MIFEPRISTONE (GLUCORTICOID RECEPTOR ANTAGONIST) REDUCED HbA1c AND BODY WEIGHT IN DIFFICULT-TO-CONTROL TYPE 2 DIABETES WITH HYPERCORTISOLISM: THE CATALYST TRIAL

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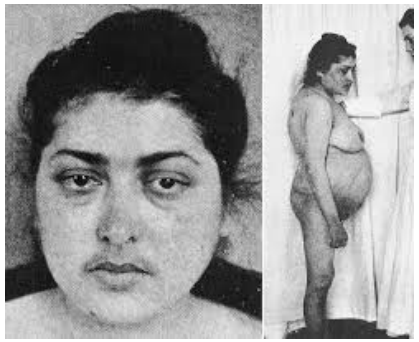
BACKGROUND

HYPERGLYCEMIA SECONDARY TO HYPERCORTISOLISM IS A COMMONLY MISSED DIAGNOSIS IN PATIENTS WITH DIFFICULT-TO-TREAT TYPE 2 DIABETES

SOME PATIENTS WITH HYPERCORTISOLISM PRESENT WITH CLASSIC PHENOTYPIC FEATURES OF CUSHING SYNDROME

- Easy bruising
- Facial plethora
- Proximal myopathy (or proximal muscle weakness)
- Striae (especially of reddish purple and >1 cm wide)
- Dorsocervical fat pad (“buffalo hump”)
- Facial fullness
- Obesity
- Supraclavicular fullness
- Acne
- Hirsutism



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MOST INDIVIDUALS WITH HYPERCORTISOLISM PRESENT WITHOUT CLASSIC PHENOTYPIC FEATURES: BIG FOUR

Type 2 Diabetes (DTC)

Hypertension (DTC)

Obesity (visceral)

Osteoporosis/
Fractures

DTC = Difficult to Control

PREVALENCE OF HYPERCORTISOLISM IN PEOPLE WITH POORLY CONTROLLED T2DM IN US: THE CATALYST TRIAL PART 1

Subjects: 1057 T2DM with A1c = 7.5-11.5%

- ≥ 3 anti-hyperglycemic drugs
- insulin and any other antihyperglycemic drug
- ≥ 2 anti-hyperglycemic drugs plus ≥ 1 micro- or macrovascular complication
- ≥ 2 anti-hyperglycemic and ≥ 2 antihypertensive drugs

Methods: 1 mg Dexamethasone Suppression Test (DST) with 1.8 ug/dl cortisol cut point after excluding patients with common causes for false positive DST

Buse JB et al. Diabetes Care, Apr 18, 2025:dc242841. doi: 10.2337/dc24-2841. Online ahead of print.

PREVALENCE OF HYPERCORTISOLISM IN CATALYST PART 1

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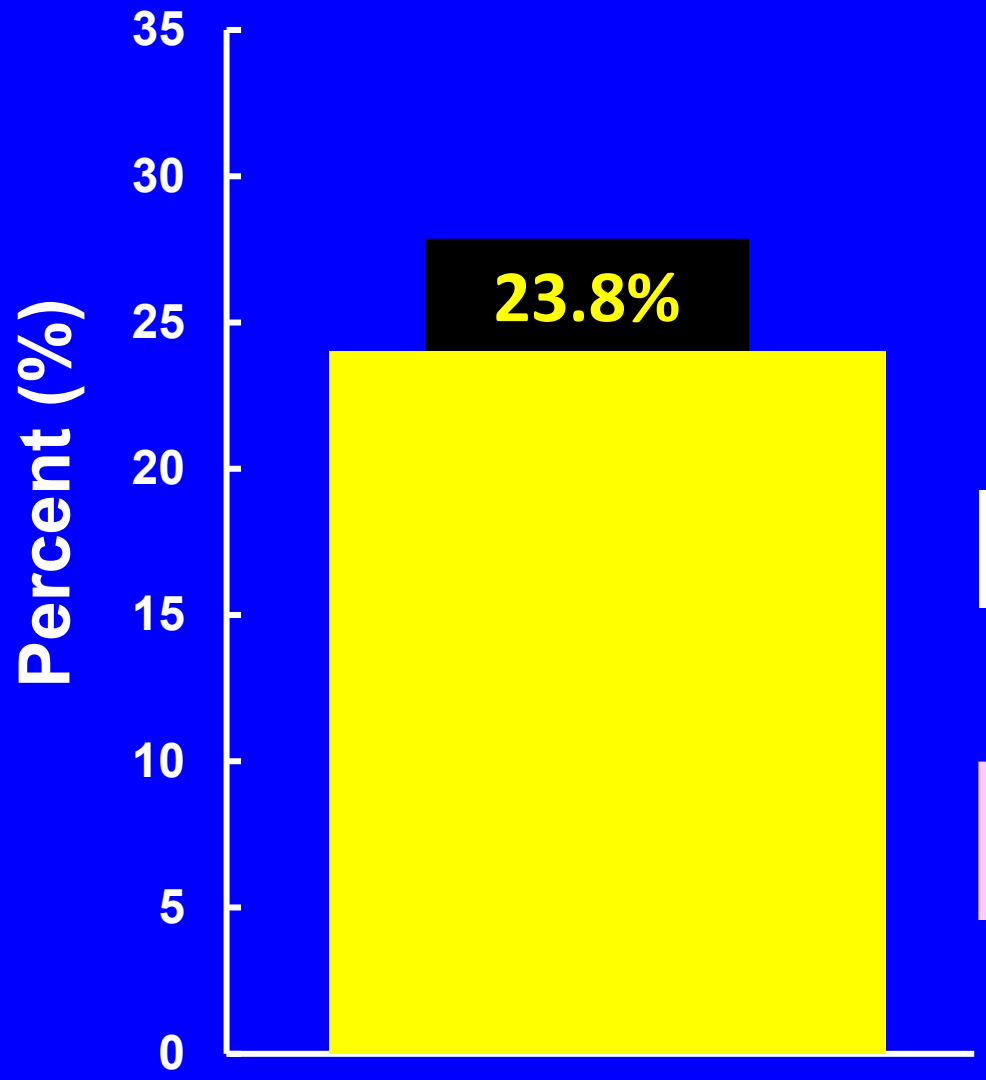
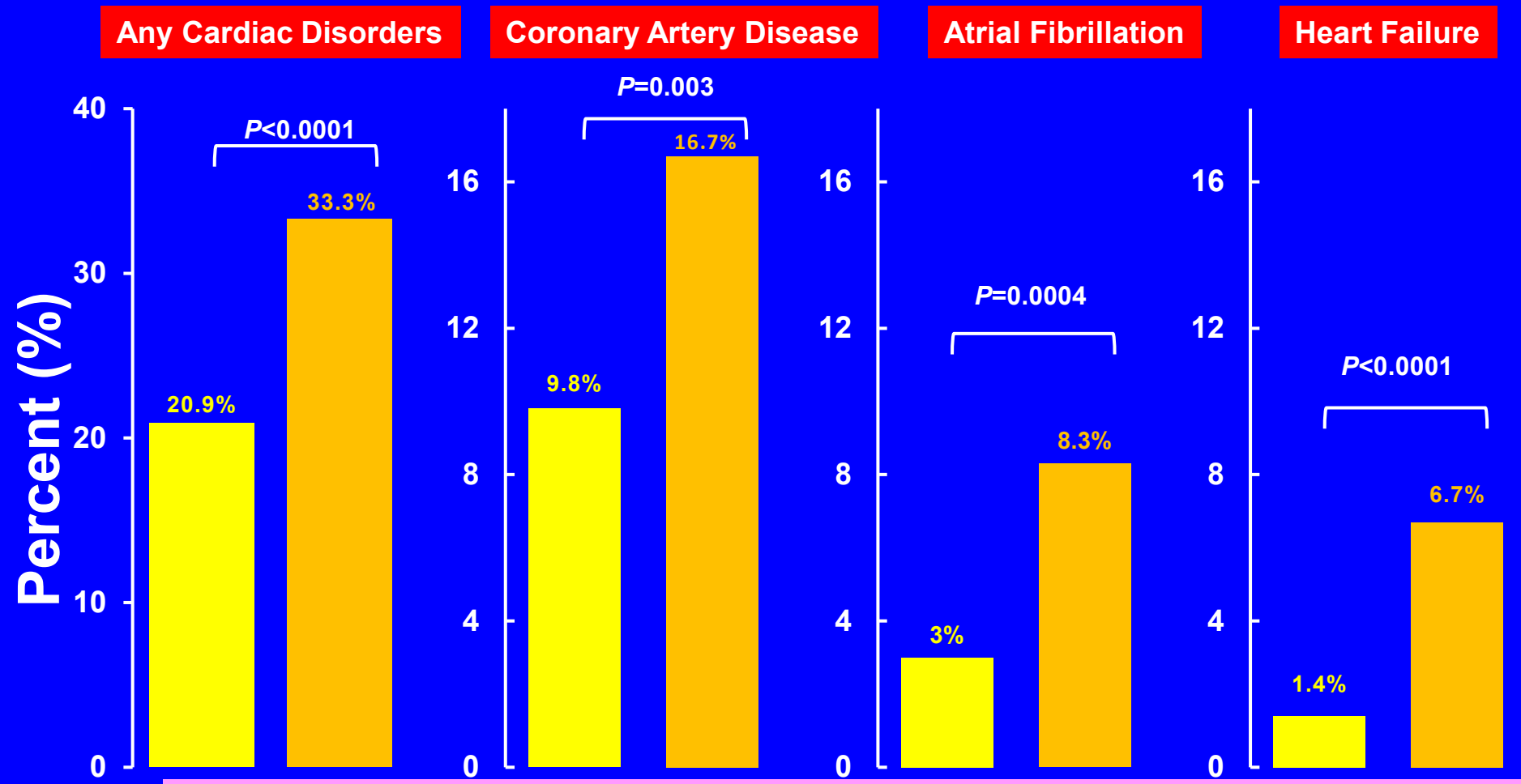


252 of 1057
CATALYST participants screened have hypercortisolism

Post-DST cortisol: 3.5 µg/dL
Post-DST dexamethasone: 413 ng/dL

Approximately 1 in 3 have an adrenal abnormality

PARTICIPANTS WITH HYPERCORTISOLISM HAD MORE CARDIOVASCULAR DISEASE



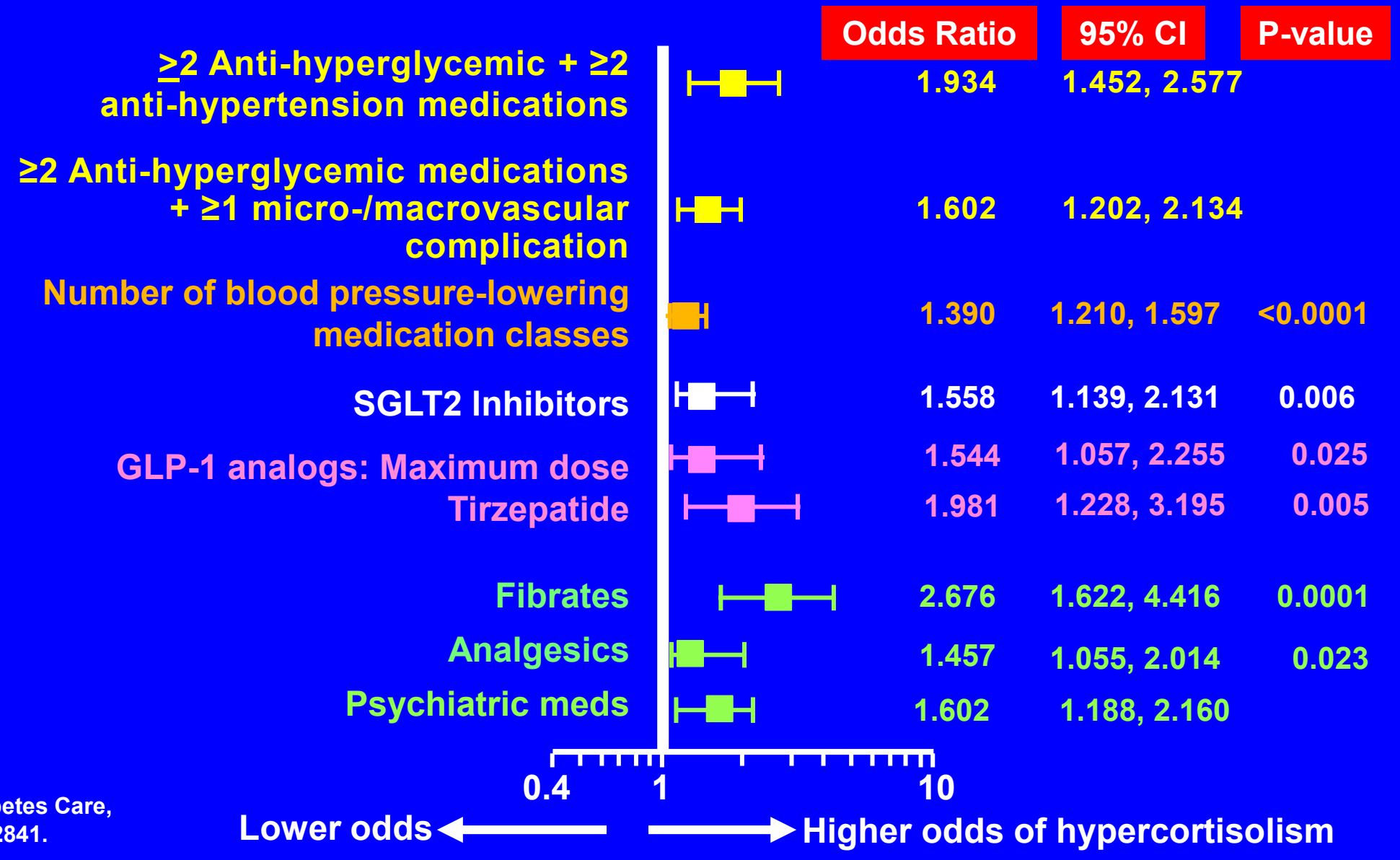
Patients with T2D are at higher CVD risk, and this risk appears to increase further in those who also have hypercortisolism

Post-DST Cortisol < 1.8mg/dl

Post-DST Cortisol ≥1.8mg/dl

Buse JB et al. Diabetes Care, Apr 18, 2025:dc242841.

HIGHER LIKELIHOOD OF HYPERCORTISOLISM IN THOSE WITH HYPERGLYCEMIA PLUS HYPERTENSION, MICRO-/MACROVASCULAR COMPLICATIONS, AND MEDICATION BURDEN



Buse JB et al. Diabetes Care, Apr 18, 2025:dc242841.

EFFECT OF MIFEPRISTONE IN PATIENTS WITH INADEQUATELY CONTROLLED T2D WITH HYPERCORTISOLISM: THE CATALYST TRIAL – PART 2

Subjects: 136 T2DM diagnosed with hypercortisolism based on DST (cortisol >1.8 µg/dl)

Methods: Patients randomized to placebo or mifepristone (300 mg/day with titration to 900 mg/day, as indicated) for 24 weeks.

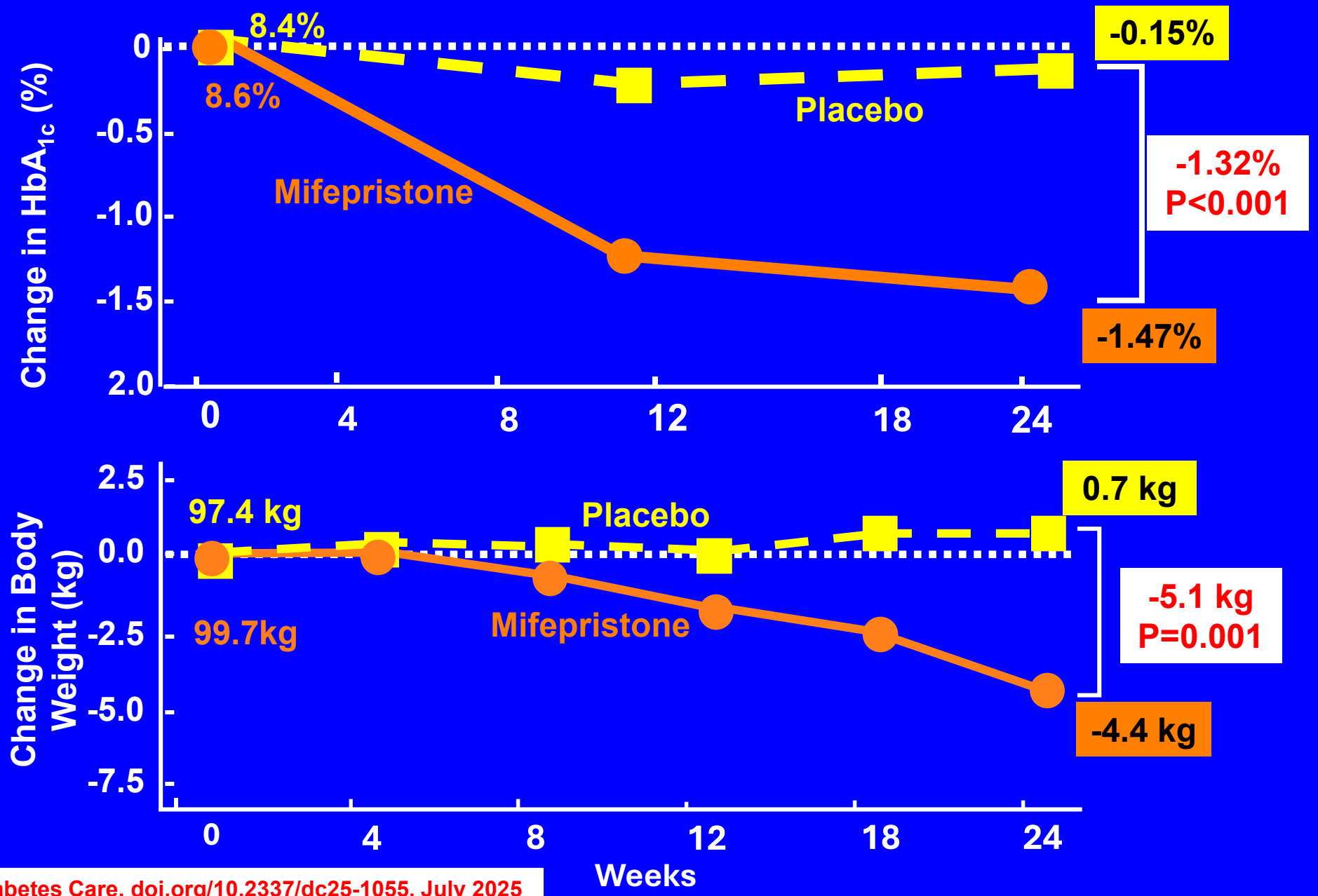
- Potassium, blood pressure, glycemic control monitored every 2-4 weeks
- Weight, waist circumference measured every 4 weeks
- Adverse events recorded at every visit
- A1c measured at 12 and 24 weeks

Primary End Point: A1c

Secondary End Points: Glucose/blood pressure lowering meds, weight, waist circumference, FPG, lipids, blood pressure

DeFronzo RA et al, Diabetes Care, doi.org/10.2337/dc25-1055, July 2025

DECREASE IN A1c AND BODY WEIGHT OVER TIME IN MIFEPRISTONE-TREATED PATIENTS: CATALYST PART 2



DeFronzo RA et al, Diabetes Care, doi.org/10.2337/dc25-1055, July 2025

REDUCTION IN GLUCOSE-LOWERING MEDICATIONS IN CATALYST PART 2

MEDICATION	MIFEPRISTONE	PLACEBO
Fast-acting insulin	30%	11%
Long-acting insulin	49%	13%
Sulfonylurea	22%	11%

DeFronzo RA et al, Diabetes Care, doi.org/10.2337/dc25-1055, July 2025

TREATMENT-EMERGENT ADVERSE EVENTS REPORTED IN >10% OF PARTICIPANTS

Preferred Term n (%)	Mifepristone (n=91)	Placebo (N=43)
At least one TEAE event	86 (94.5%)	36 (83.7%)
At least one treatment-related AE	56 (61.5%)	14 (32.6%)
TEAEs leading to treatment discontinuation	26 (28.6%)	1 (2.3%)
Serious TEAE	29 (31.9%)	2 (4.7%)
Most common TEAEs		
Hypokalemia	27 (29.7%)	0
Fatigue	19 (20.9%)	7 (16.3%)
Nausea	19 (20.9%)	5 (11.6%)
Vomiting	14 (15.4%)	3 (7.0%)
Peripheral edema	14 (15.4%)	1 (2.3%)
Headache	11 (12.1%)	5 (11.6%)
Diarrhea	10 (11.0%)	3 (7.0%)
Dizziness	10 (11.0%)	3 (7.0%)

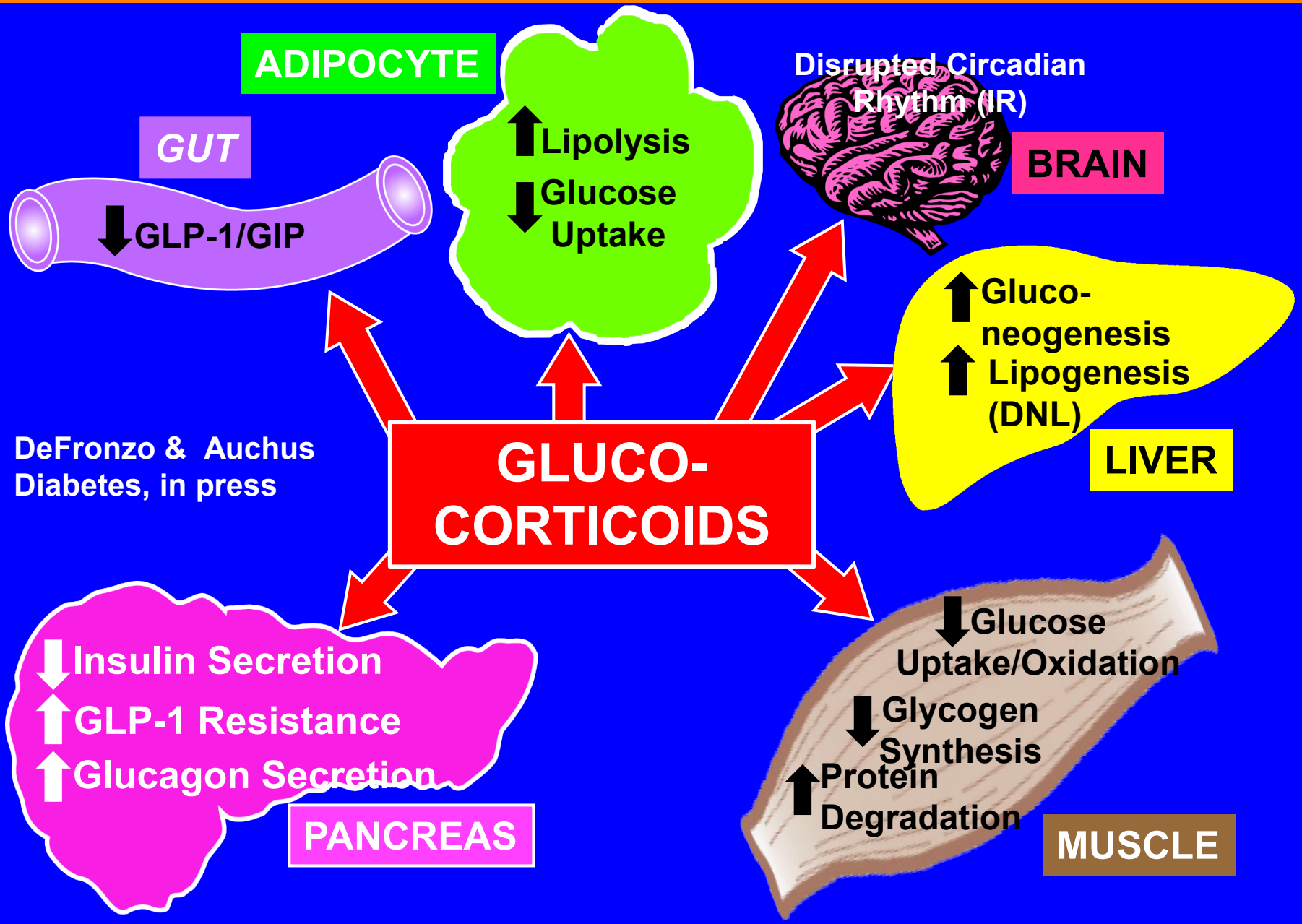
Hypokalemia, a known side-effect of mifepristone, was the most common adverse event

May be due to overstimulation of the mineralocorticoid receptor

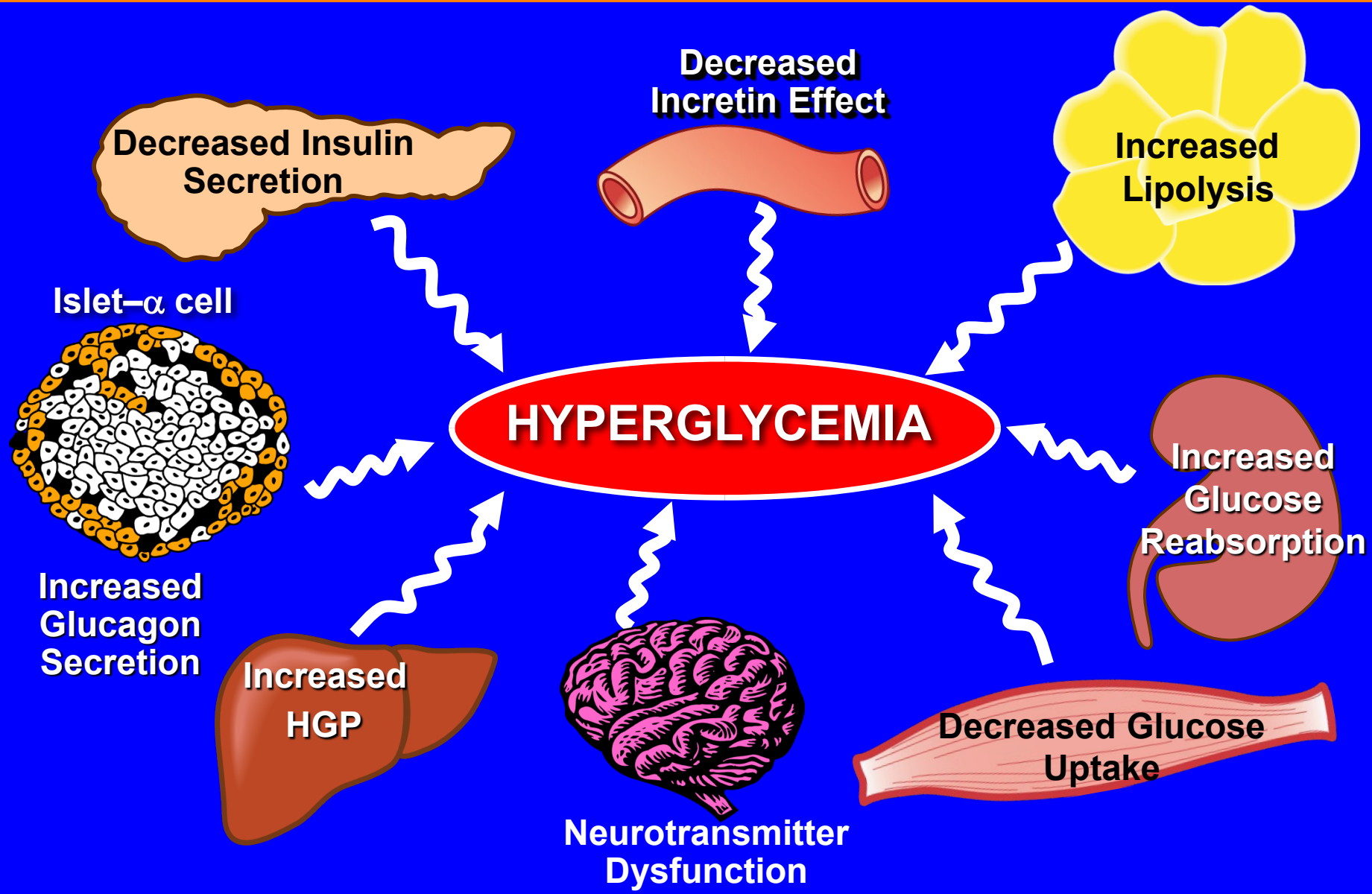
DeFronzo RA et al, Diabetes Care, doi.org/10.2337/dc25-1055, July 2025

HOW DOES HYPERCORTISOLISM CAUSE HYPERGLYCEMIA?

CORTISOL-INDUCED GLUCOSE INTOLERANCE: MECHANISM OF ACTION



OMINOUS OCTET



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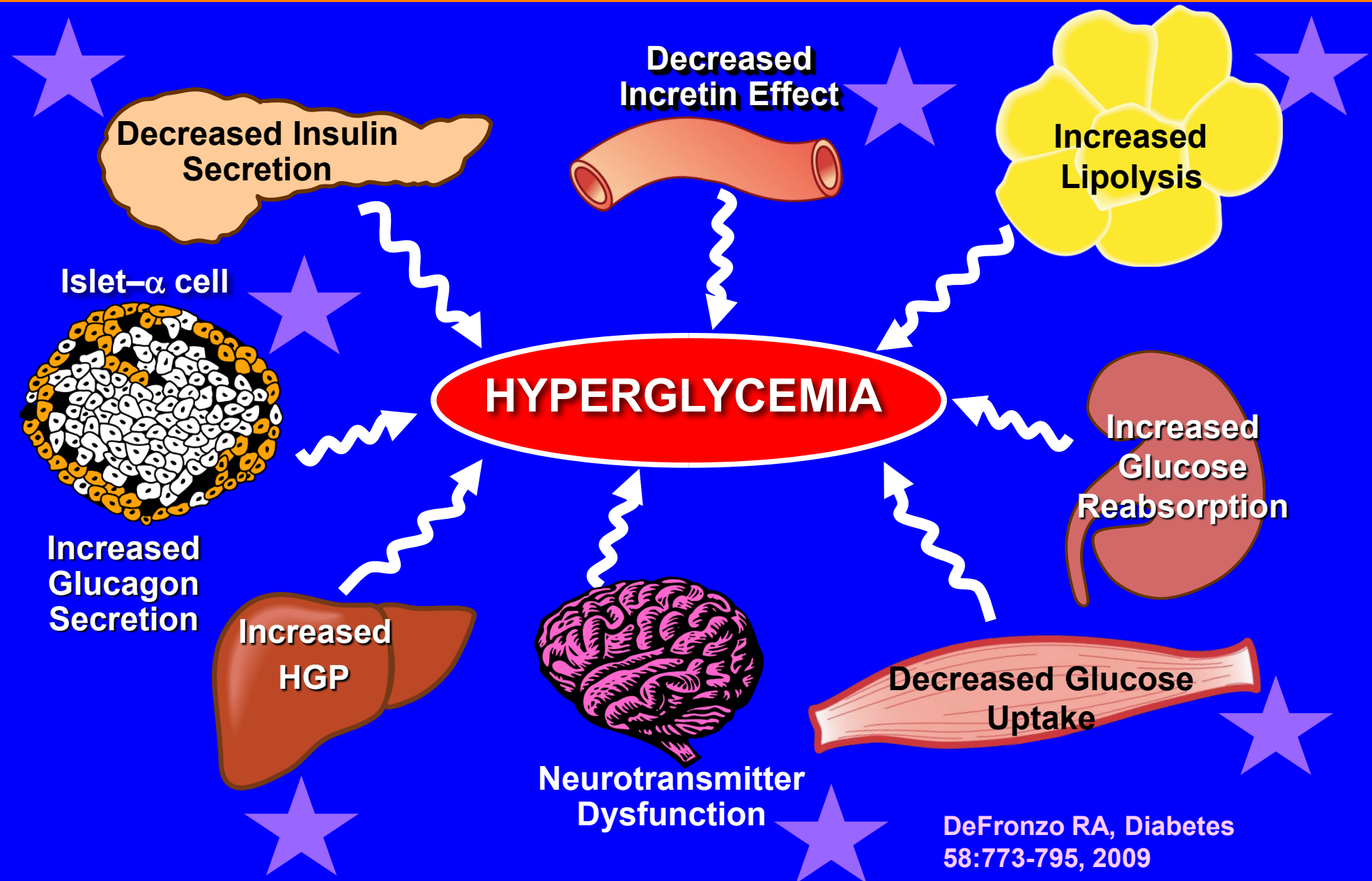
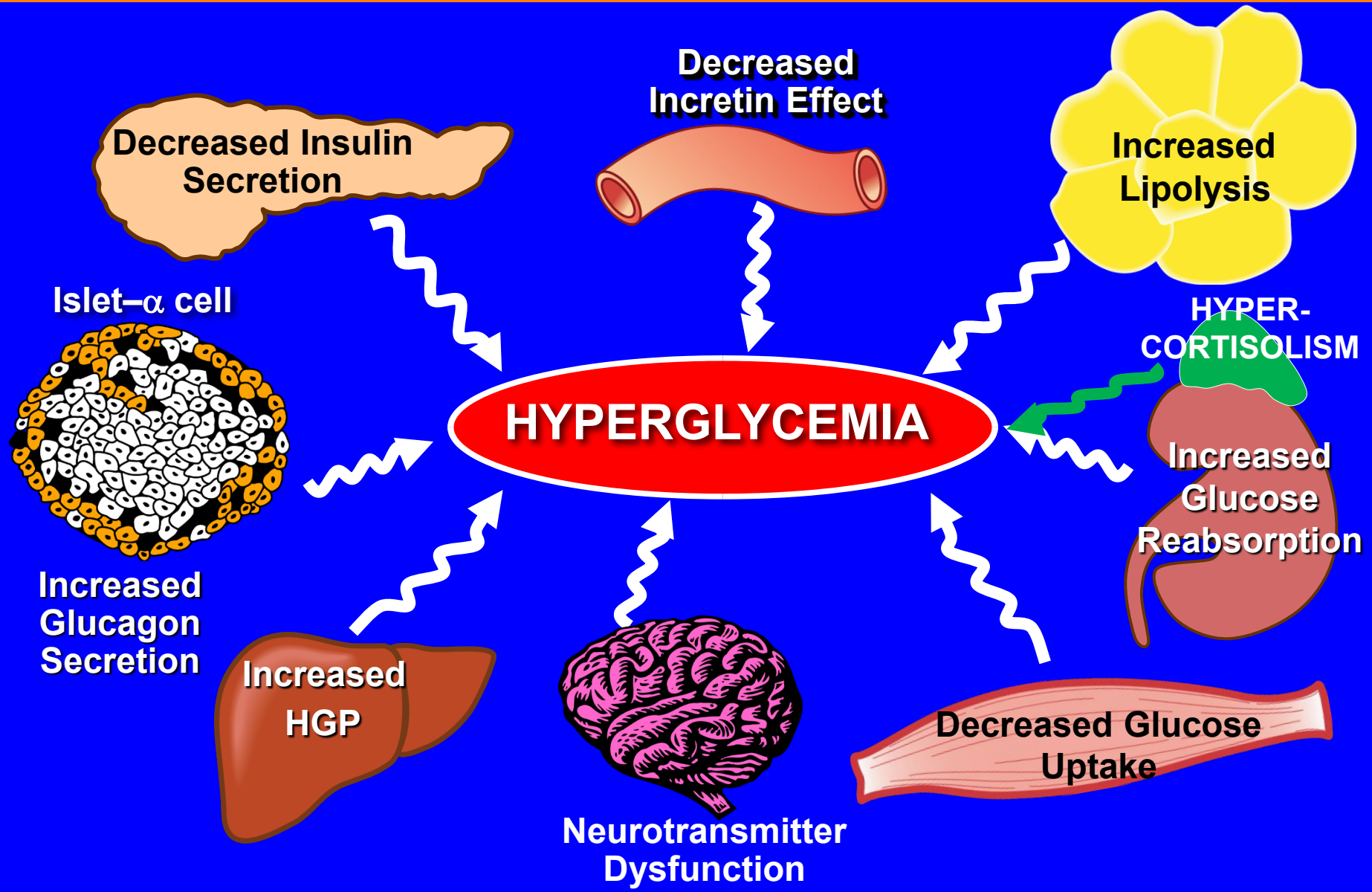


DeFronzo RA, Diabetes 58:773-795, 2009

THE NOXIOUS NINE



SUMMARY

- Hypercortisolism prevalence was **23.8%** among the 1057 CATALYST participants
- **Baseline characteristics that increased odds of having hypercortisolism:**
  - higher medication burden for glucose control, hypertension, lipids, and psych disease
  - presence of cardiovascular disease
- In patients with difficult-to-control T2D and hypercortisolism, mifepristone significantly reduced HbA1c (1.32%) and body weight (5.1 kg)

THANK YOU!