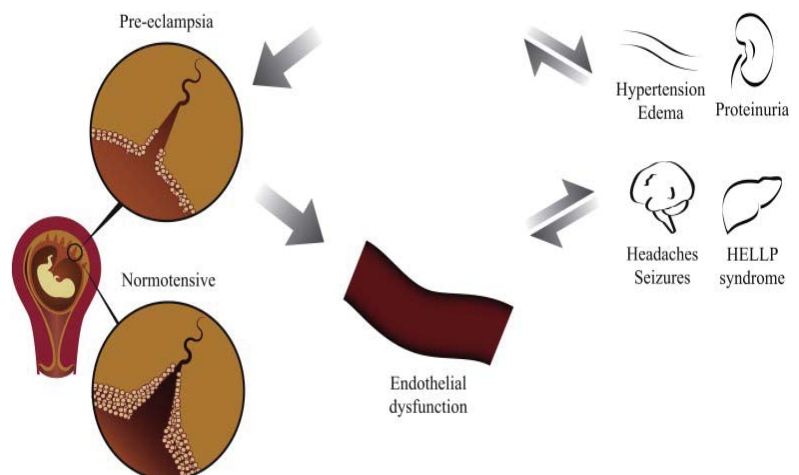


## Hypertension in Pregnancy



Genetic factors	Ischemia	Inflammation and Infection	Immunological factors
Oxidative stress	Angiogenic factors	RAS activation	Other factors?

Hypertensive disorders of pregnancy represent a spectrum ranging in severity from **gestational HTN**, to **PrE**, to **severe PrE** (i.e., eclampsia) and **HELLP syndrome**



# Hypertension in Pregnancy



- Women with a Hx of PrE have a **3.7-fold** increased risk (2.7-5.1) of **chronic HTN** (and 1.8-fold increased risk of DMT2; 1.3-2.6) within 10 y postpartum – up to **1/3** of women with HDP

## PrE: risk factor or consequence ('metabolic stress test')?

- PrE is associated with an increased risk of **premature CVD** - with a RR of **2.0** (1.8-2.2) for mild PrE and up to **9.5** (4.5-20.3) for severe PrE

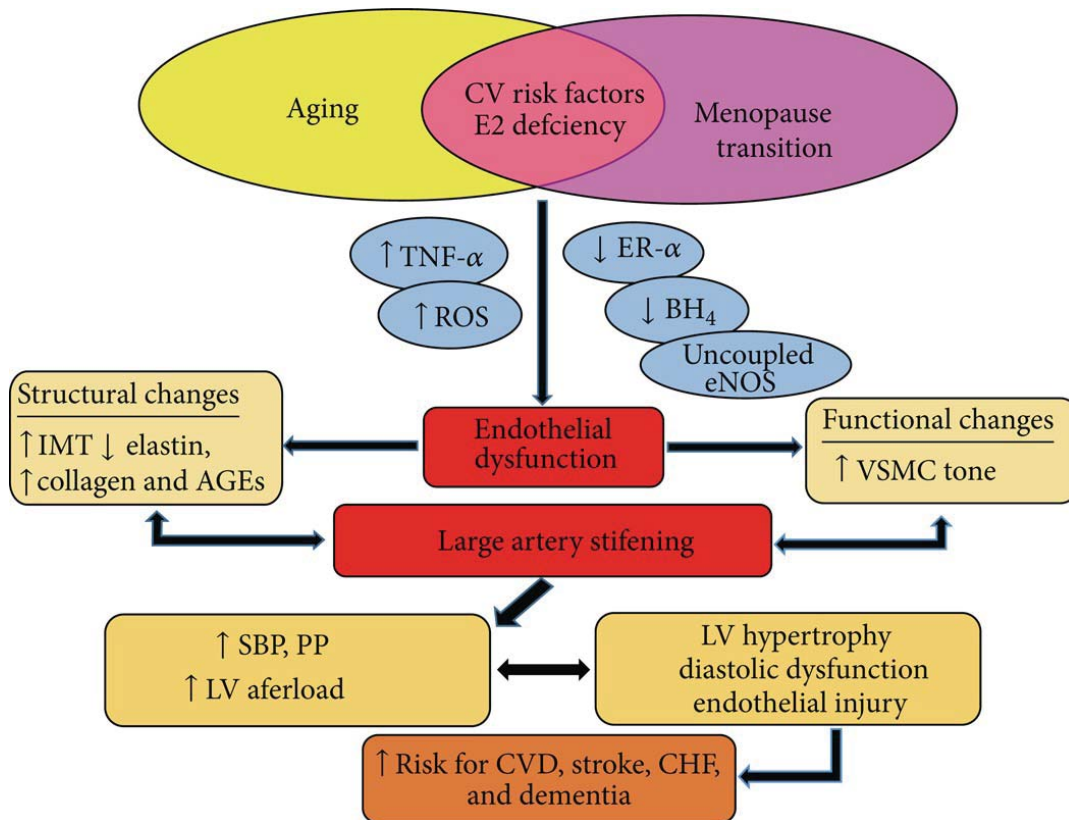
Bellamy L, et al. BMJ 2007;335:974; Lykke JA, et al. Hypertension 2009;53:944-51

McDonald SD, et al. Am Heart J 2008;156:918-30; Mongraw-Chaffin ML, et al. Hypertension 2010;56:166-71

# Hypertension in Pregnancy



**American Heart Association** in its “Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women--2011 Update,”—for the first time—included a history of pregnancy complications (gestational diabetes and HDP) in assessing vascular disease risk in women



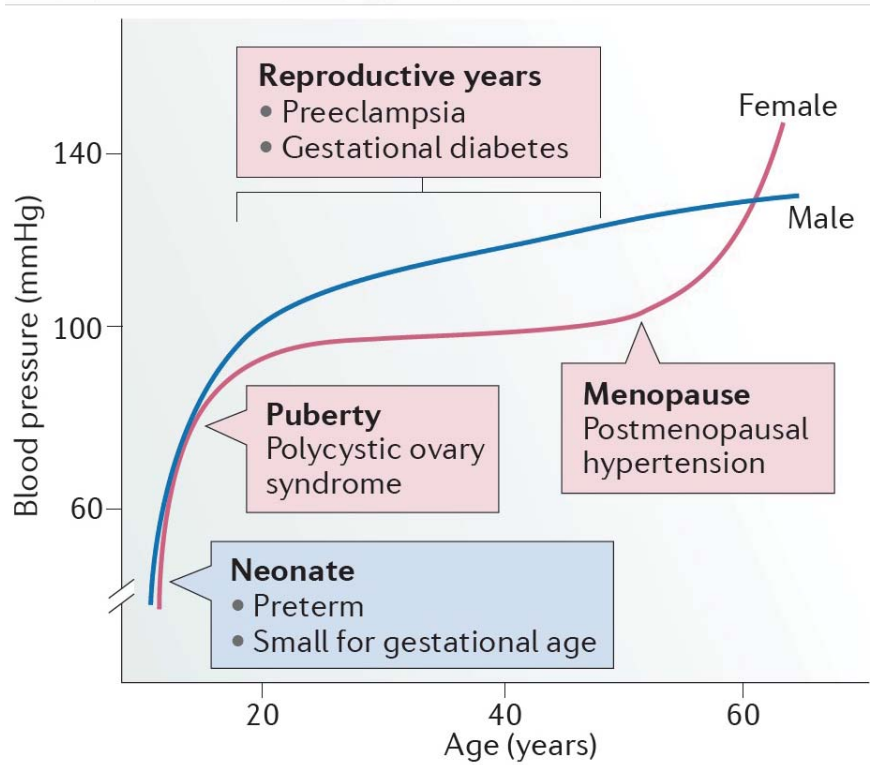
Moreau KL, Hildreth KL. Adv Vasc Med. 2014;2014:204390

## Hypertension in Elderly Women



- Elderly women have more severe HTN and lower BP control rates vs middle-aged and young women
- Potentially due to biological factors, inadequate treatment intensity (physician inertia or adherence), or inappropriate drug choices

# Blood Pressure Across Lifespan in Men and Women



Colafella KMM, Denton KM. Nat Rev Nephrol 2018;14:185-201

# Treatment & Outcomes of HTN in Women & Men





- Women **underrepresented** – at best up to 40%
  - SPRINT ~36%
- **No direct comparison** of treatment efficacy in women vs men
  - Extrapolation
  - Subgroup analysis
  - Adjustment

- In general, **no major differences in treatment efficacy** in women vs men
- Absolute risk reduction: in women the benefit is seen primarily for **strokes**, whereas in men treatment prevented **all CV events**

Women have more drug-related **adverse events**:

- ACEi-induced cough
- CCB-related peripheral edema
- diuretic-associated hyponatremia or hypokalemia

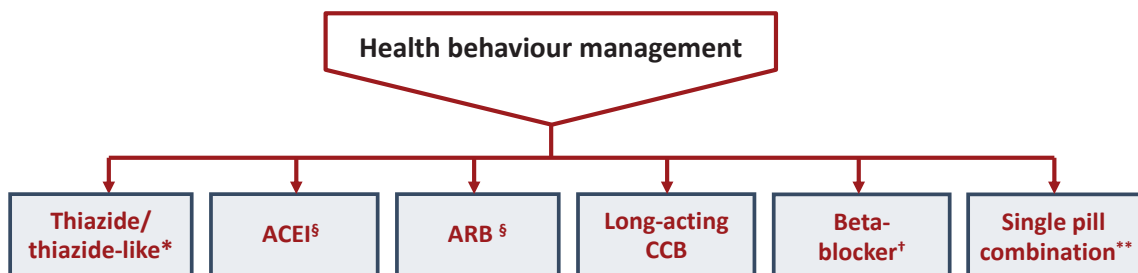
- Sex differences in distribution volumes
  - Hydrophilic vs. lipophilic drugs
- Sex differences in drug clearance
- Sex differences in CYP enzyme activity
  - Men have more active CYP1A2, CYP2D6 and CYP 2E1
  - Women have more active CYP 3A4 (CCB, statins)



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

TARGET <135/85 mmHg (AOBP) or < 140/9085 mmHg (OBPM)

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

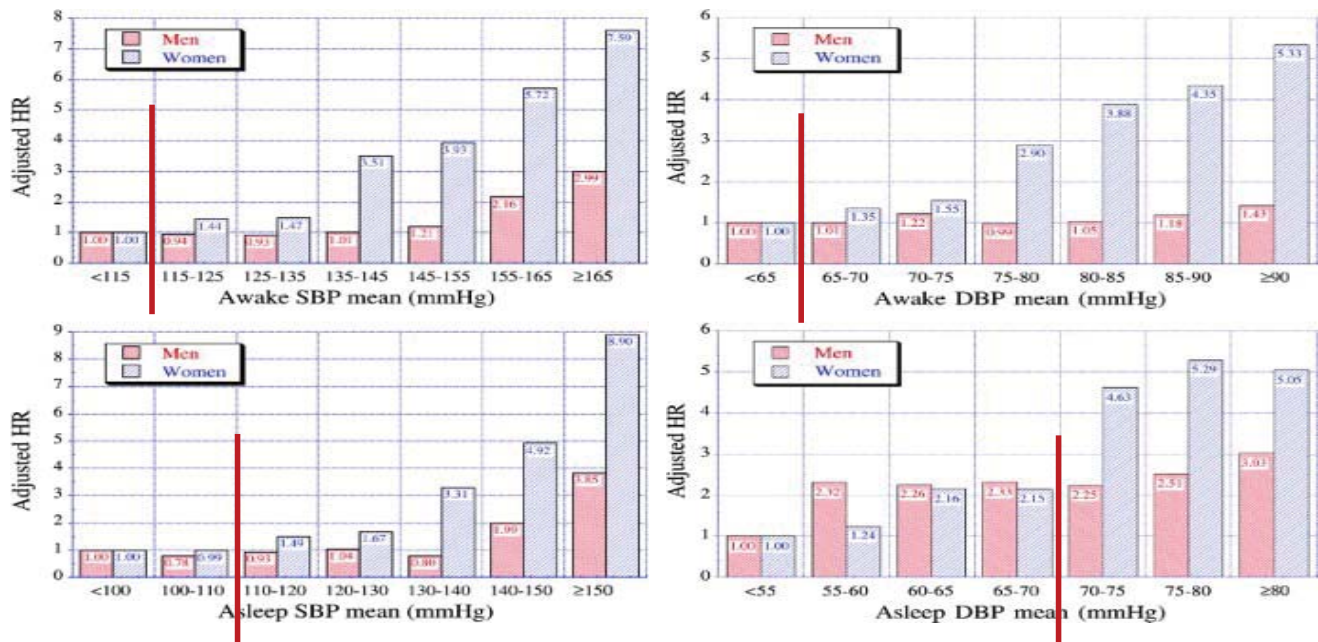
- Lack of strong and direct evidence to support recommendations to treat women and men with HTN differently
- **Global individual CV risk**, rather than sex, could be the strongest predictor for future CV events and should guide treatment of HTN
- Level of **achieved BP** might be more important than the medication used

Ljungman C, et al. J Womens Health 2009;18:1049-62

## Do Women and Men have the Same BP Thresholds?



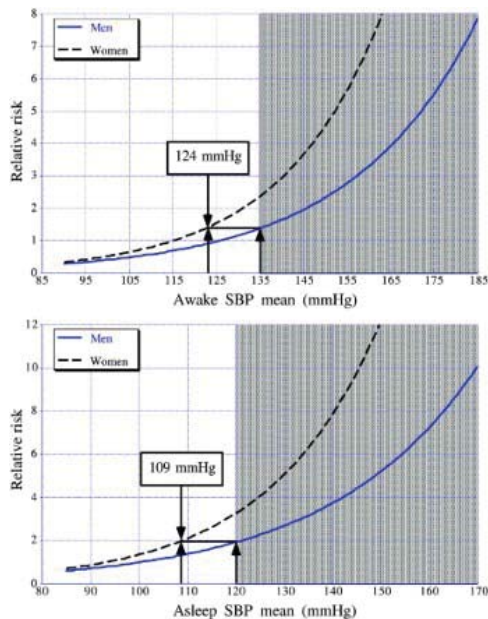
# BP Thresholds Might be Lower in Women



Adjusted HRs of total CVD events in men and women as a function of awake (top) and asleep (bottom) SBP and DBP means

Hermida RC, et al. Chronobiol Int 2013; 30:221-32

# BP Thresholds Might be Lower in Women



Diagnostic threshold for ABPM based on CVD outcomes in men and women

ABPM	Men	Women
Awake mean		
SBP	135	125
DBP	85	80
Asleep mean		
SBP	120	110
DBP	70	65

Outcome-based reference thresholds for the diagnosis of hypertension are **10/5 mmHg lower** for ambulatory SBP/DBP in women than men

Hermida RC, et al. Chronobiol Int 2013; 30:221-32

# Conclusions – Take Home Message



- Single pill combination is a first-line option with several benefits
- The systolic BP threshold and target for the “SPRINT” patient are lower, 130 and 120 mmHg, respectively
- HTN is a major risk factor for women, esp after the 6<sup>th</sup> decade
- HTN awareness, treatment, and control have declined in recent years particularly in older women in Canada
- Hormonal changes across the lifespan affect BP
- No clear indication for specific antihypertensive medications in women, possibly due to the lack of sex-specific studies
- Sex-specific HTN guidelines are needed

**Thank you!**



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