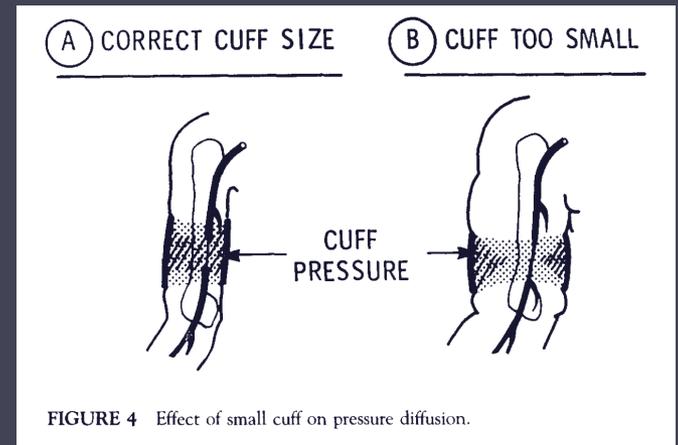


Management of Hypertension in Obesity



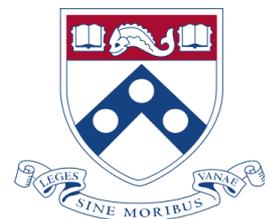
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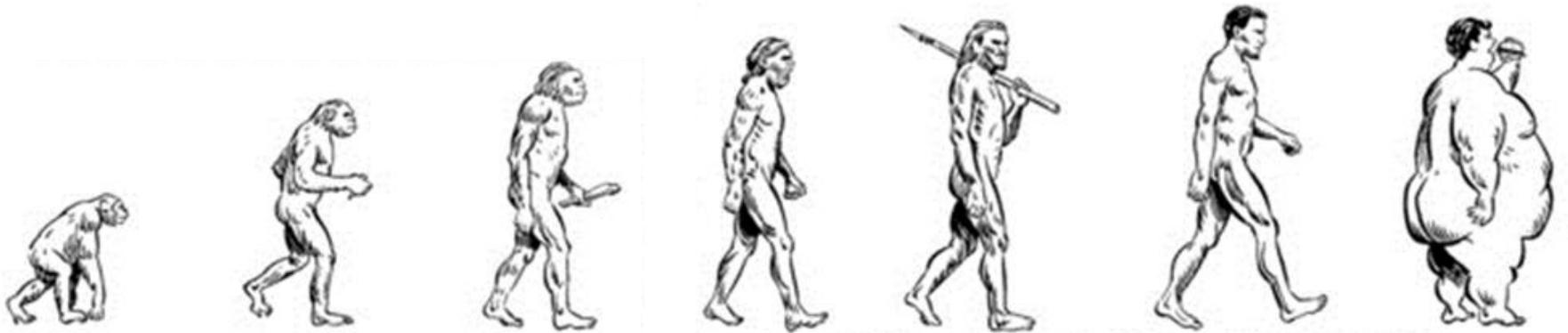
Disclosures

- Dr. Jordy Cohen has no financial conflicts of interest to disclose relevant to this activity.
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- **Off-Label Use:** My presentation does not include discussion of off-label or investigational use

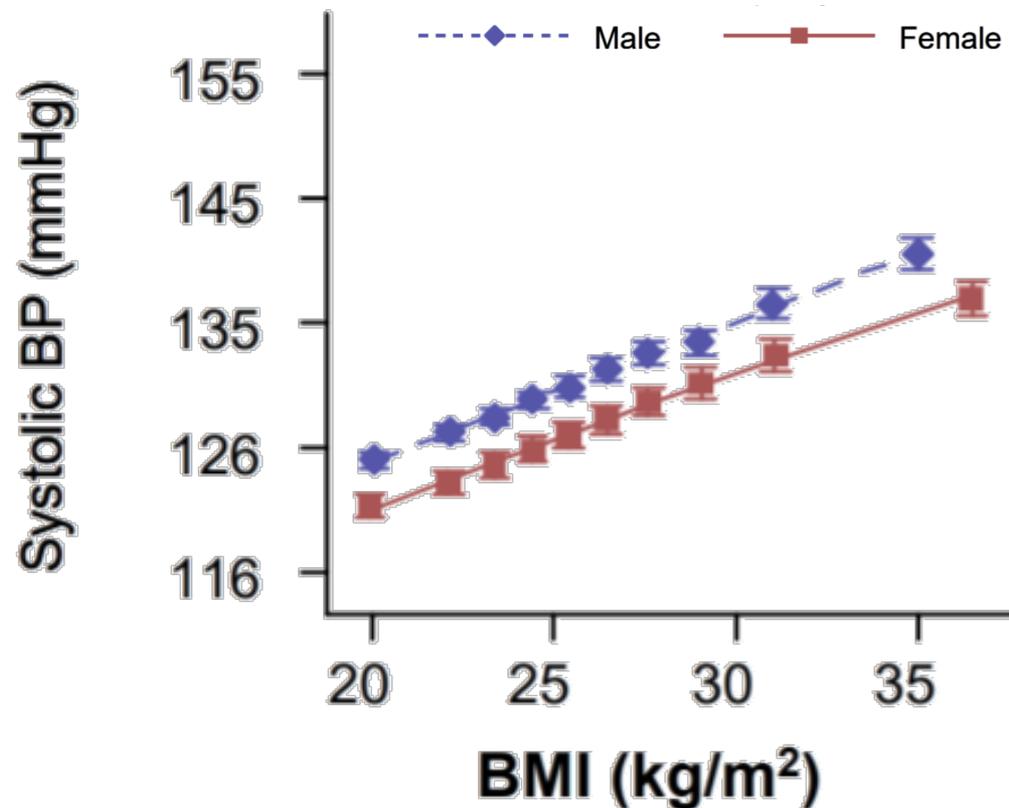
Learning Objectives

- Review the epidemiology of hypertension in obesity
- Discuss the challenges in the measurement of hypertension in obesity
- Identify distinctive pathophysiology of hypertension in obesity
- Review challenges in the management of hypertension in obesity
- Suggest an approach to hypertension in obesity

- Obesity is a critical public health issue in the US and other developed countries

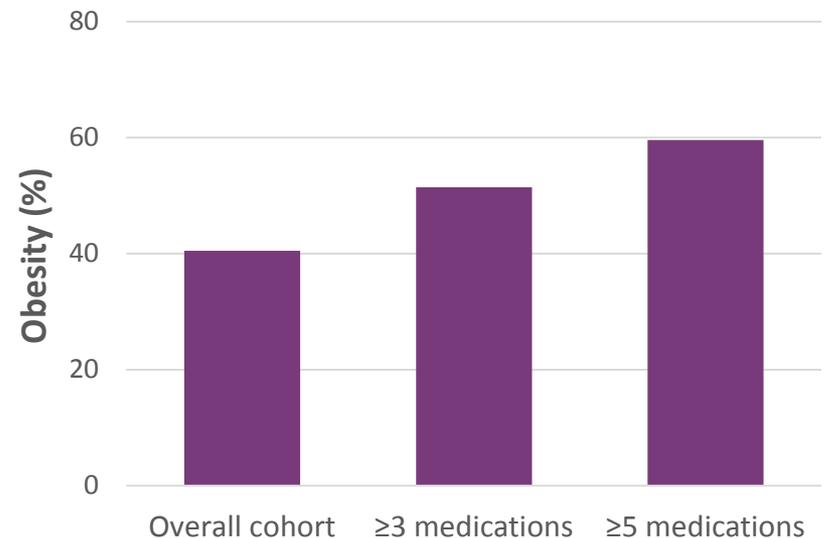
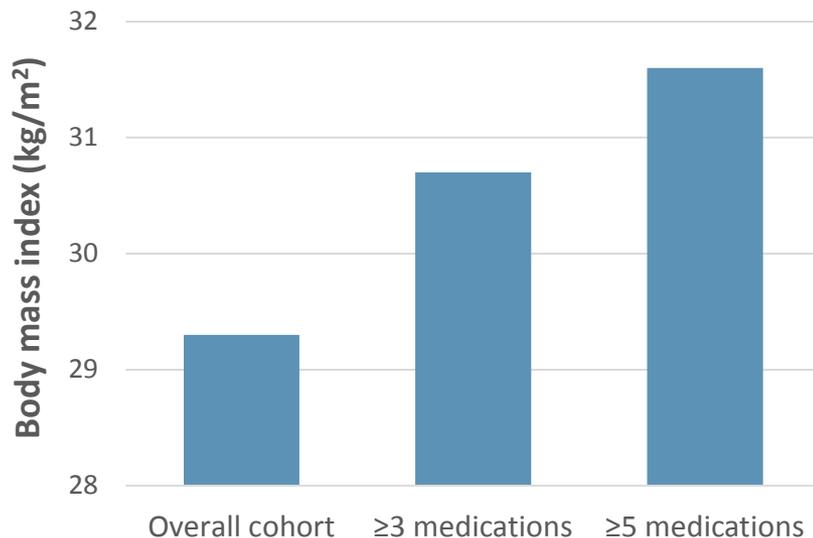


As body mass increases, mean systolic blood pressure increases



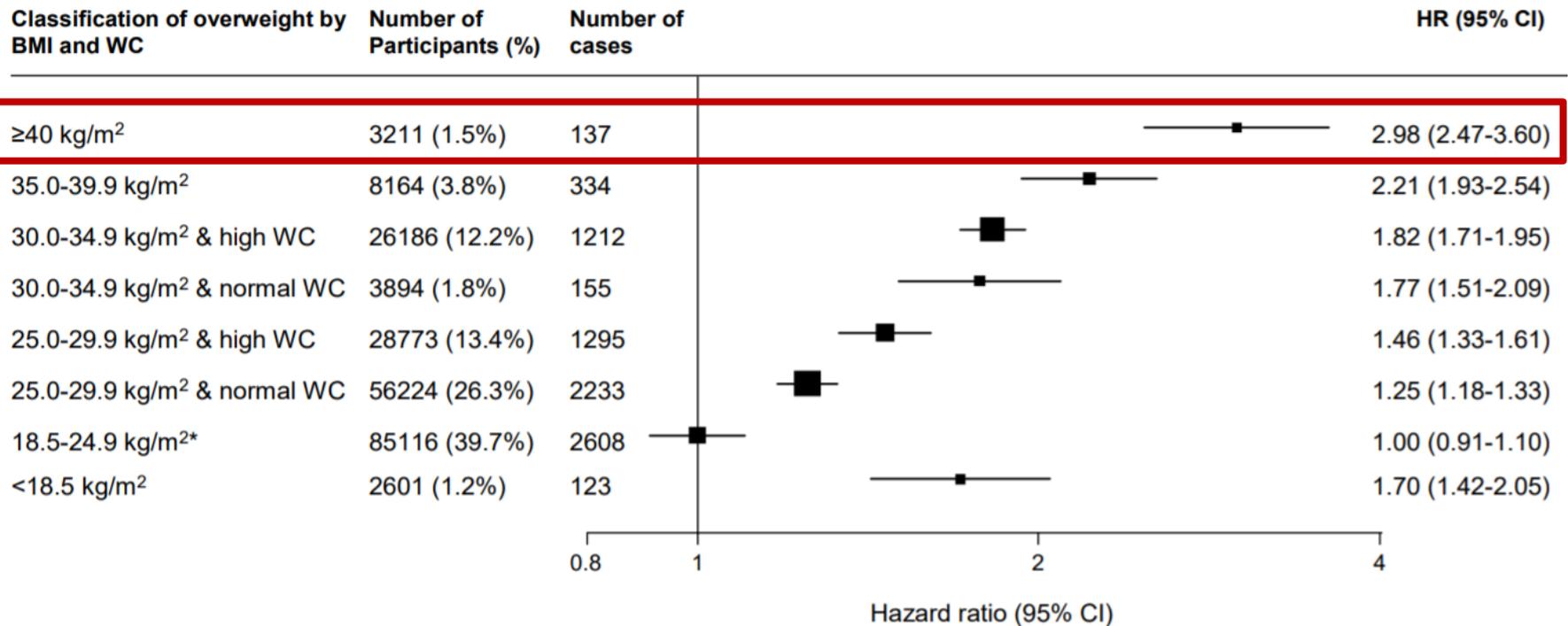
As body mass increases, hypertension is more difficult to control

- Among 70,997 patients with treated hypertension in the Spanish APBM Registry, 11,972 had apparent treatment resistant (≥ 3 medications) or refractory hypertension (≥ 5 medications)



Obesity is strongly associated with development of cardiovascular disease

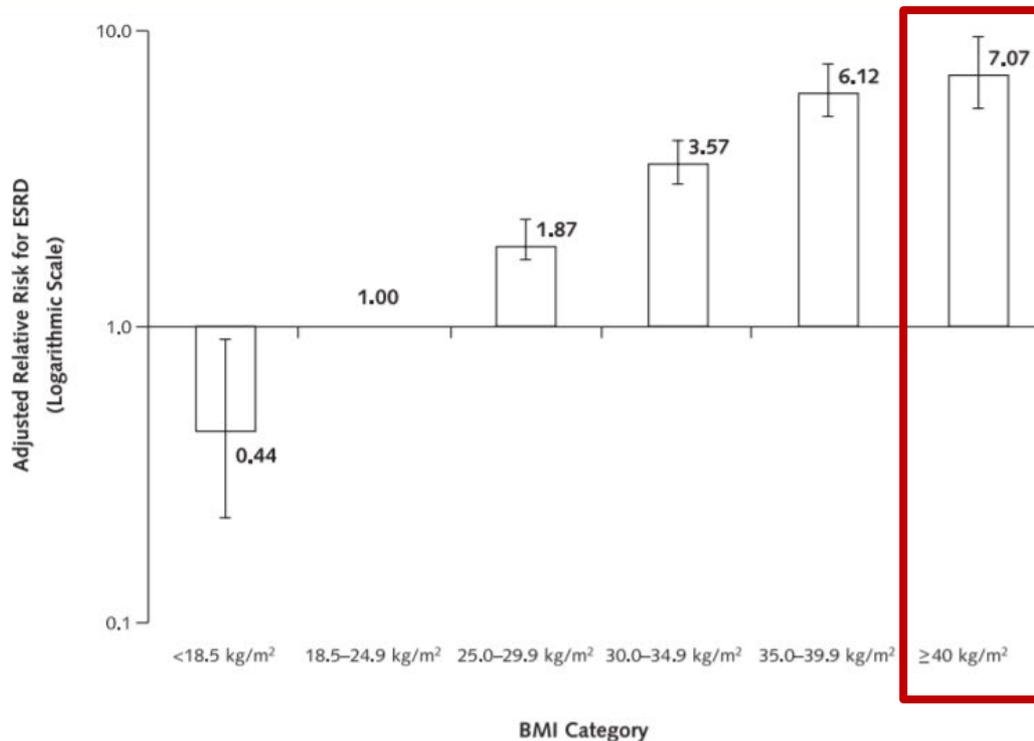
Hazard ratios for coronary artery disease by BMI and waist circumference



Obesity is strongly associated with development of ESRD

- US cohort of 320,252 primary care patients (Kaiser Permanente)

Figure. Adjusted relative risk for end-stage renal disease (ESRD) by body mass index (BMI).



Challenges in the **measurement** of hypertension in obesity

Measurement error of blood pressure in obesity

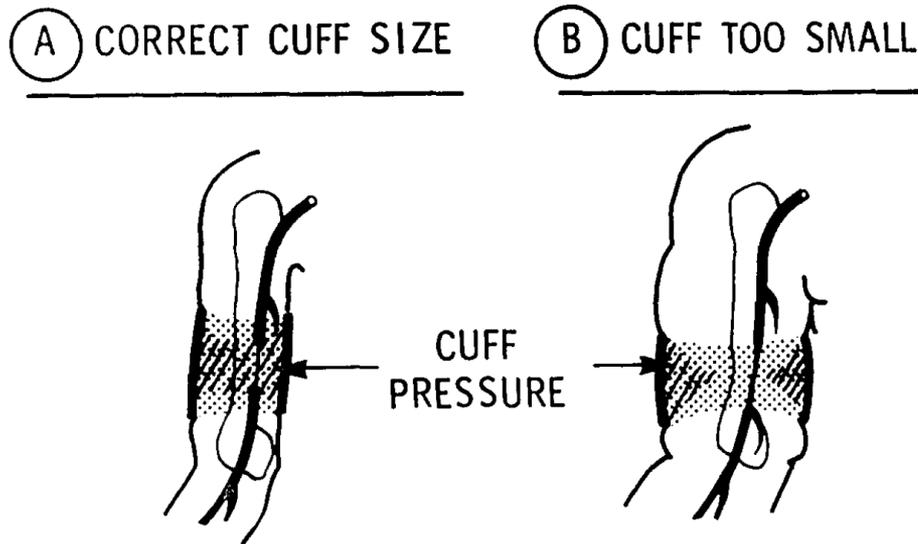
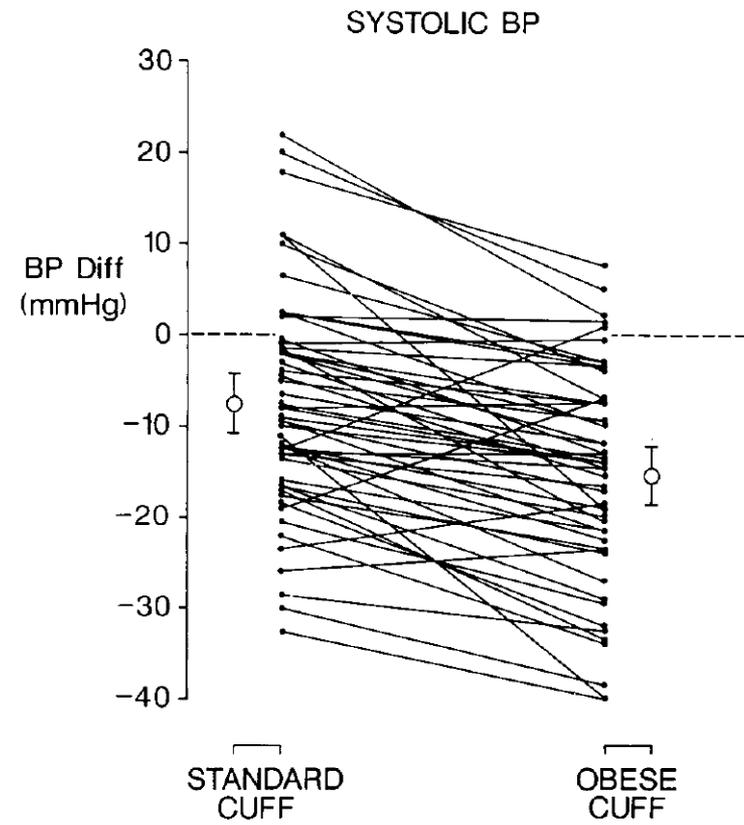
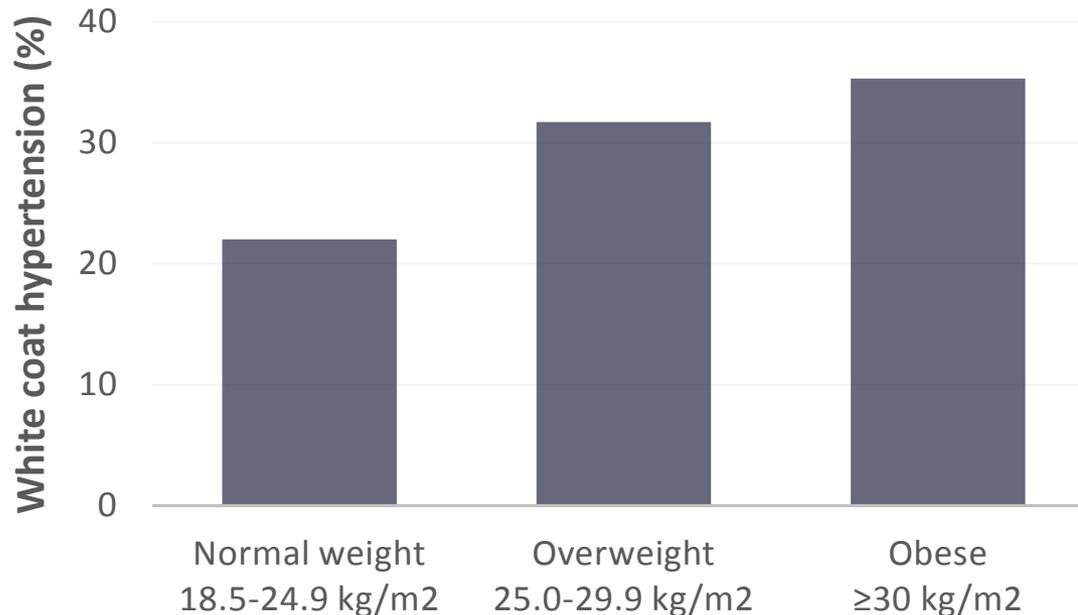


FIGURE 4 Effect of small cuff on pressure diffusion.



The prevalence of isolated office hypertension increases with increasing body mass

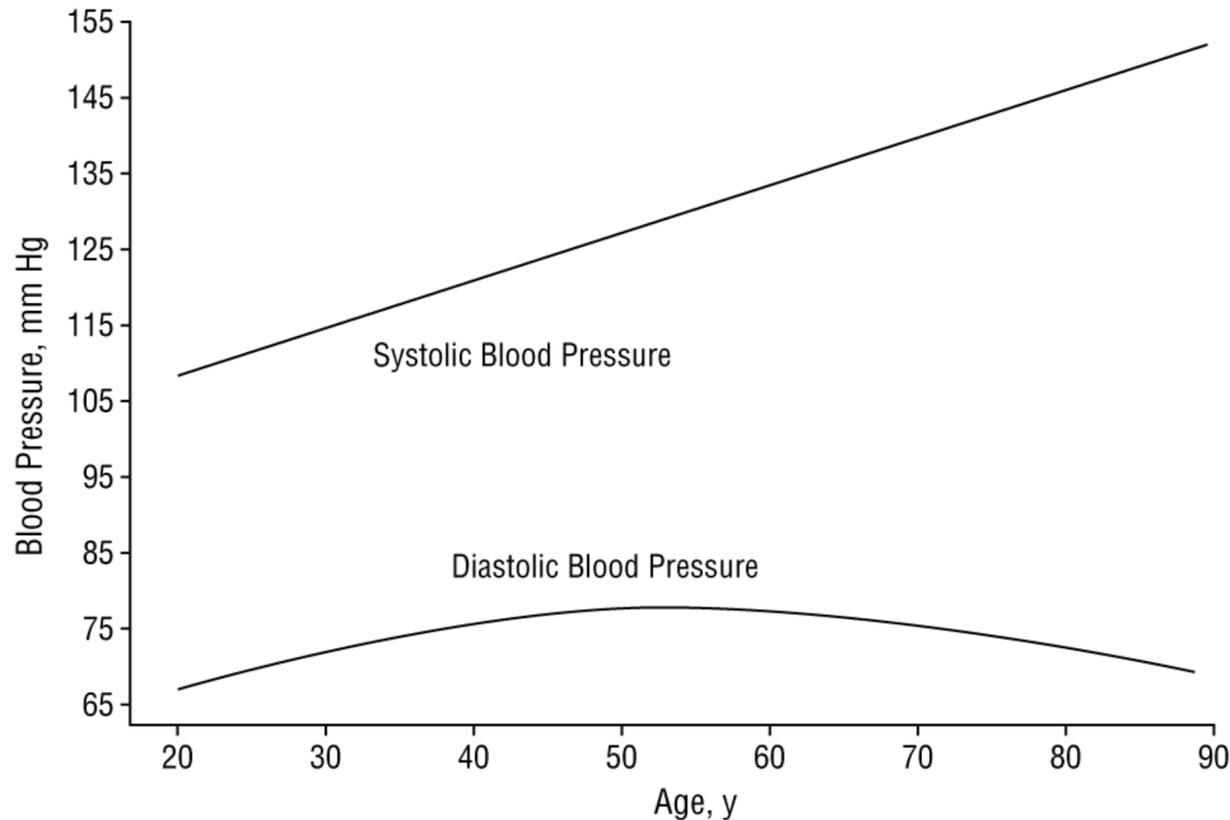
- 3216 patients who underwent 24-hour ambulatory blood pressure monitoring in Greece from 1996-2004



Distinctive pathophysiology of hypertension in obesity

Physiologic contributors to hypertension in the general population:

Aging and vascular stiffness

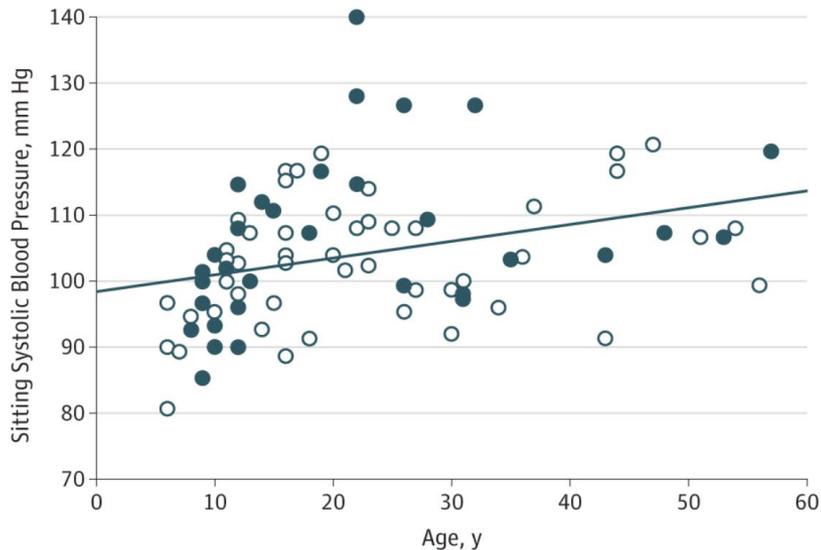


Physiologic contributors to hypertension in the general population:

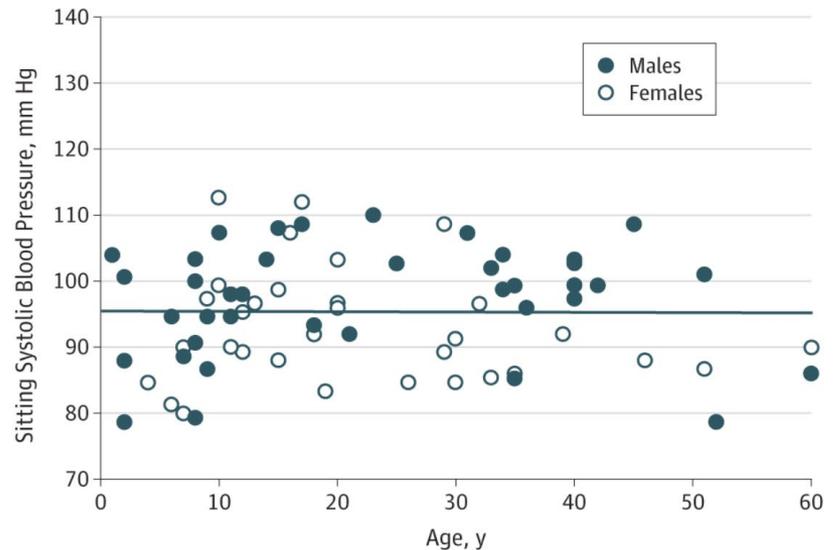
Dietary exposures

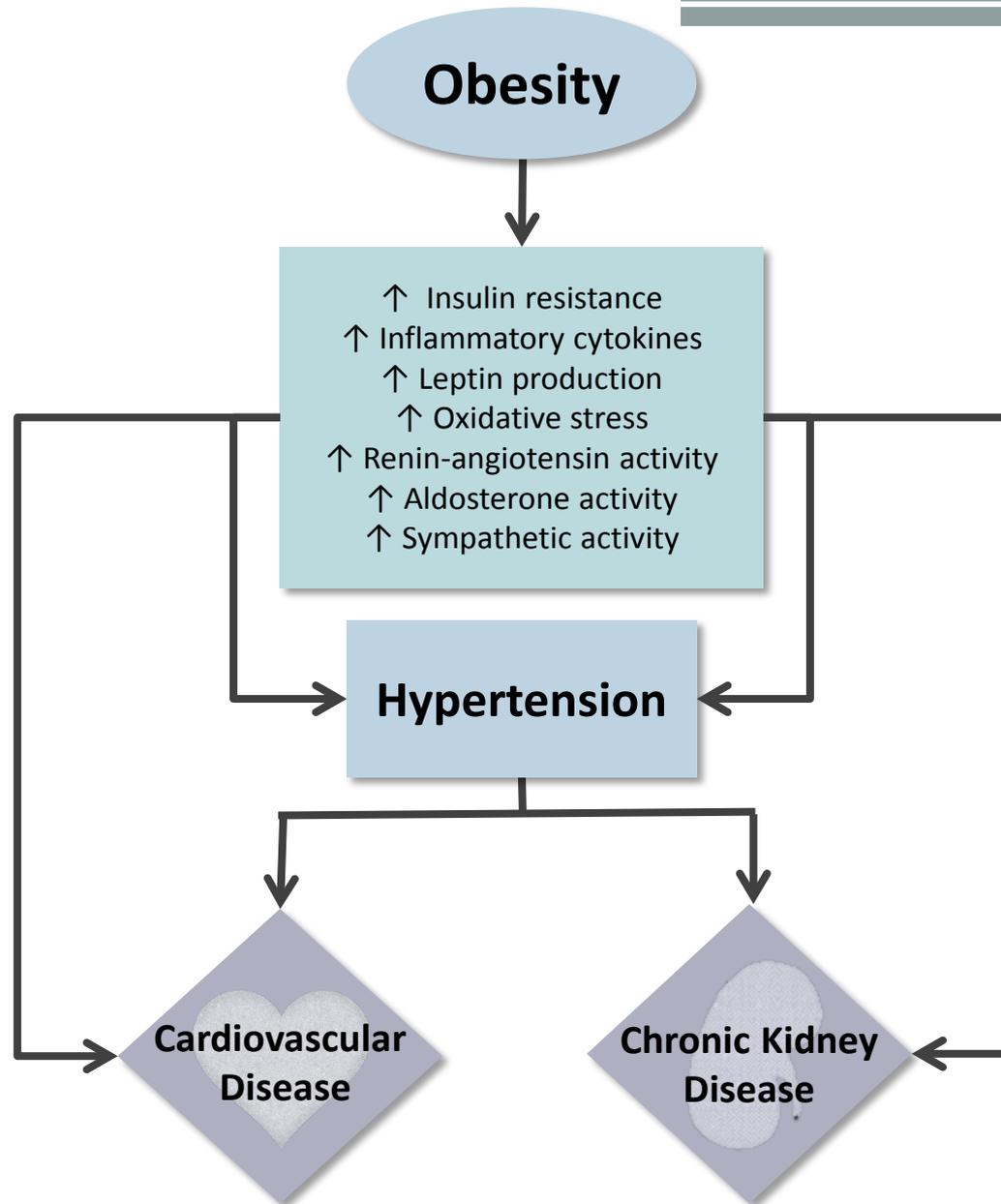
- “Rise in BP with age may not be natural, but rather a consequent of unnatural Western exposures”

A Age-systolic blood pressure slope for Yekwana individuals



B Age-systolic blood pressure slope for Yanomami individuals

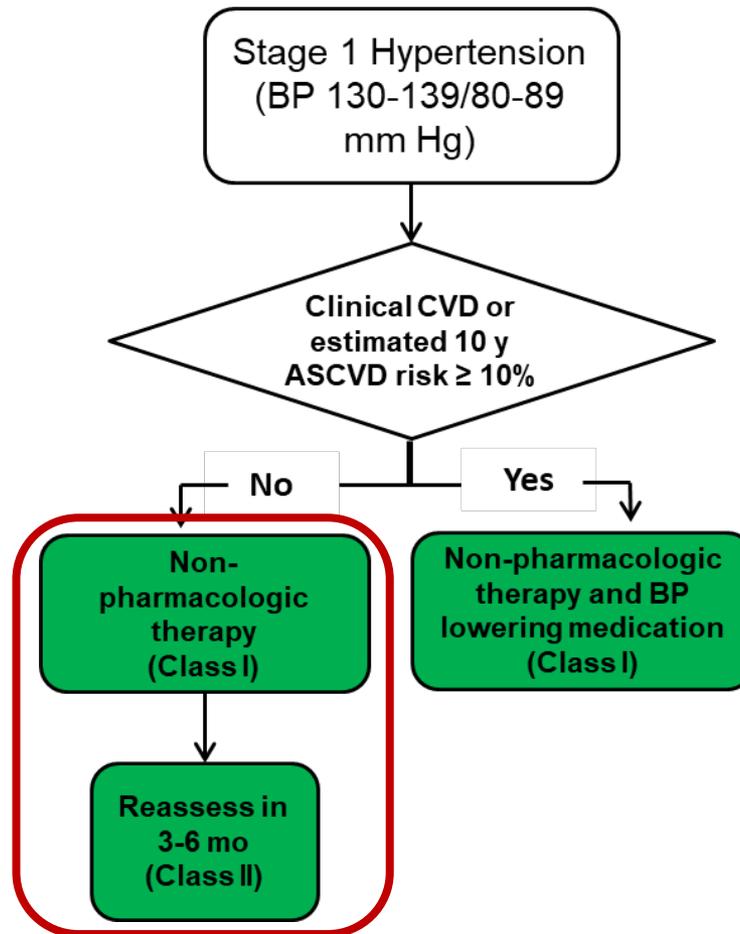




Challenges in the management of hypertension in obesity



Lifestyle modifications are an important tool in trying to manage hypertension in obesity



Lifestyle modifications are an important tool in trying to manage hypertension in obesity

COR	LOE	2017 Recommendations for Nonpharmacological Interventions
I	A	<u><i>Weight loss</i></u> is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese.

Lifestyle modifications are an important tool in trying to manage hypertension in obesity

However, sustained weight loss is unusual

- Cochrane systematic review and meta-analysis of randomized control trials evaluating behavioral counseling with diet, exercise, or both
 - Does not result in persistent weight loss
 - Does not attenuate long-term adverse cardiovascular outcomes
- Lack of guidance on what to do when lifestyle modifications fail

Medication-mediated weight loss and blood pressure control

- Changes in weight and blood pressure relative to placebo following 1-year of treatment with drugs approved for long-term weight management:

Drug	% Weight change	SBP change, mmHg	DBP change, mmHg
Orlistat*	- 3.0 (~)	- 1.1	- 1.1
Lorcaserin	- 3.3	- 0.7	- 0.6
Liraglutide 3.0 mg	- 5.2	- 2.8	- 0.9
Phentermine/topiramate	- 8.9	- 3.1	- 1.0
Naltrexone/bupropion	- 4.2	+ 1.5	+ 1.2

Bariatric surgery-mediated weight loss and blood pressure control

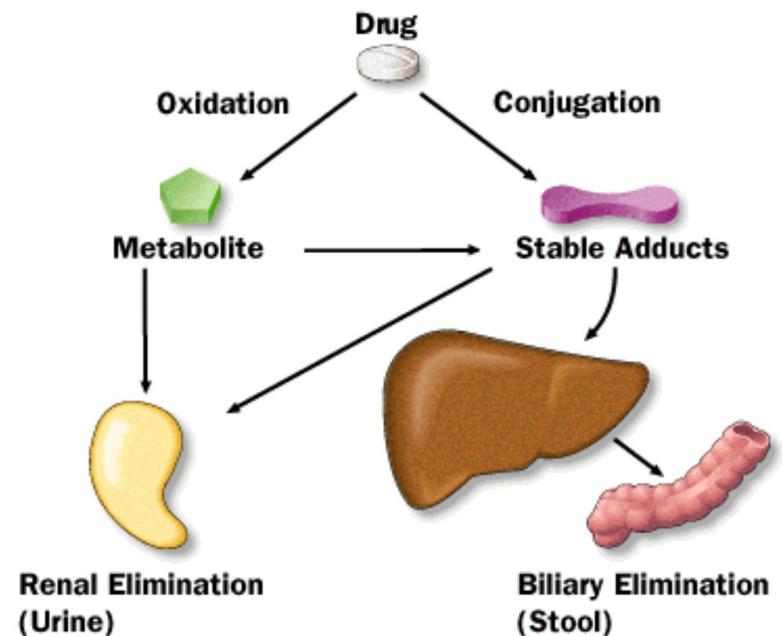
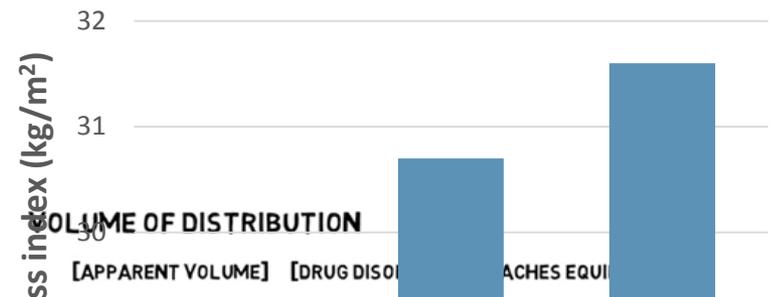
Table 3. Meta-analyses of Surgery Risk and Comorbidities Remission Outcomes^a

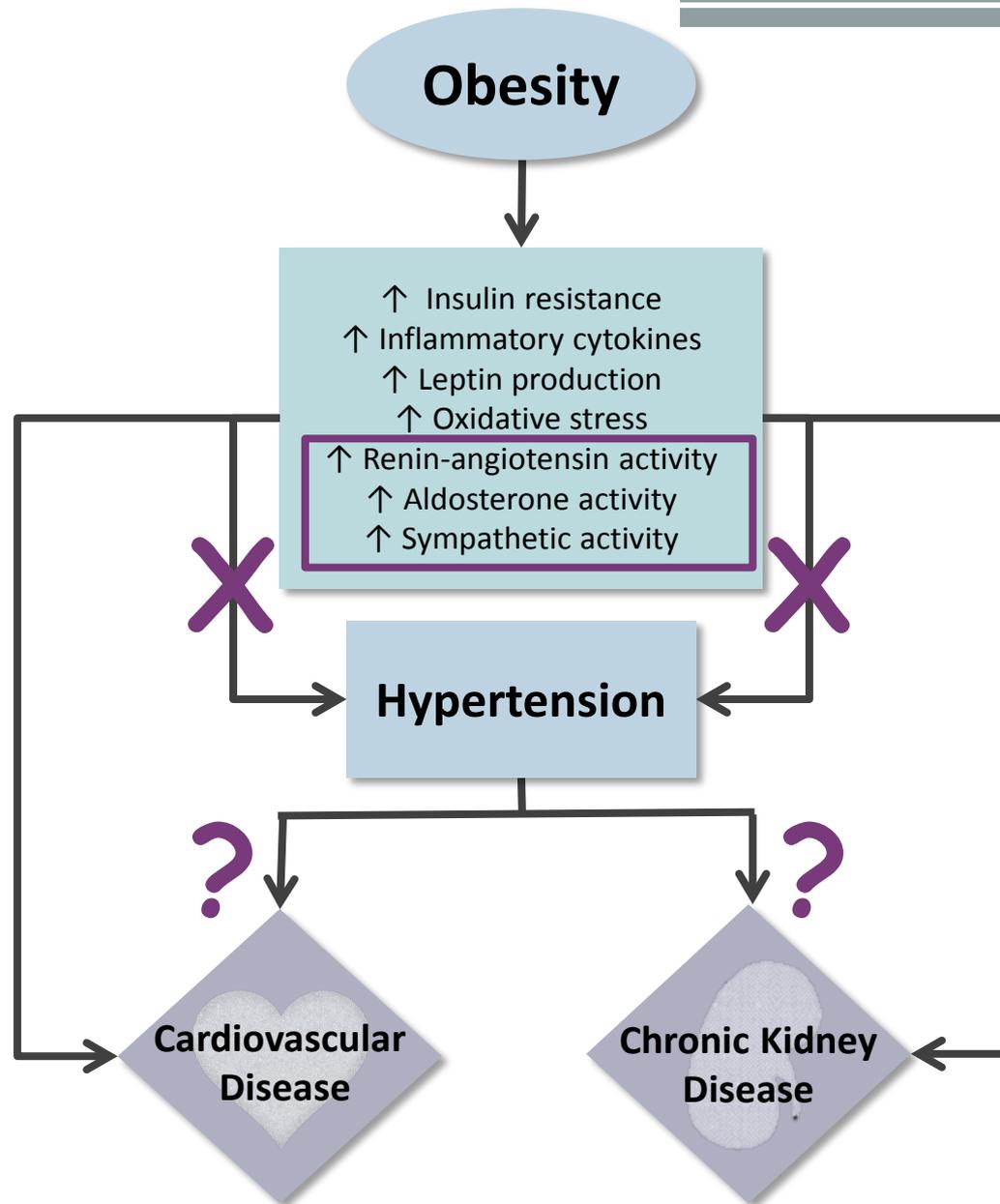
	Mean (95% CI)	
	Control	Overall
Hypertension remission rates		
RCT		
Estimates, %	49.00 (0.00-99.00)	75.18 (61.52-86.35)
Study/arm/No. of patients	1/1/27	8/15/243
OBS		
Estimates, %	15.00 (1.40-53.00)	74.36 (66.53-81.19)
Study/arm/No. of patients	2/2/82	37/47/16 962

- Bariatric surgery is associated with persistent declines in leptin and muscle sympathetic activity, likely contributing to the observed decline in BP
- Compared to non-surgical weight loss, there is a risk of perioperative adverse events (surgical complications, reoperation, acute kidney injury, mortality)

Pathophysiologic changes in obesity alter pharmacologic handling

- Drug resistant hypertension
 - Maladaptive neurohormonal pathways
- Altered volume of distribution
 - Expanded plasma volume
 - Drug lipophilia
- Altered clearance
 - Dysfunctional hepatic metabolism
 - Increased cardiac output
 - Impaired estimation of renal clearance





Is there a differential class effect of anti-hypertensives in obesity?

ACE-Inhibitors and ARB's

- Captopril
 - Obese vs. lean patients
 - Greater renal vasodilatory response in obesity ($r=0.55$, $p<0.001$)
- Ramipril vs. placebo
 - Obese vs. lean patients (REIN: proteinuric)
 - Greater risk reduction of ESRD in obese patients (79% vs. 45%)
- ACE-Is/ARBs vs. other antihypertensives
 - Obese patients only
 - RAS blockade did not provide long-term renal benefit (HR 1.11, 95% CI 1.03-1.20)

Differences in Urinary Protein Excretion
(Relative to Baseline)

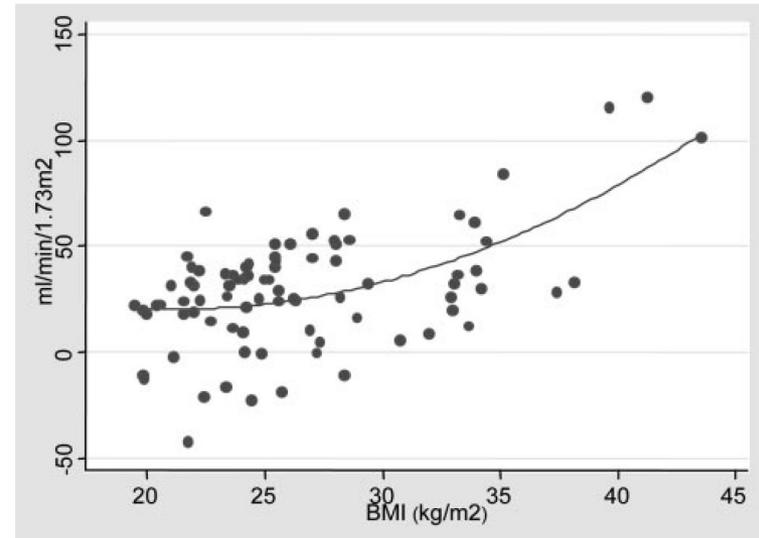


Figure 1. Age- and baseline PRA-adjusted RPF response to captopril vs BMI.

Ahmed et al. *Hypertension* 2005; 46:1316-20
Mallamaci et al. *J Am Soc Nephrol* 2011; 22
Cohen JB et al. *Am J Nephrol* 2016; 43:431-40

Is there a differential class effect of anti-hypertensives in obesity?

- **Combined alpha- and beta-adrenergic blocker**

- Obese vs. lean patients
- Greater blood pressure response (n=24; 130.0+/-2.5 vs. 138.9+/-2.1 mmHg, p=0.02)

- **Thiazide and thiazide-like diuretics**

- ALLHAT subgroup of obese patients
 - Highest frequency of BP control (<140/90 mmHg) was in patients on chlorthalidone
- ACCOMPLISH
 - Greatest reduction in adverse cardiovascular outcomes in obese patients on the thiazide diuretic

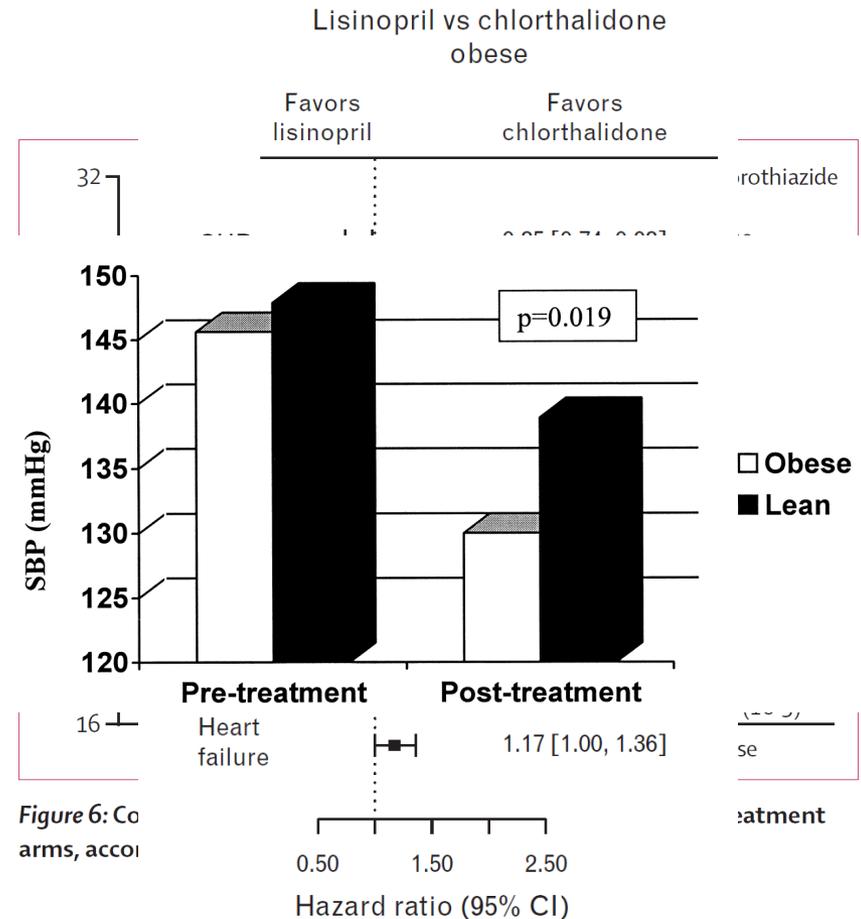


Figure 6: Co arms, accoi

Wofford et al. *Am J Hypertens* 2001; 14:694-8
 Reisin et al. *J Hypertens* 2014; 32(7):1503-13
 Weber et al. *Lancet* 2013; 381: 537-45

Approach to hypertension in obesity

- **1) Measure blood pressure carefully**
 - Appropriate cuff size
 - Out-of-office measurements
- **2) Monitor for end-organ damage and related comorbidities**
 - BMP, UPr/UCr or microalbumin, lipid panel
- **3) Promote weight loss**
 - Lifestyle modifications are **important to emphasize and reemphasize**
 - Weight-loss medications do not meaningfully improve hypertension
 - Refer for bariatric surgery in motivated patients
- **4) Tailor medications**
 - Among obese patients, BP ↓ from thiazide diuretics compared to other classes
 - Compared to lean patients, BP ↓ from ACE-I/ARB's and β-blockers
 - Compared to lean patients, greater cardiac benefit from ACE-I/ARB
 - Be prepared to require multiple classes

Questions?