CATALYST Implications—
A New Paradigm for Understanding and Treating Type 2 Diabetes

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85TH SCIENTIFIC SESSIONS

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- Permission is granted to take pictures

Agenda

- Summary
- Implications for understanding type 2 diabetes
- Implications for treatment

Summary – Screening phase

- Hypercortisolism prevalence was 23.8% among the 1057 CATALYST participants with difficult-to-control T2D
  - "Difficult-to-control T2D" defined as A1c 7.5–11.5% on 3+ antihyperglycemic agents [AHA], and/or insulin and any other AHA, and/or 2+ AHA with a complication, and/or 2+ AHA and 2+ antihypertensive agents
  - Very common phenotype, not based on appearance, but ***based on multimorbidity and medication burden***. Baseline characteristics increasing the odds of having hypercortisolism, included ethnicity, age, lower BMI, higher medication burden for hypertension, taking analgesics or fibrates, and taking SGLT2 inhibitors, tirzepatide and high-dose GLP-1 receptor agonists
  - Prevalence of hypercortisolism was 36.6% among those who took ≥3 blood pressure-lowering medications in addition to their glucose-lowering medications
  - Hypercortisolism prevalence was 33% in those with cardiovascular disease vs 21% in those without CVD
- In one third of participants with hypercortisolism, a standard abdominal CT scan revealed an adrenal abnormality

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

Summary – Screening phase

- Screening was easy to perform
  - A single 1-mg overnight dexamethasone suppression test with AM cortisol >1.8 µg/dL (50 nmol/L) and simultaneous dexamethasome level ≥140 ng/dL (with subsequent morning ACTH and DHEA-S) is sufficient testing to establish ACTH-independent hypercortisolism
- An adrenal CT should be performed to establish whether there is potentially surgically remediable disease
- Common causes of false positive tests need to be excluded
  - Use of oral contraceptive pills
  - Use of exogenous steroids
  - Severe psychiatric, medical, or surgical illness
  - Night shift worker (i.e., awake from ~11 PM to 7 AM)
  - Excessive alcohol consumption
  - Severe untreated sleep apnea
  - Hemodialysis or end-stage renal disease

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

Summary – Treatment phase

- Mifepristone therapy reduced A1c by 1.47%
  (LSM change at week 24; 95% CI, -1.79 to -1.14%; baseline A1c, 8.62%)
  - Placebo-adjusted LSM reduction in A1c was -1.32% (95% CI, -1.81 to -0.83; P<0.001)
  - Despite greater glucose-lowering medication dose reduction or discontinuation
  - No difference among those with and without adrenal imaging abnormalities
  - Sensitivity analyses (on treatment and completers) support the findings
- Mifepristone was associated with clinically meaningful changes in body weight (placebo-adjusted LSM, -5.1 kg; 95% CI, -8.2 to -2.0), BMI and waist circumference

LSM, least square mean; CI, confidence interval

Summary – Treatment phase

- Fewer completers in the mifepristone arm, 53.8%, compared with 82.2% in the placebo arm
  - The most common reasons for treatment discontinuation in the mifepristone arm were adverse events (61.9%)
- While mean blood pressure on mifepristone remained at or near the recommended target of less than 130/80 mmHg throughout the study, mean SBP increased from 125.0 to 131.7 mmHg in the mifepristone arm compared to a reduction from 125.4 to 123.0 mmHg in the placebo arm

LSM, least square mean; CI, confidence interval

Summary – Treatment phase

- No new safety signals for mifepristone were identified
- One death was reported during the study in the placebo arm (attributed to cardiovascular disease)
- Serious treatment-emergent adverse events were reported more frequently in the mifepristone arm (32% versus 5%)
  - Serious treatment-emergent adverse events occurring in more than 3% of participants were hypokalemia (5%; mifepristone) and euglycemic ketoacidosis (3%; mifepristone [all on SGLT2i])
- Many of the most common adverse events were consistent with glucocorticoid withdrawal, which can occur with any treatment for hypercortisolism
- Hypokalemia, a know adverse event of mifepristone, may be better addressed in clinical practice by proactive use of potassium-sparing diuretics

LSM, least square mean; CI, confidence interval

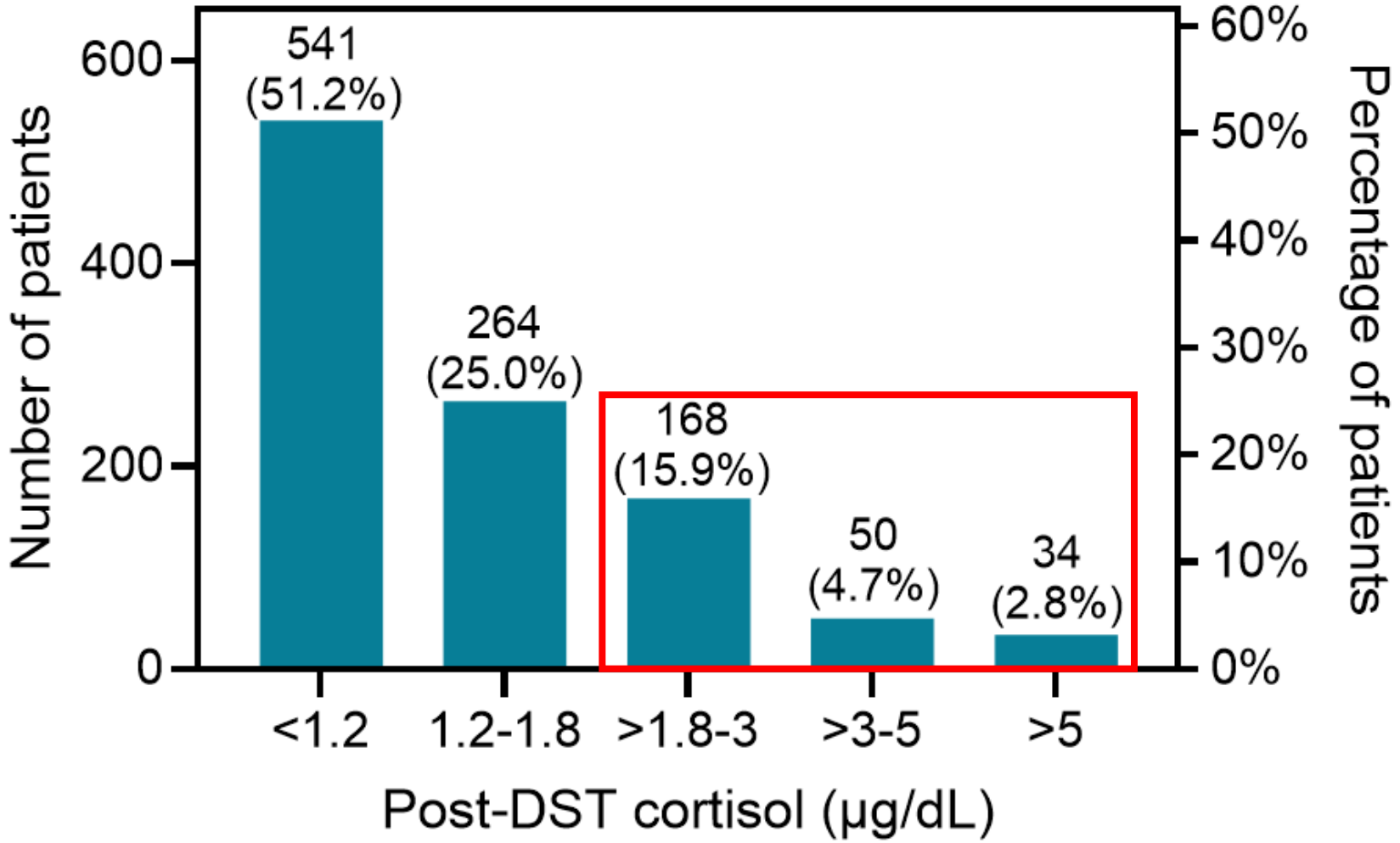
Action Steps

CATALYST implications

- Screen for hypercortisolism in people whose T2D is challenging to treat adequately
- The mifepristone results provide a proof of concept that identifying and addressing hypercortisolism is a novel path to improving diabetes care in millions of people worldwide
- Mifepristone for the treatment of hypercortisolism requires individual, patient-centered considerations[1]
  - Drug-drug interactions
  - Set expectations appropriately with patients regarding steroid withdrawal symptoms
  - Treat hypokalemia proactively, consider preemptively prescribing mineralocorticoid receptor antagonists
- ***Guidelines should reflect the insights from CATALYST***

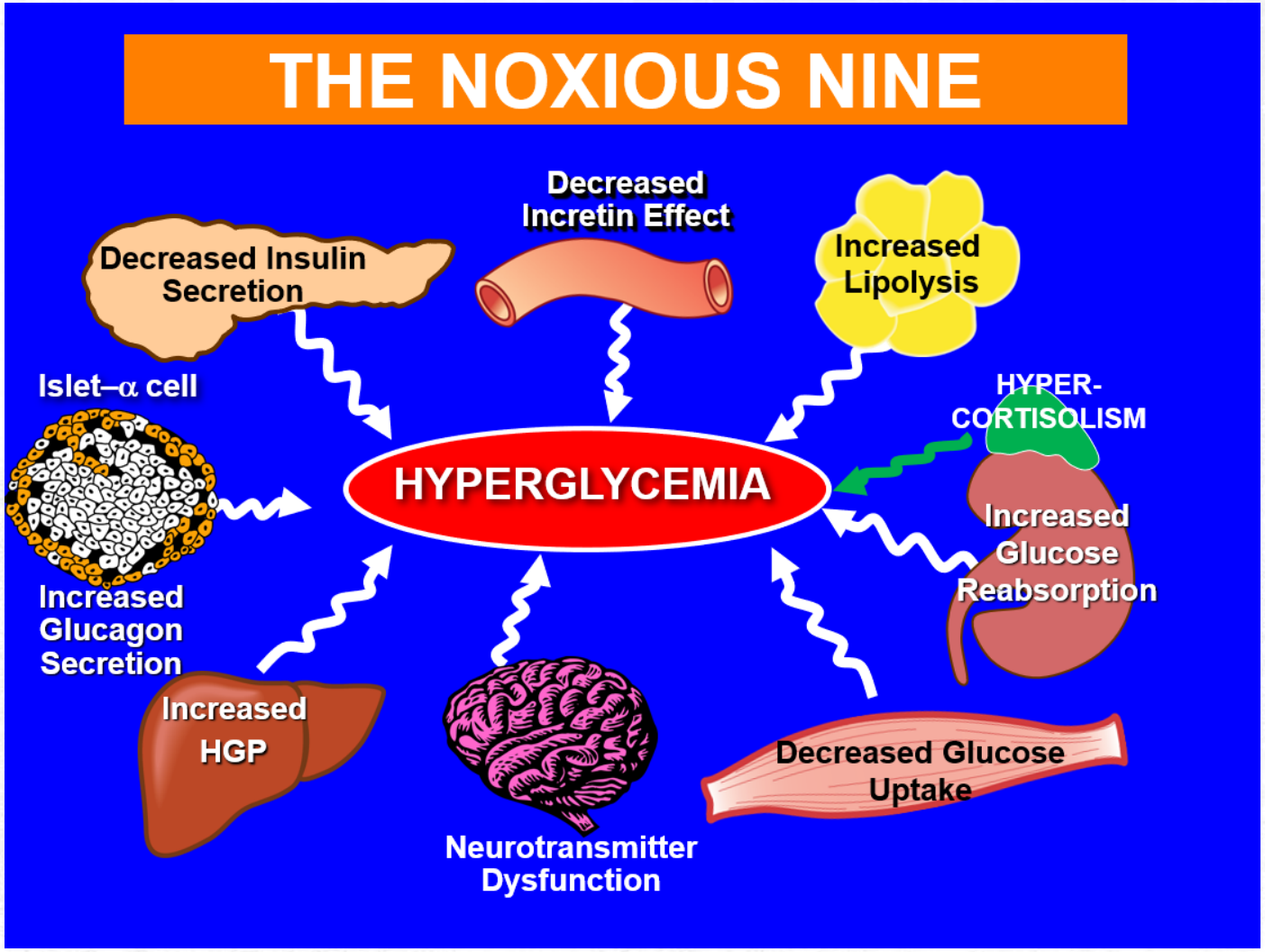
1. Brown et al. *Clinical Diabetes and Endocrinology* (2020) 6:18

Post-DST cortisol values among participants who completed the DST with dexamethasone level ≥140 ng/dL



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

Hypercortisolism is part of the general pathophysiology of type 2 diabetes



Slide adapted from ADA 2024 presentation with permission from Dr. Ralph DeFronzo, San Antonio

Analogy to Hyperaldosteronism and Resistant Hypertension

- 1955: Conn's syndrome described as a case series
- Today we understand that hyperaldosteronism is etiologic in ~10–30% of HTN and ~1/3rd have solitary adrenal adenoma
- Still, consistent screening for hyperaldosteronism is not routine
- But, anti-mineralocorticoid therapy is being adopted as a customary 2nd or 3rd line therapy

Primary Aldosteronism Foundation. primaryaldosteronism.org

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