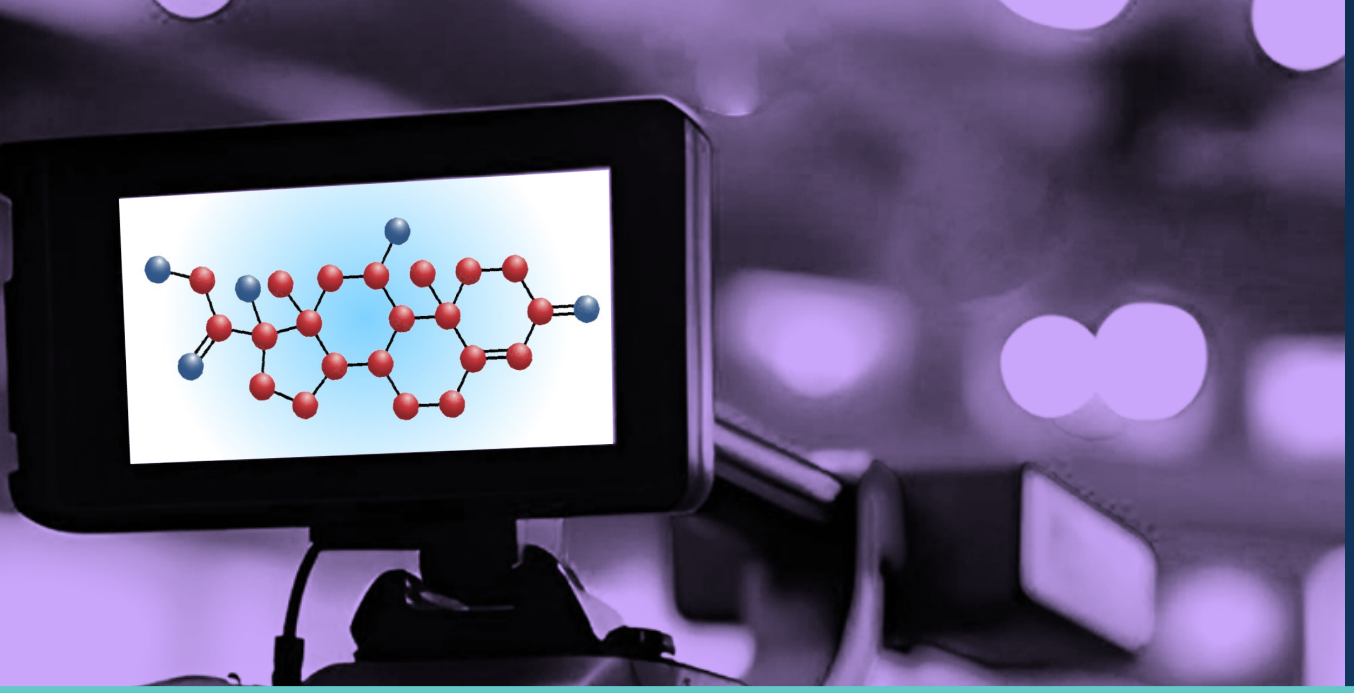
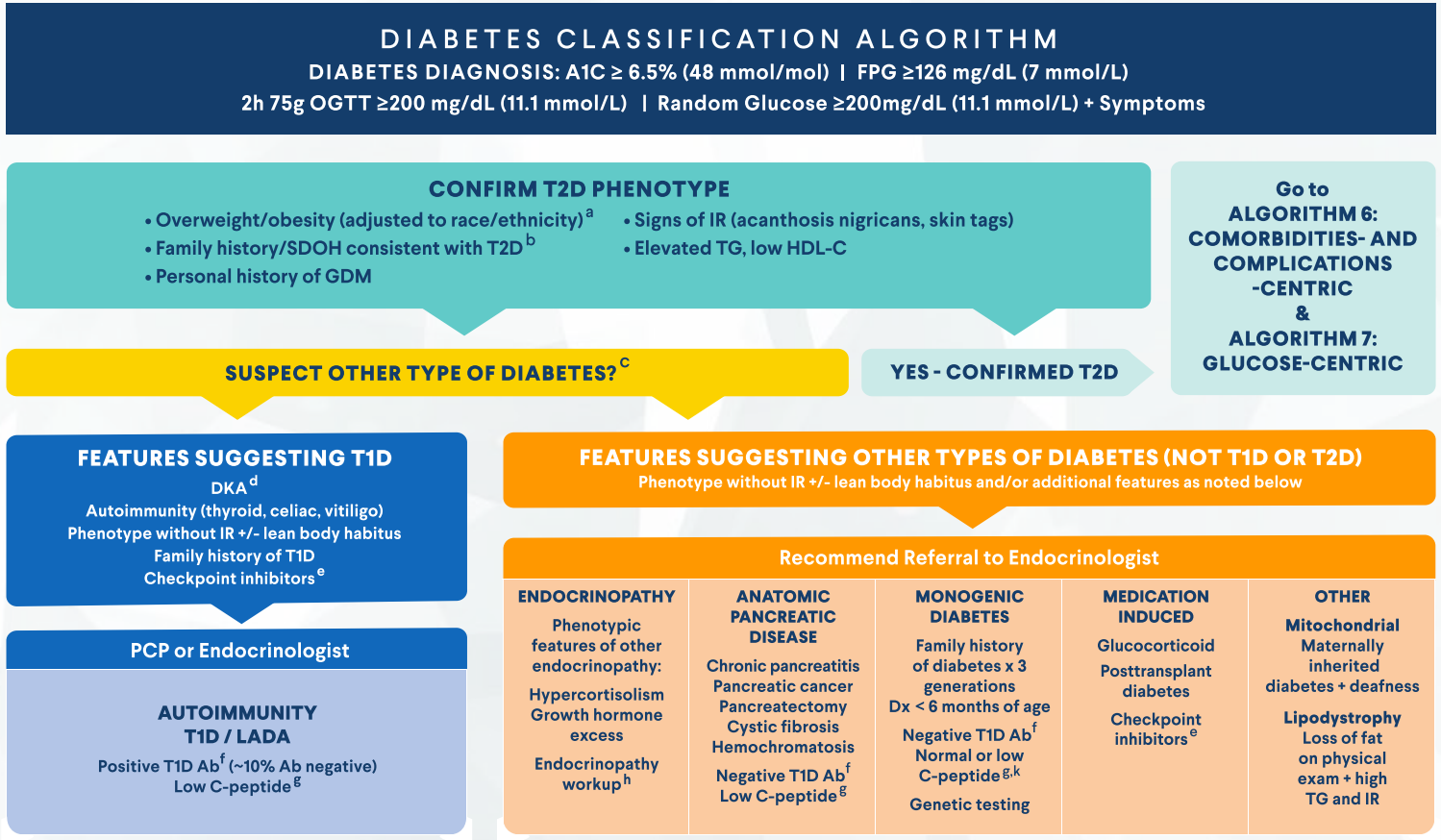


The Cortisol Reports

Episode 5 - AACE Guidance in Action: When to Suspect and Treat Hypercortisolism in Adults with Diabetes

AACE Guidance in Action: *New Addition!*



[a]Lower BMI cut-off values for overweight and obesity may be applicable to individuals of Asian descent. [b]A strong family history of obesity and diabetes in multiple family members and SDOH increases the likelihood of T2D versus other types (eg, monogenic diabetes). [c]Despite appropriate therapy and adherence, glucose levels remain above target. [d]DKA should prompt evaluation for T1D. DKA also can occur with a T2D phenotype (eg, ketosis-prone diabetes). [e]Checkpoint inhibitor–associated autoimmune diabetes may be Ab positive (50%), with low C-peptide, often presenting with DKA, and requires insulin therapy independent of Ab status and is irreversible. [f]T1D Ab: glutamic acid decarboxylase Ab, IA-2 Ab, zinc transporter 8 Ab and insulin Ab (if insulin naïve). Corticosteroids or immunosuppression may mask Ab positivity. [g]Check concomitant glucose for C-peptide interpretation (glucose >72 mg/dL [>4 mmol/L]). C-peptide is suppressed with hypoglycemia and severe hyperglycemia/DKA. May need to repeat C-peptide assessment for clarification of Dx. [h]Unexpected degree of insulin resistance especially with features of hypercortisolism or acromegaly. [k]C-peptide declines in most monogenic diabetes (eg, HNF1α may require insulin later in course).

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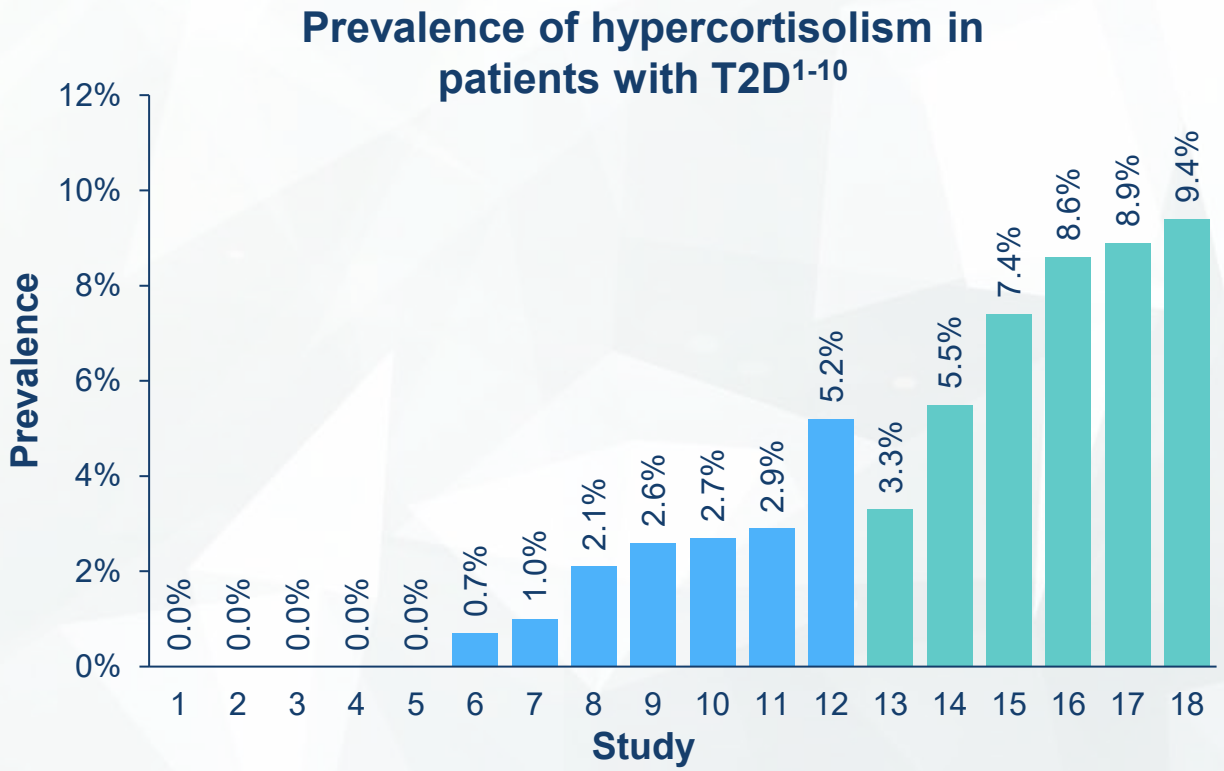
Samson S, et al. *Endocr Pract.* 2026.

Hypercortisolism in Patients with T2D



It may be worth screening patients with poorly controlled metabolic disorders for underlying hypercortisolism

No.	Study	N	Population	Prevalence
1	Liu (2005)[1,2]	141	T2D (outpatients)	0%
2	Newsome (2008)[1,2]	171	T2D (outpatients)	0%
3	Mullan (2010)[1,2]	201	T2D (outpatients)	0%
4	Gagliardi (2010)[1,2]	100	T2D (outpatients)	0%
5	Budyal (2015)[1,2]	993	T2D (outpatients)	0%
6	Terzolo (2012)[1,2]	813	T2D (outpatients)	0.7%
7	Reimondo (2007)[1,2]	100	T2D (newly diagnosed)	1%
8	Contreras (2000)[1,3]	48	T2D (outpatients)	2.1%
9	Taniguchi (2008)[4]	77	T2D (inpatients)	2.6%
10	Mert (2012)[1]	148	Obese T2D	2.7%
11	Caetano (2007)[1,2]	103	T2D (outpatients)	2.9%
12	Steffensen (2019)[1,5]	384	T2D (newly diagnosed)	5.2%

No.	Study	N	Population	Prevalence
13	Leibowitz (1996)[6]	90	Obese with **uncontrolled T2D** (inpatients)	**3.3%**
14	Catargi (2003)[7]	200	Overweight or obese T2D (**poor metabolic control**[a]; inpatients)	**5.5%**
15	León-Justel (2016)[8]	353	Obese or **uncontrolled** T2D/HTN (outpatients)	**7.4%**
16	Costa (2016)[9]	393	T2D + **high CV risk**[b] (outpatients)	**8.6%**
17	Murakami (2010)[1,2]	90	T2D (**inpatients**)	**8.9%**
18	Chiodini (2005)[2,10]	289	T2D (**poor metabolic control**; inpatients)	**9.4%**

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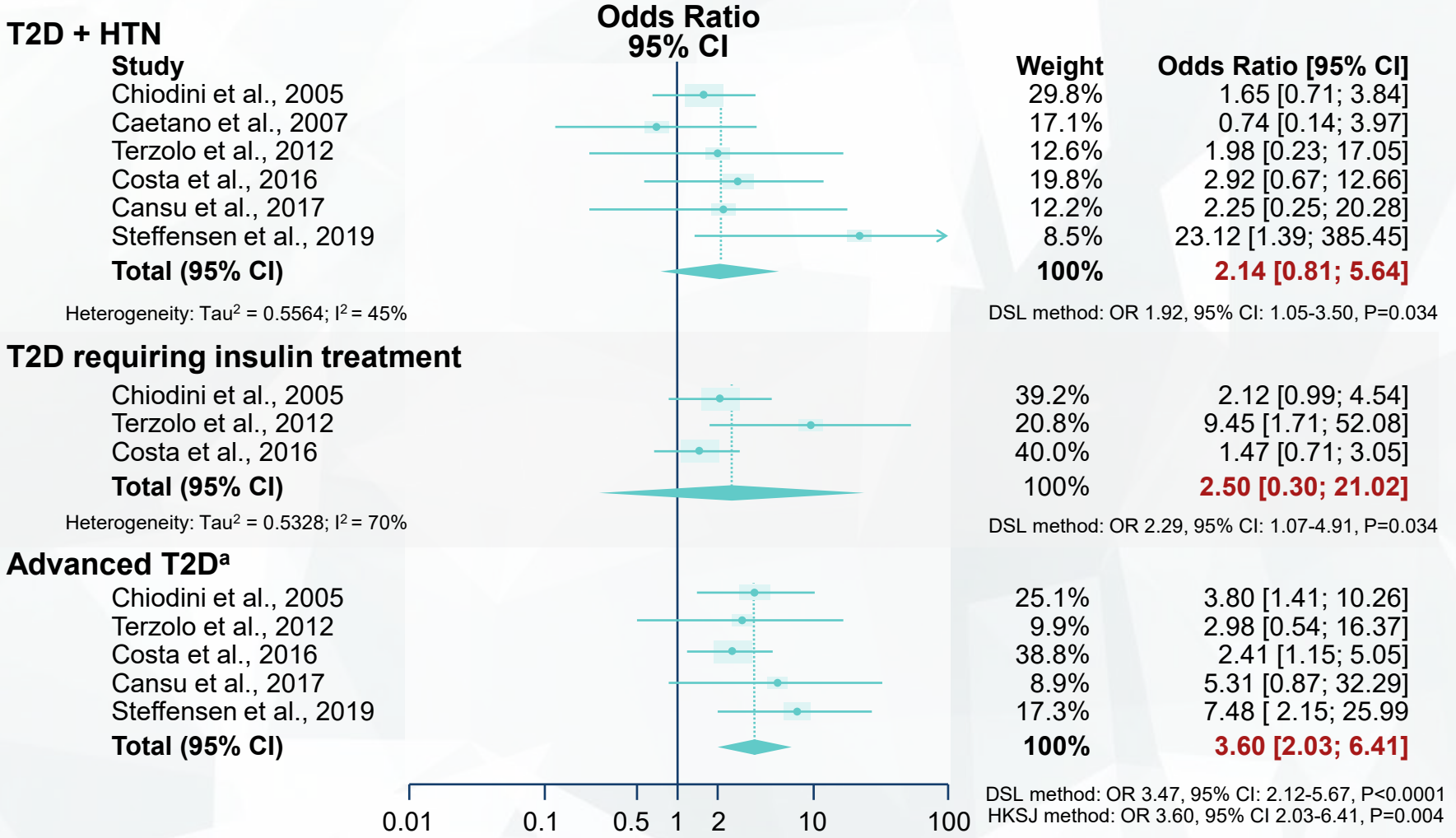
[a]HbA1C >8%. [b]Included any microvascular or macrovascular complication, with ≥2 other modifiable cardiovascular risk factors.

Giovanelli L, et al. *J Endocrinol Invest*. 2021; Scaroni C, et al. *Endocr Rev*. 2017; Contreras LN, et al. *Medicina (B Aires)*. 2000; Taniguchi T, et al. *Endocr J*. 2008; Steffensen C, et al. *Horm Metab Res*. 2019; Leibowitz G, et al. *Clin Endocrinol (Oxf)*. 1996; Catargi B, et al. *J Clin Endocrinol Metab*. 2003; León-Justel A, et al. *J Clin Endocrinol Metab*. 2016; Costa DS, et al. *J Diabetes Complications*. 2016; Chiodini I, et al. *Eur J Endocrinol*. 2005.

Patients with Advanced T2D have a High Prevalence of Hypercortisolism



DSL=DerSimonian and Laird method; HKSJ=Hartung-Knapp-Sidik-Jonkman method.
[a]Presence of microvascular and/or macrovascular complications or presence of insulin treatment plus HTN or presence of HTN treated with 2 or more drugs.
Aresta C, et al. *Endocr Pract*. 2021.

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CATALYST Enrollment Criteria:

HbA1c 7.5%–11.5% and

- ≥3 AHA
- Insulin plus any AHA
- ≥2 AHA + micro or macrovascular
- ≥2 AHA + ≥2 antihypertensives

Exclusion:

- EOCPs
- Alcohol
- Severe, untreated OSA
- Hemodialysis/ESRD
- Night-shift
- Severe illness

N = 1057

O/N 1 mg Dexamethasone
Cortisol ≥1.8 mg/dL

n = 252

23.8% of total
33.3% with CVD
36.6% HTN on ≥3 Rx

n = 219

Abdominal CT

- No imaging abnormality (65.3%)
- Other adrenal imaging abnormality (3.7%)
- Uni/Bilateral adrenal enlargement (3.7%)
- Bilateral adrenal nodules (4.6%)
- Unilateral adrenal nodule(s) (22.8%)

34.7% with adrenal abnormality on CT

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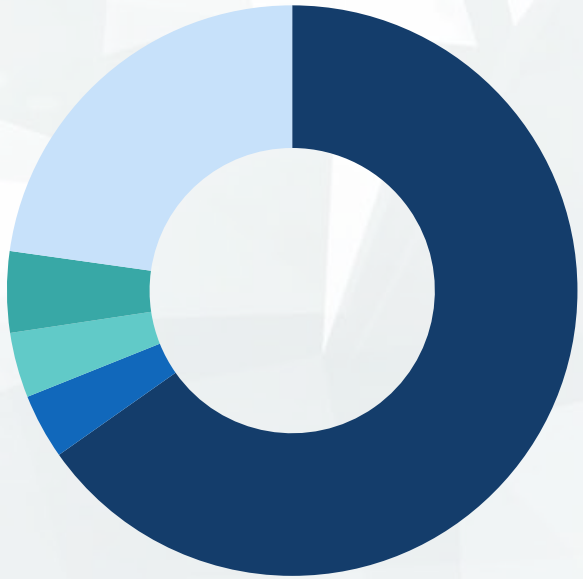
AHA- Antihyperglycemic agent; EOCPs, estrogen containing oral contraceptive pills; OSA obstructive sleep apnea.

Buse JB, et al. *Diabetes Care*. 2025.

Focus on Adrenal Imaging

n = 219
Abdominal CT

34.7% with adrenal abnormality on CT



- No imaging abnormality 65.30%
- Other adrenal imaging abnormality 3.70%
- Uni/Bilateral adrenal enlargement 3.70%
- Bilateral adrenal nodules 4.60%
- Unilateral adrenal nodule(s) 22.80%

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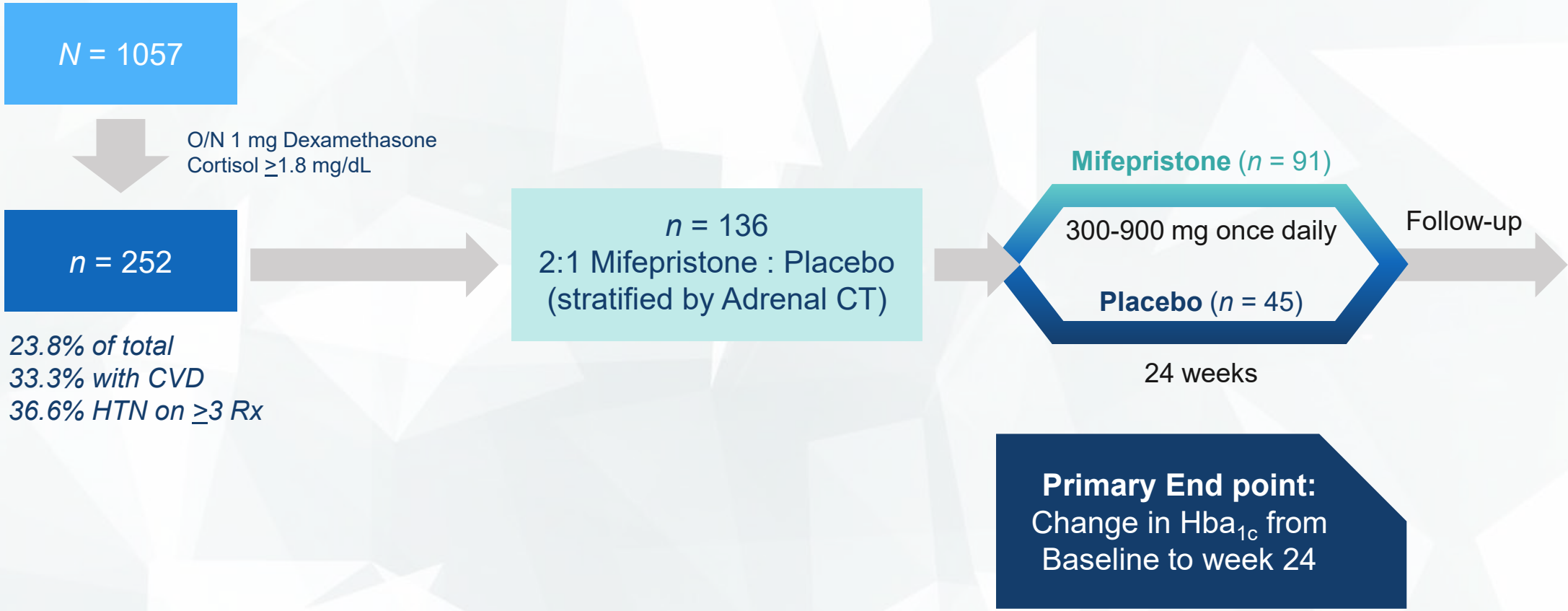
Buse JB, et al. *Diabetes Care*. 2025.

Enrollment in Treatment Phase



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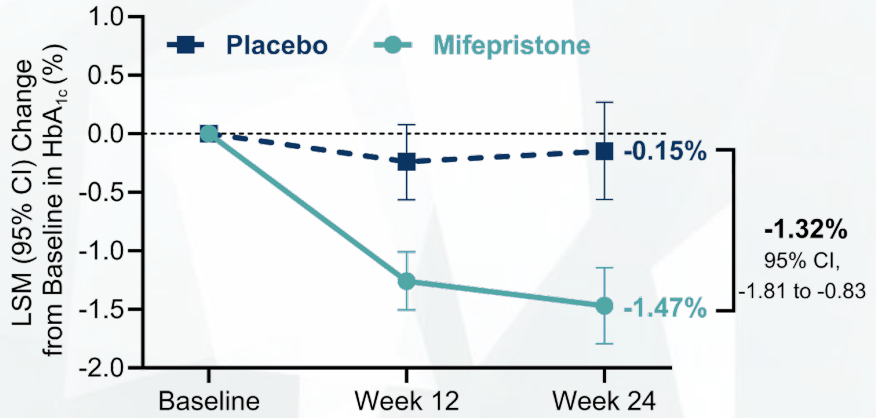
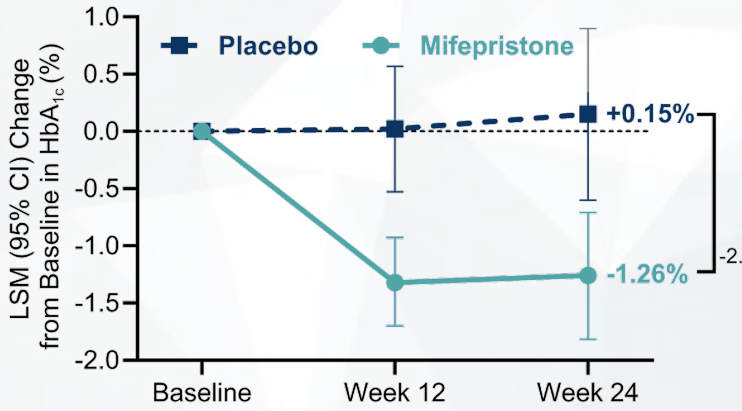
Buse JB, et al. *Diabetes Care*. 2025.

CATALYST Results



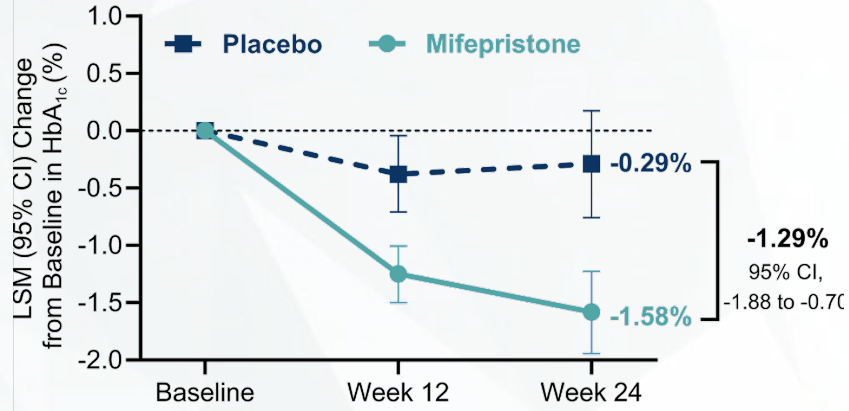
Number of participants			
Mifepristone	86	74	62
Placebo	44	40	38
P value for LSM difference from placebo		<0.001	<0.001

A1c reduction in patients WITH adrenal abnormalities



Number of participants			
Mifepristone	25	22	19
Placebo	13	11	11

A1c reduction in patients WITHOUT adrenal abnormalities



Number of participants			
Mifepristone	61	52	43
Placebo	31	29	27

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AACME® AMERICAN ACADEMY OF CME, INC.

DeFrono RA, et al. *Diabetes Care*. 2025.

CATALYST Results: Other Key Findings

- Improvements in glycemic control were accompanied by reductions in:
  - Glucose-lowering medications (e.g., insulin, sulfonylureas)
  - Body weight (-4.4 kg)
  - BMI and waist circumference (-1.5 kg/m^2 and -5.2 cm)
- Safety:
  - 53.8% completed 24 weeks on mifepristone (82.2% placebo)
  - Adverse events were manageable and consistent with known safety profile (SEISMIC)
  - Adverse events occurring in >10%: hypokalemia, fatigue, nausea, vomiting, headache, peripheral edema, diarrhea, and dizziness
  - Increase in blood pressure also occurred
    - Secondary to increased action of cortisol at the aldosterone receptor
    - A mineralocorticoid antagonist, such as spironolactone, can be used to counteract that effect

DeFrono RA, et al. *Diabetes Care*. 2025.

Differences: CATALYST and Overt CS

- Only a Dexamethasone suppression test was used in CATALYST with the maximally sensitive cortisol threshold of ≥1.8 mg/dL which can have a high false positive rate (10%)
- When diagnosing overt Cushing syndrome, other adjunct tests are required (with at least 2/3 positive)
  - 24-hour urine free cortisol
  - Late night saliva cortisol
- Further work-up is required to determine ACTH dependent or independent disease
  - ACTH, DHEAS
  - Localization of disease to adrenal, ectopic or pituitary source
- The usual symptoms and signs of overt Cushing syndrome may not always be present in mild adrenal disease such as MACS but the metabolic impact can be seen

Neiman LK, et al. *Diabetes Care*. 2025.

Review: Clinical Presentation of Cushing Syndrome

Clinical features that best discriminate hypercortisolism (not correlated to disease severity):

- Easy bruising
- Facial plethora
- Proximal myopathy/muscle weakness
- Reddish-purple striae

Typical severity of hypercortisolism by etiology (with exceptions):

- Pituitary CS: usually mild to moderate
- Adrenal CS: moderate to severe
- Ectopic CS: usually severe

Neiman LK, et al. *Diabetes Care*. 2025.