Hypertension: A metabolic disorder

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GLMS CME

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Overview

- Burden of metabolic syndrome (Met S)
- Mechanisms of hypertension in metabolic dysfunction
- Therapeutic approaches to hypertension in Met S
  - Pharmacological considerations
  - Effect of GLP1 receptor agonists

“Syndrome X”

- 1988 – Reaven
  - Insulin resistance
  - Abdominal obesity
  - Hypertension
  - Dyslipidemia
- Hypertension present in >80% of patients
- 1/3 of patients with essential hypertension

“Syndrome X”

- Higher prevalence of end organ damage
  - LV hypertrophy & atrial enlargement
  - Albuminuria & lower eGFR
  - Hypertensive retinopathy
  - Increased intima-media thickness

Table 1 The definitions of metabolic syndrome

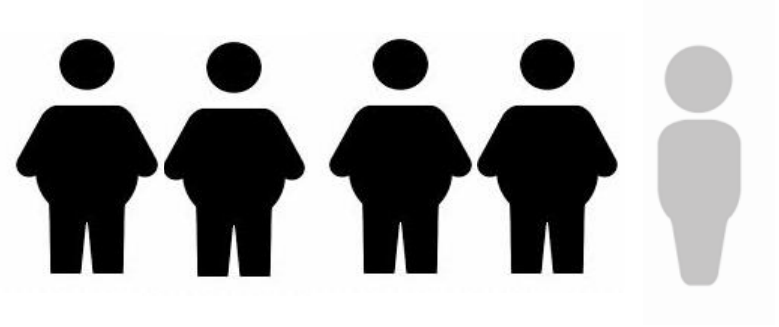
		WHO [9]	NCEP [11]	Modified NCEP [12]	IDF [13]	JIS [14]
Criteria for diagnosis of MetS		Diabetes diagnosis or FBG ≥ 110 mg/dL or IR with ≥ 2 of the following	Presence of any 3 of 5 of the following	Presence of any 3 of 5 of the following	WC: > 94 cm (men); > 80 cm (women) with the presence of ≥ 2 of the following	Presence of any 3 of 5 of the following
Hyperglycemia	Fasting glucose	Already required	≥ 110 mg/dl	≥ 100 mg/dL or on Rx for elevated glucose	≥ 100 mg/dl or diagnosed diabetes	≥ 100 mg/dl or diagnosed diabetes
Dyslipidemia	TG:	> 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dL or on TG Rx	≥ 150 mg/dl or on TG Rx	≥ 150 mg/dl or on TG Rx
	HDL-C:	M: < 35 mg/dl F: < 40 mg/dl	M: < 40 mg/dl F: < 50 mg/dl or on HDL-C Rx	M: ≤ 40 mg/dL F: ≤ 50 mg/dL or on HDL-C Rx	M: < 40 mg/dl F: < 50 mg/dl or on HDL-C Rx	M: < 40 mg/dl F: < 50 mg/dl in women or on HDL-C Rx
Hypertension	Blood pressure	≥ 140/90 mmHg	≥ 130/85 mmHg	SBP: ≥ 130 mmHg or DBP: ≥ 85 mmHg or on hypertension Rx	SBP: ≥ 130 mmHg or DBP: ≥ 85 mmHg or on hypertension Rx	SBP: ≥ 130 mmHg or DBP: ≥ 85 mmHg or on hypertension Rx
Obesity	WC		M: > 102 cm F: > 88 cm	M: ≥ 102 cm F: ≥ 88 cm	Already required	Ethnic dependent
	Waist/hip ratio:	M: > 0.9 F: > 0.85 or BMI > 30 kg/m^2				
Other		UAE ≥ 20 μg/min				

BMI: body mass index; DBP: diastolic blood pressure; F: female; FBG: fasting blood glucose; HDL-C: high density lipoprotein cholesterol; IDF: International Diabetes Federation; IR: insulin resistance; JIS: Joint Interim Statement; M: male; NCEP: National Cholesterol Education Program; Rx: treatment; SBP: systolic blood pressure; TG: triglyceride; UAE: urinary albumin excretion; WHO: World Health Organization; WC: waist circumstance

MetS is prevalent in patients with diabetes

General adult population

20 – 25%



Type 2 diabetes

Up to 80%

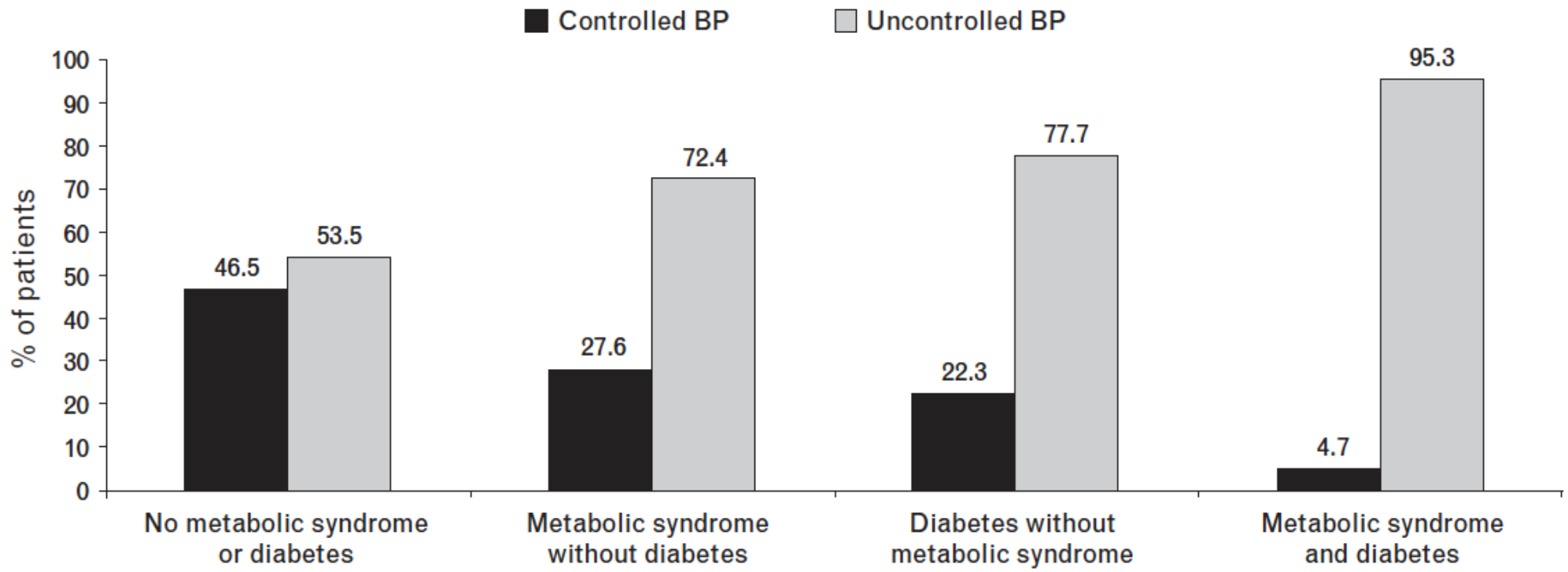
Type 1 diabetes

24%

F>M

Diabetol Metab Syndr 2021;13:25

Impact of Met S and T2D on BP control



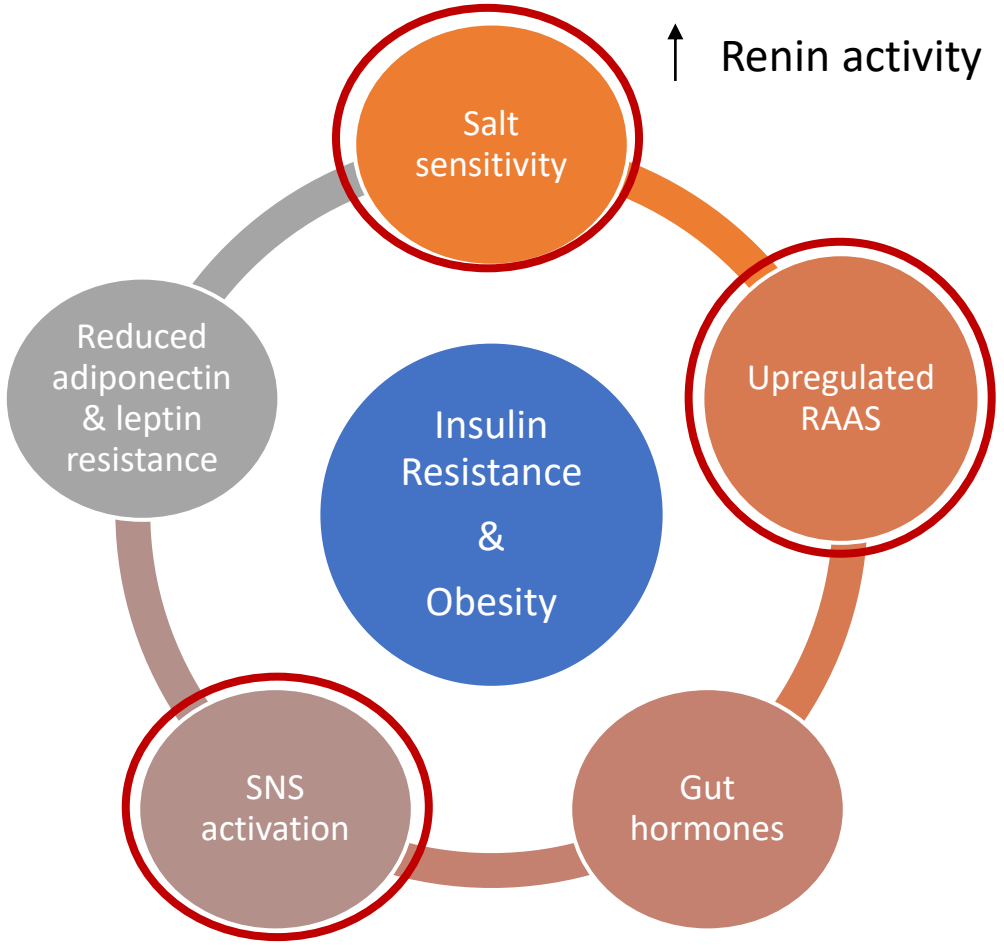
Percentage of patients with either metabolic syndrome or type 2 diabetes or both with controlled and uncontrolled blood pressure.

Met S (OR 2.56) and T2D (OR 5.16) were significant risk factors for uncontrolled BP

2-fold greater CV risk in those with Met S compared with those without (3.23 vs 1.76 events per 100 patient years)

J Hypertension 2008, 26:2064 – 2070
J Am Coll Cardiol 2004; 43:1817 – 1822

Inter-relationship of HTN mechanisms in Met S

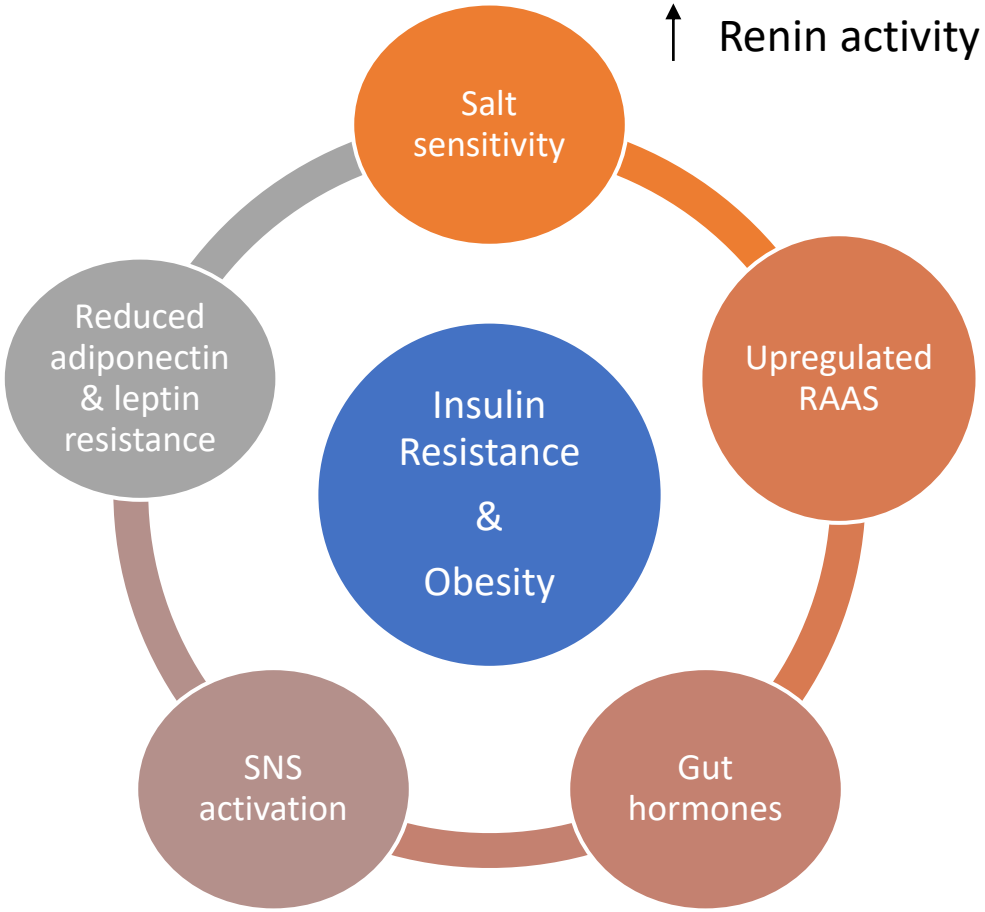


High caloric intake
Increased leptin & leptin resistance
Baroreflex dysfunction

Curr Hypertens Rep (2019) 21: 63
Curr Hypertension Reviews 2020; 16: 12 – 18.

Inter-relationship of HTN mechanisms in Met S

1. Hypertrophied adipocytes
   - Pro-inflammatory /atherosclerotic adipokines
2. Low adiponectin
   - Increased SGLT 2 cotransporters in kidney
   - Salt sensitivity
3. Leptin resistance
   - Exacerbates insulin resistance
   - SNS activation



↑ Renin activity

↑ Angiotensinogen & aldosterone
Renal injury and glomerulomegaly

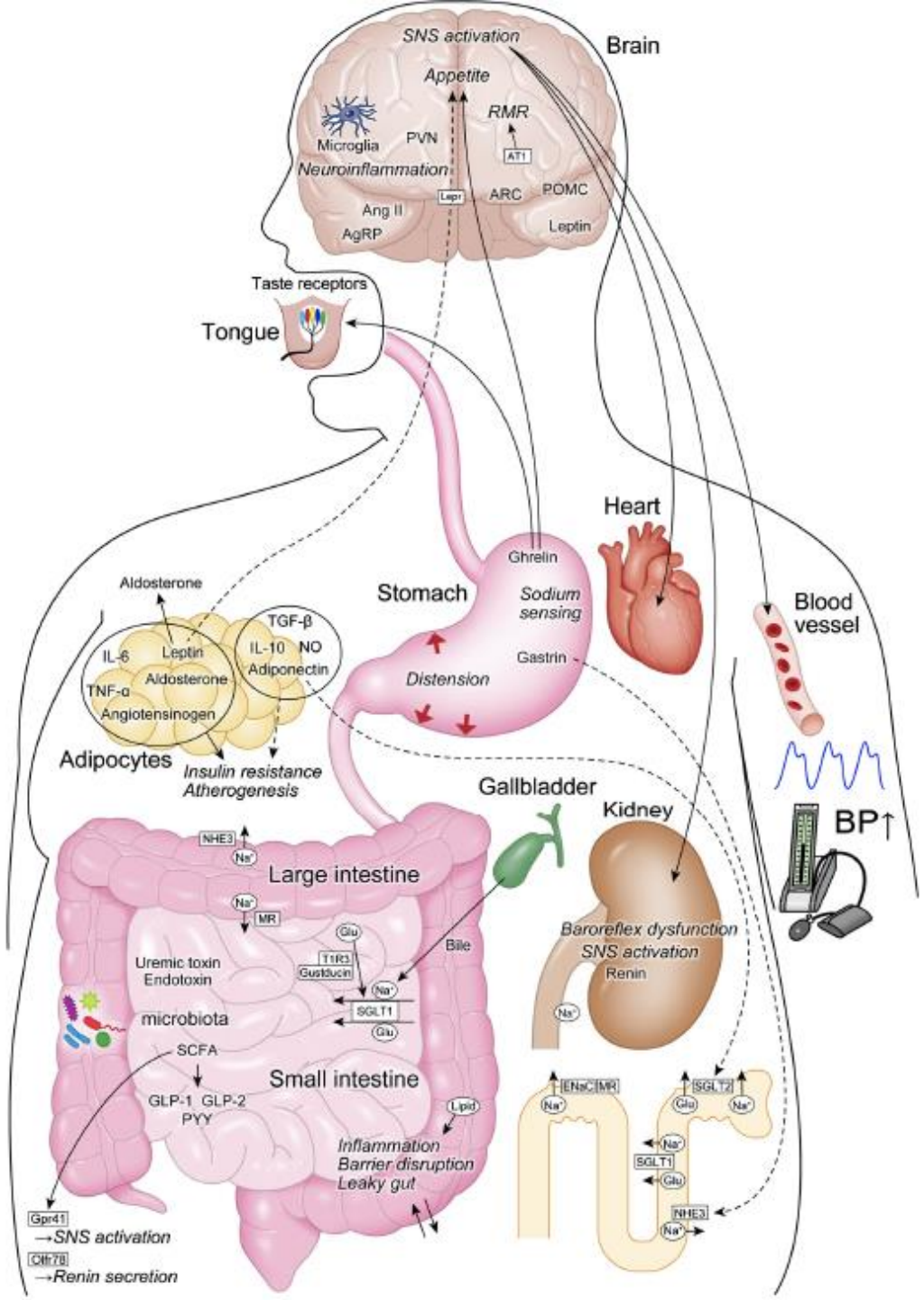
High caloric intake
Increased leptin resistance
Baroreflex dysfunction

Curr Hypertens Rep (2019) 21: 63
Curr Hypertension Reviews 2020; 16: 12 – 18.

Role of gut hormones

- Contribute to vascular function and BP
  - Gut microbiota – vasoactive hormones
  - Intestinal MR (+ ENaC activity)
  - G protein gustducin (+ SGLT1 expression)
  - Gastrin (reduce Na/HE3 activity)

- GLP1 – increases natriuresis via Na/HE3 activity
- Ghrelin – inhibition of Ang II

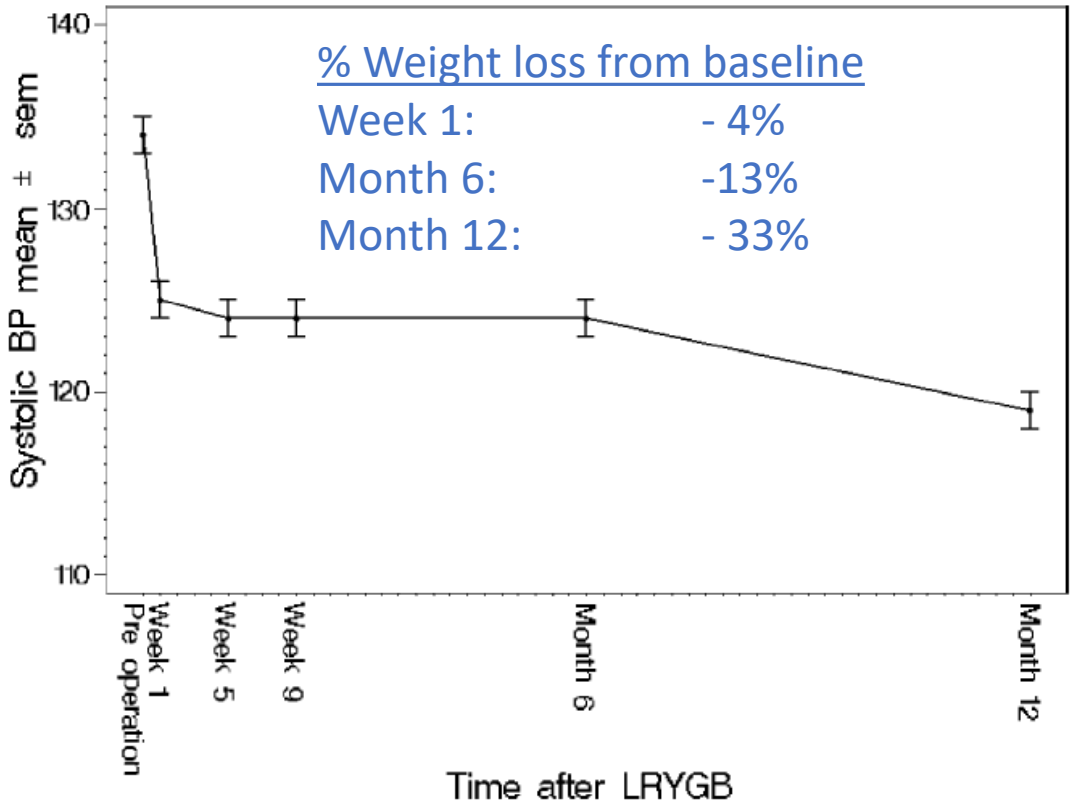


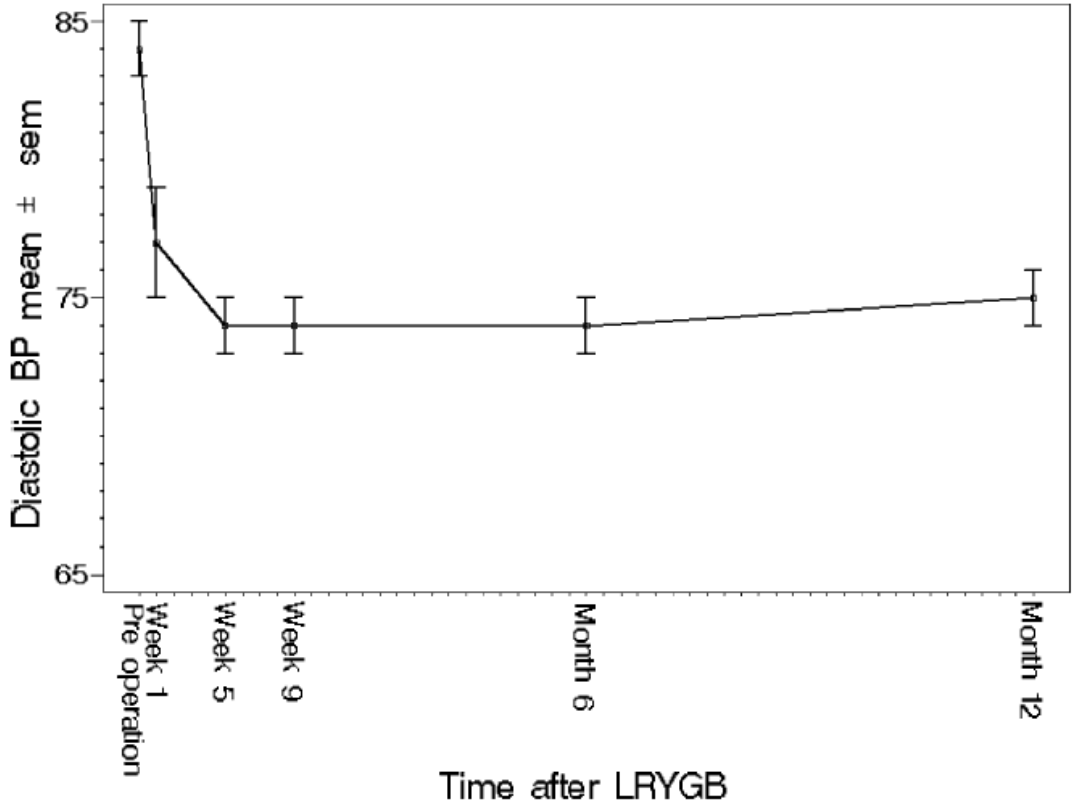
Curr Hypertens Rep (2019) 21: 63

Early BP reduction post laparoscopic Rou-en-Y bypass

N=100, 79 stage 1 HTN

Reduction in SBP 11 mmHg and DBP 7 mmHg (first 6 months post op)





Obes Surg 2009; 19: 845 – 849

Neurohormonal changes post bariatric Sx

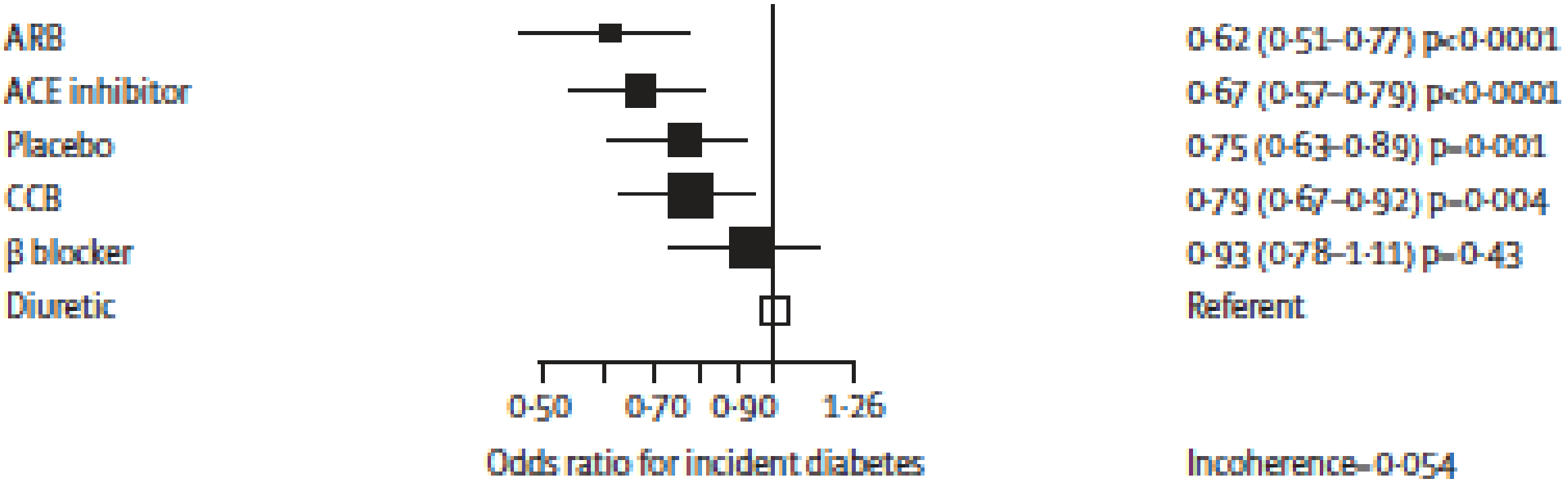
- BP reduction observed before significant weight loss achieved
  - Increased postprandial GLP-1 and peptide YY
  - Decreased leptin levels
  - Change in gut microbiota

  - Improved insulin sensitivity
  - Increase urinary sodium excretion (reduced SGLT 1 activity)
  - Reduction of SNS activity

Non-pharmacological approaches

- Lifestyle measures
  - Caloric restriction (500 – 1000 calories/day)
  - Low saturated fats, trans fatty acids and cholesterol
  - Daily minimum of 30 min moderate – intense exercise
  - Weight loss 7 – 10% over 6- 12 months, with long term maintenance
  - Smoking cessation

Effect of types of antihypertensive treatment in risk of incident diabetes

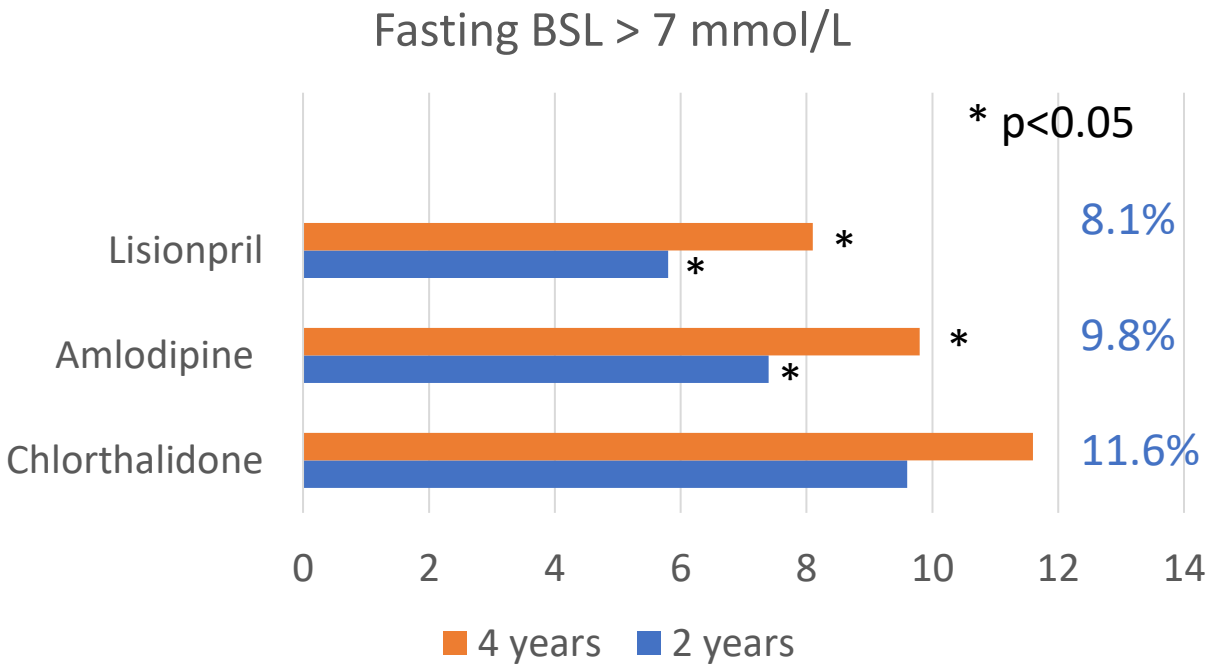


Lancet 2007; 369: 201 - 07

Pharmacological considerations

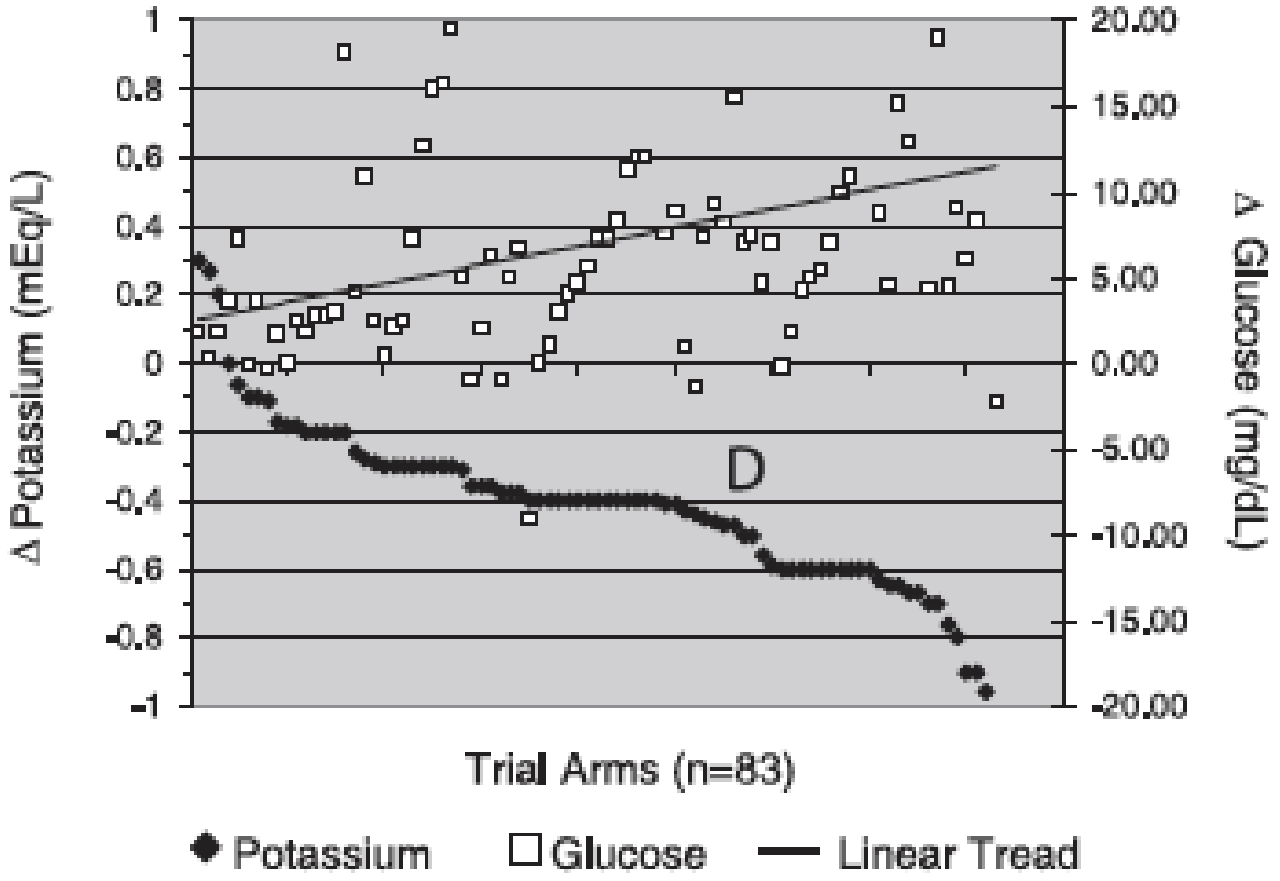
Thiazide diuretics

- Potential diabetogenic effect
- No increased CV risk in patients with IGT or diabetes on Chlorthalidone compared with patients on ACEi or CCB



ALLHAT Hypertension. 2006;48:219-224

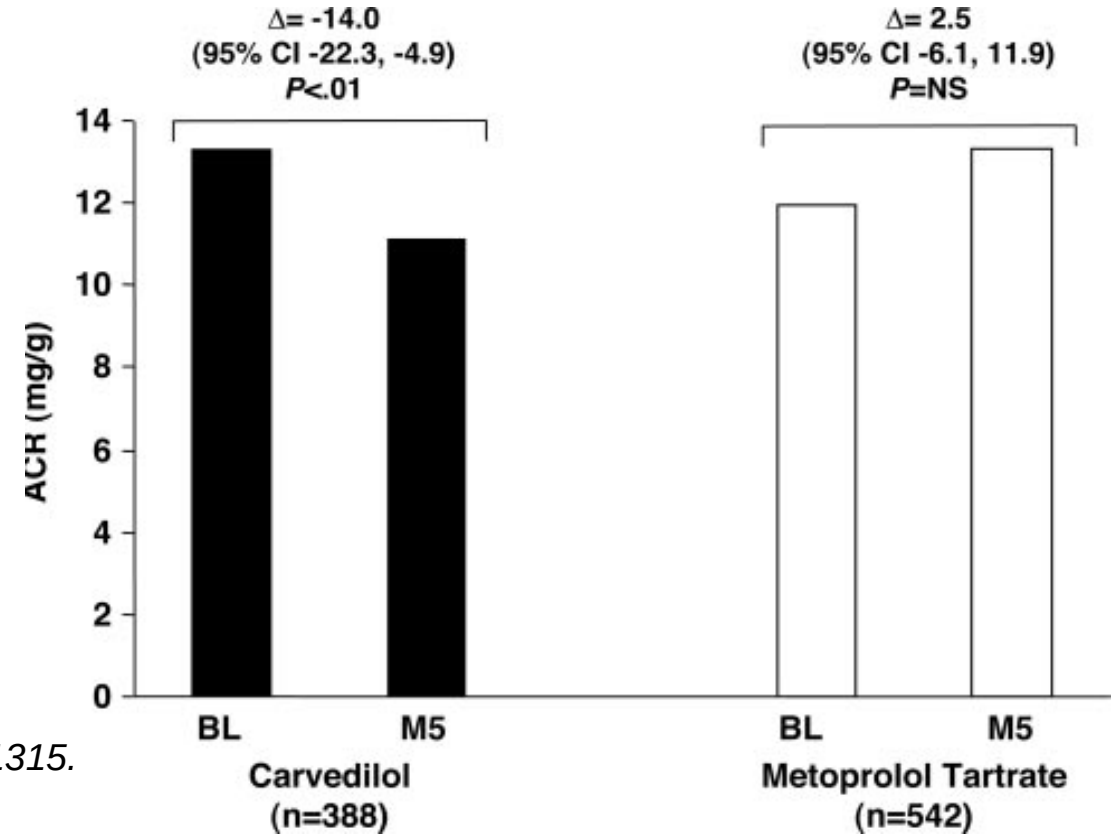
- Decreased insulin release in low-potassium state



Hypertension. 2006; 48:219-224

Pharmacological considerations

- **Beta blockers**
  - Higher incidence of new onset diabetes (LIFE, ASCOT)
  - Carvedilol – better metabolic profile compared to traditional beta blockers



GEMINI trial Hypertension 2005; 46:1309-1315.

Lancet 2002; 359: 9311:995 – 1003
Diabetes Care 2008; 31: 982 - 988

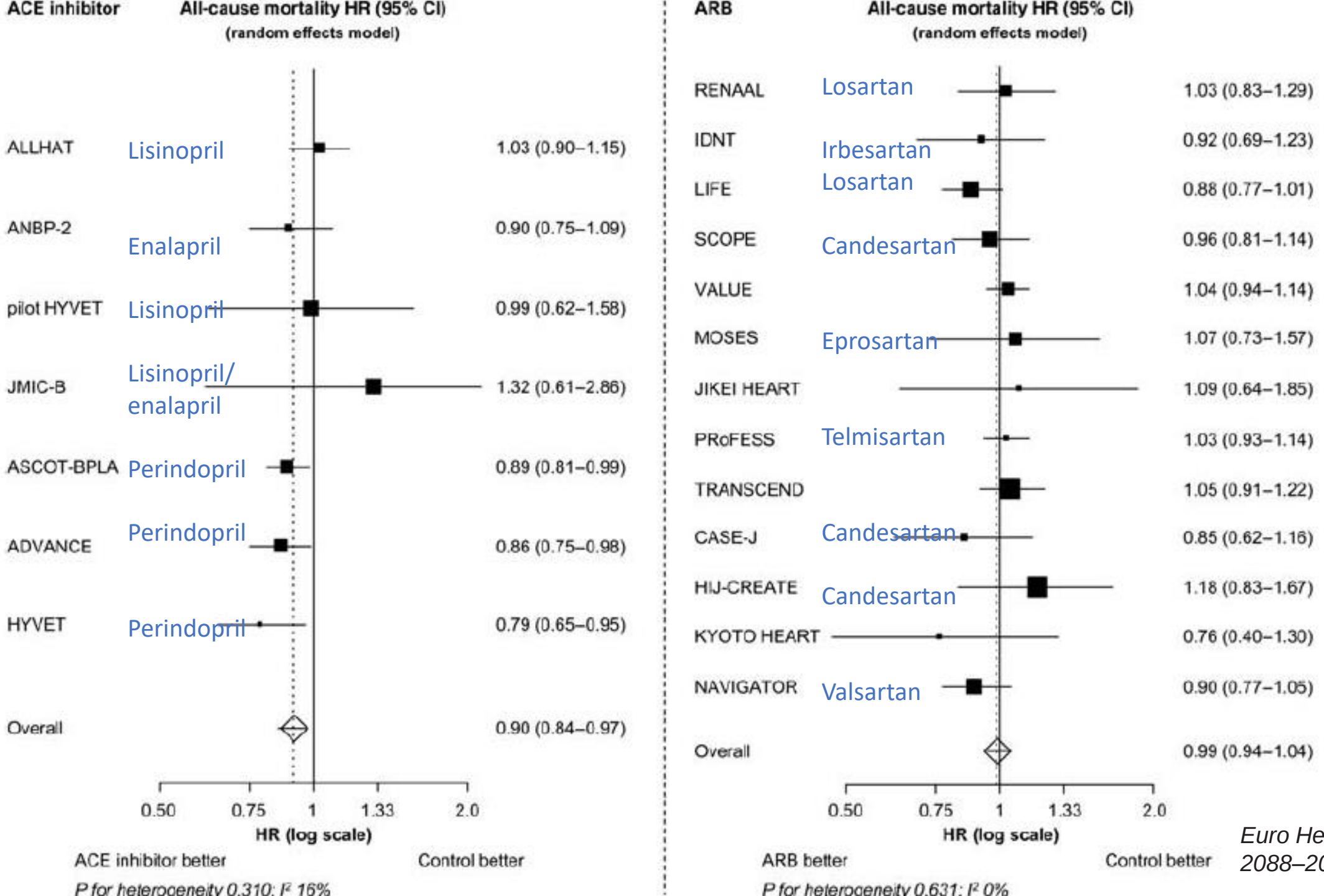
Table 3. Cardiovascular and Metabolic Measures in the Modified Intention-to-Treat Population*

Parameter	Carvedilol (n = 454)				Metoprolol (n = 657)				Treatment Difference	
	No. of Participants	Baseline	Maintenance Month 5 or Last Observation Carried Forward	% Change	No. of Participants	Baseline	Maintenance Month 5 or Last Observation Carried Forward	% Change	% Change (95% CI)†	*P* Value
BP, mean (SE), mm Hg‡										
Systolic	454	149.4 (0.6)	131.3 (0.7)	–17.9 (0.7)	636	149.2 (0.5)	132.3 (0.6)	–16.9 (0.6)	–1.0 (–2.60 to 0.58)	.21
Diastolic	454	87.0 (0.4)	77.1 (0.4)	–10.0 (0.4)	636	86.3 (0.4)	76.8 (0.3)	–10.3 (0.3)	0.29 (–0.61 to 1.20)	.53
Heart rate/min, mean (SE)‡	454	73.7 (0.5)	67.6 (0.4)	–6.7 (0.4)	636	74.5 (0.4)	66.0 (0.4)	–8.3 (0.4)	1.6 (0.70 to 2.58)	<.001
Mean ACR, mg/g§	388	13.3	11.1	–14.0	542	12.0	13.3	2.5	–16.2 (–25.31 to –5.87)	.003
Mean HOMA-IR§	371	6.0	5.8	–9.1	540	5.8	6.2	–2.0	–7.2 (–13.8 to –0.2)	.004
Mean plasma glucose, mg/dL‡	419	147.0	154.7	6.6	607	147.4	158.6	10.6	–4.0 (–8.73 to 0.78)	.10
Mean serum insulin, μIU/mL‡	387	21.6	19.6	–19.4	561	21.2	20.2	–15.1	–4.2 (–16.7 to 8.24)	.51
Mean body weight, kg‡	456	98.2	97.2	0.17	650	97.0	98.2	1.2	–1.0 (–1.43 to –0.60)	<.001
Mean serum cholesterol levels, mg/dL§										
Total	433	185.6	181.7	–3.3	625	185.6	185.6	–0.4	–2.9 (–4.60 to –1.15)	.001
LDL	411	186.6	96.7	–4.0	572	100.5	96.7	–2.7	–1.3 (–4.31 to 1.78)	.40
HDL	432	46.4	42.5	–5.5	625	46.4	42.5	–5.7	0.2 (–1.68 to 2.12)	.83
Mean triglycerides, mg/dL§	433	159.4	168.3	2.2	625	168.3	186.0	13.2	–9.8 (–13.68 to –5.75)	<.001

JAMA 2004; 292 (18): 2227 - 2236

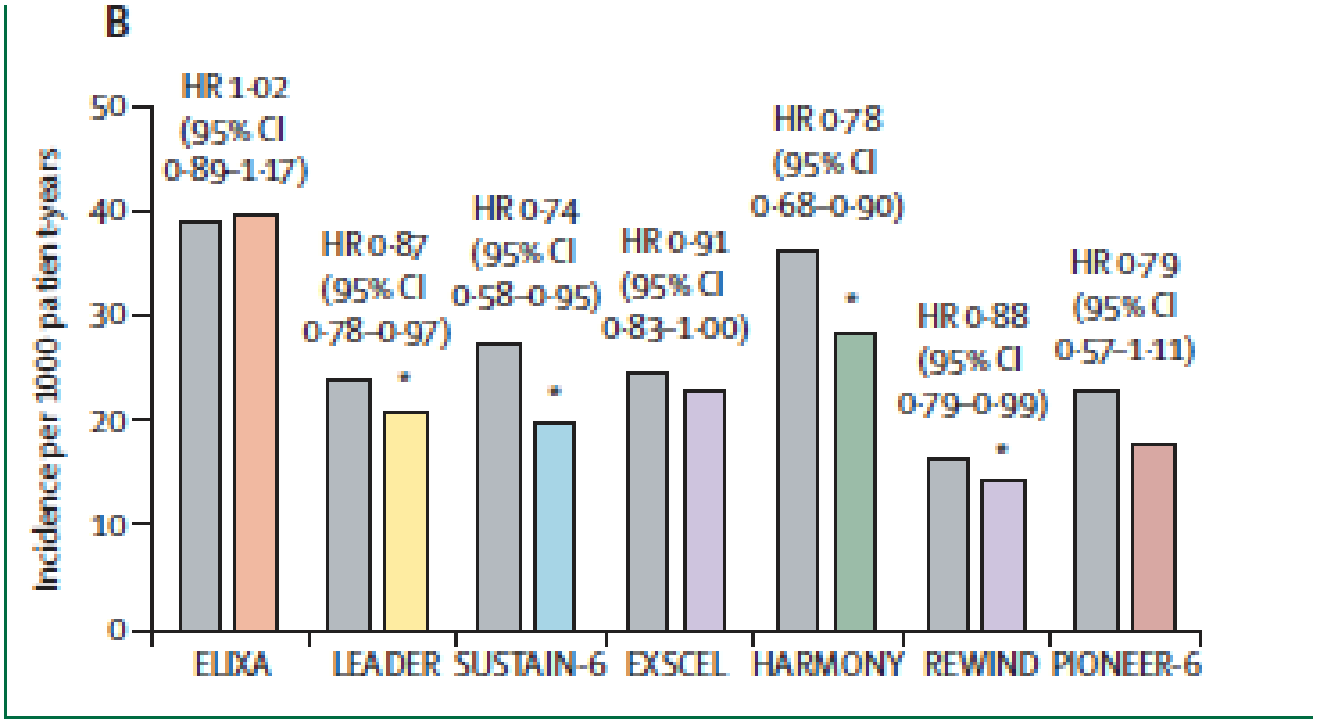
Pharmacological considerations

- RAS inhibitors
  - Drugs with neutral effect on glucose and lipid metabolism
  - No difference between ACEi and ARB in risk of incident diabetes
  - ? Difference in CV events and mortality



Euro Heart J 2012; 33, 2088–2097

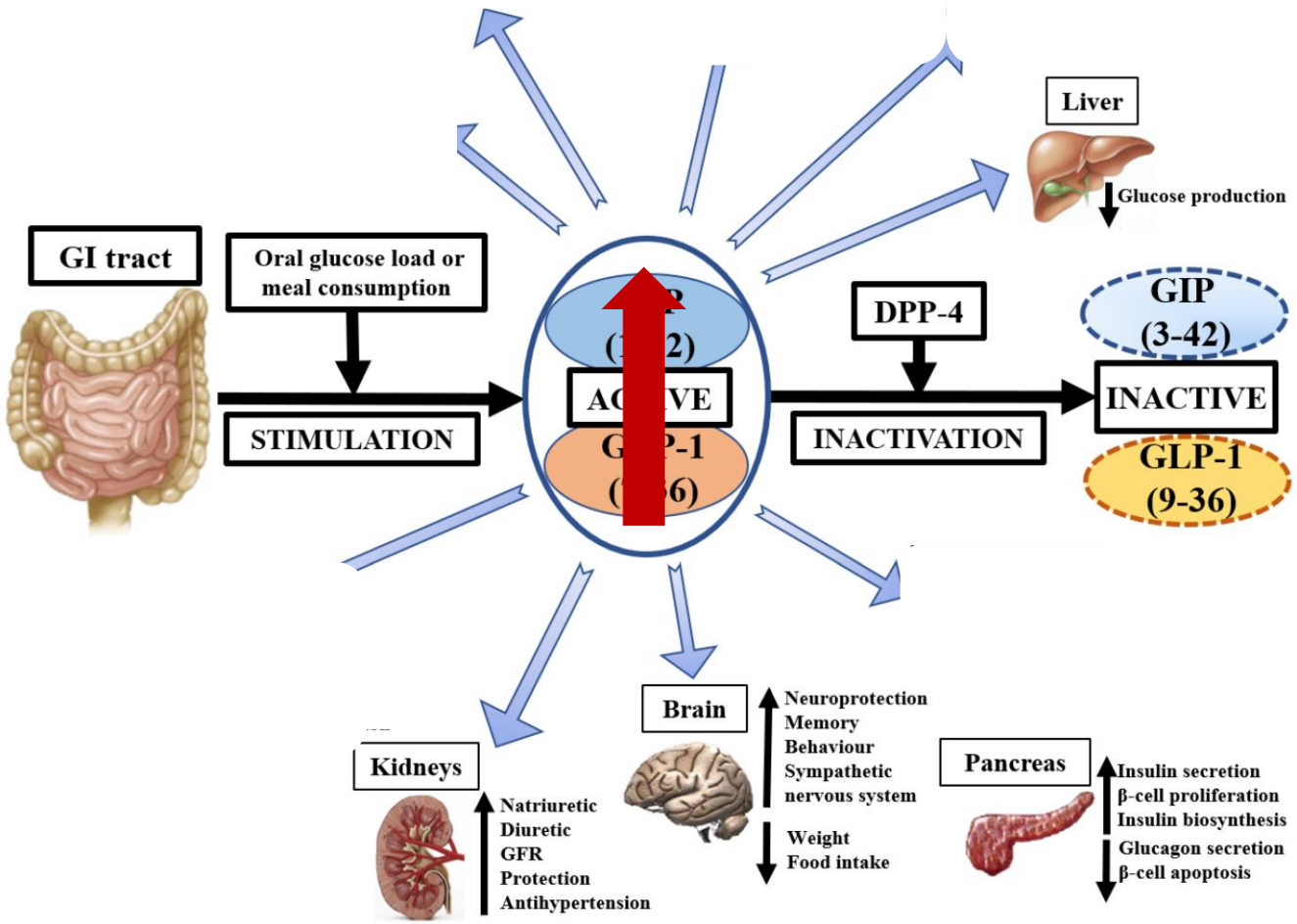
Role of GLP1 agonists



Lancet 2021; 398: 262 - 276

- Clinical trials in patients with T2D and hypertension
  - Extensively with Liraglutide
  - Reduced SBP by 7.7 mmHg over 7 weeks and loss of 2L extracellular fluid
  - Reduced MACE and all-cause mortality by 12% (HR 0·88, 95% CI 0·82–0·94)

Actions of incretins (GLP1 and GIP)



DPP IV inhibitor (Vildagliptin)

GLP1R agonist (Dulaglutide)

resistant to DPP 4

Improve glucose metabolism

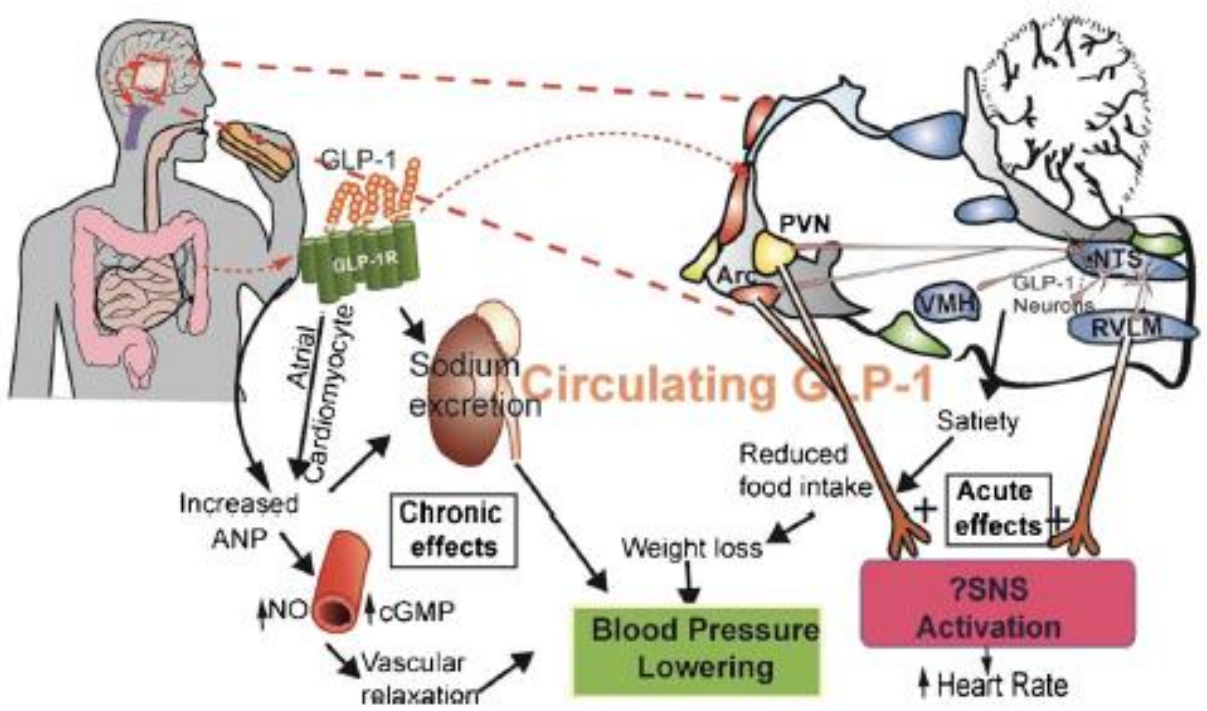
increase insulin secretion

suppress glucagon

hypothalamic appetite suppression

Reduction in weight

Incretins and BP regulation



Curr Hypertens Rep (2016) 18: 16

- GIP and GLP1 secreted from intestinal cells post food ingestion
- GLP1R expressed in gut, kidneys, heart, lungs, etc
- DPP4 expression upregulated in T2D
  - Proximal tubules
  - Podocytes & mesangial cells
  - Preglomerular vascular SM
- GLP1R downregulated in glomeruli and tubules in diabetic rats

- Mechanisms in experimental models

Am J Physiol Renal Physiol 2018; 315(6): F1519–F1525.

Discussion

- Met S and hypertension have a bidirectional relationship
- Met S contributes to poorly controlled hypertension and increased CV risk
- Complex inter-relationship of multiple hypertensive mechanisms
- RAS blockers appear to be most appropriate pharmacotherapy
- GLP1 R agonist therapies/ surgical bariatric surgery may address other mechanisms of hypertension in MetS
- Further studies required to explore the utility of GLP1R agonists in Met S without diabetes

Patient approach: Metabolic hypertension

- Evaluate potential causes for increased BMI
- Weight reduction and maintenance
- Address other risk factors in metabolic syndrome
- Individualize pharmacotherapy
- Salt reduction

Thanks for your attention.

Questions?

Greenlane
Medical Specialists