
# Leading-Edge Strategies for Diagnosis and Medical Management of Cushing Syndrome/ Hypercortisolism

# Cushing's at the Core

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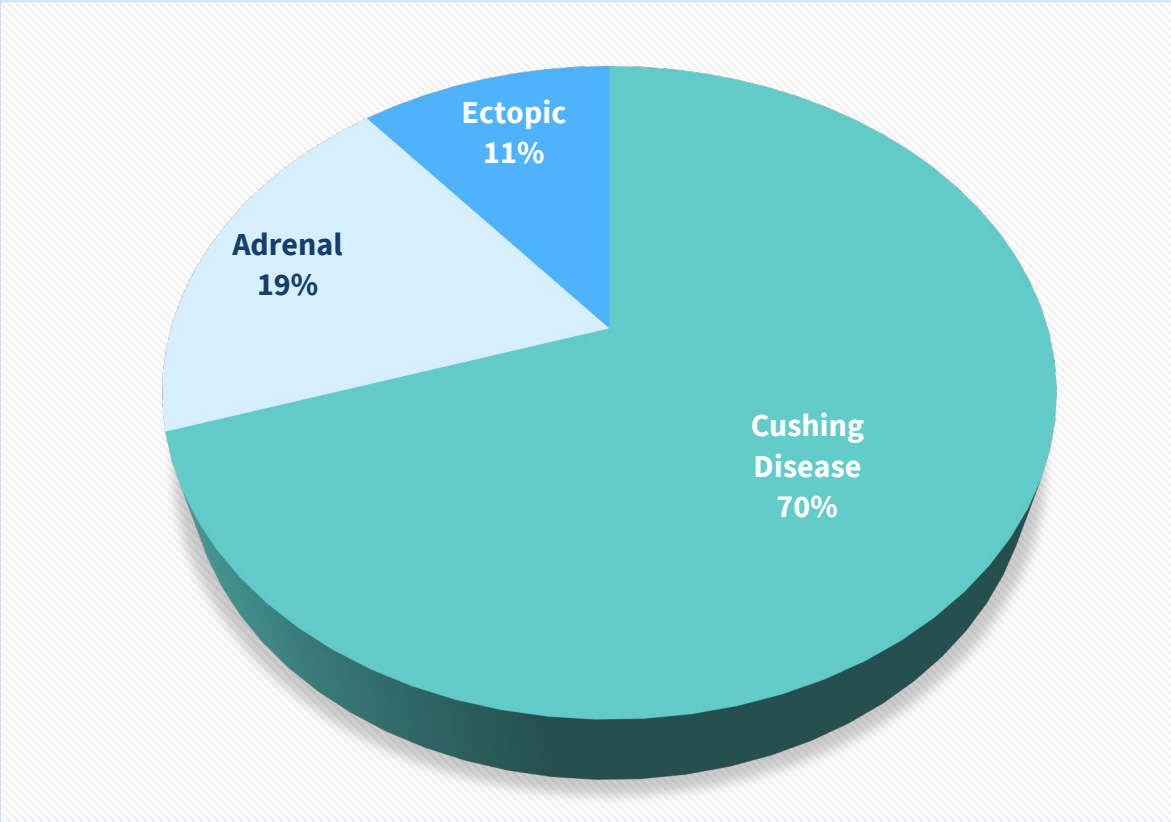
# Cortisol Clues: Review of Screening for and Diagnosing Mild Cushing Syndrome


# Cortisol Clues: Who to Screen?

# The Etiologies of Endogenous Cushing Syndrome

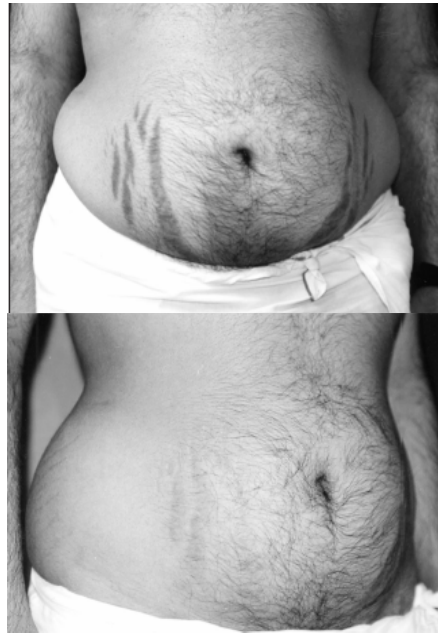



Incidence:10–15 new cases per million per year
Prevalence:40–70 cases per million

**It is estimated that up to 1 million people in the US may have MACS**

Tritos NA, et al. *Nat Rev Endocrinol*. 2011; Jing Y, et al. *Ann Intern Med*. 2022.

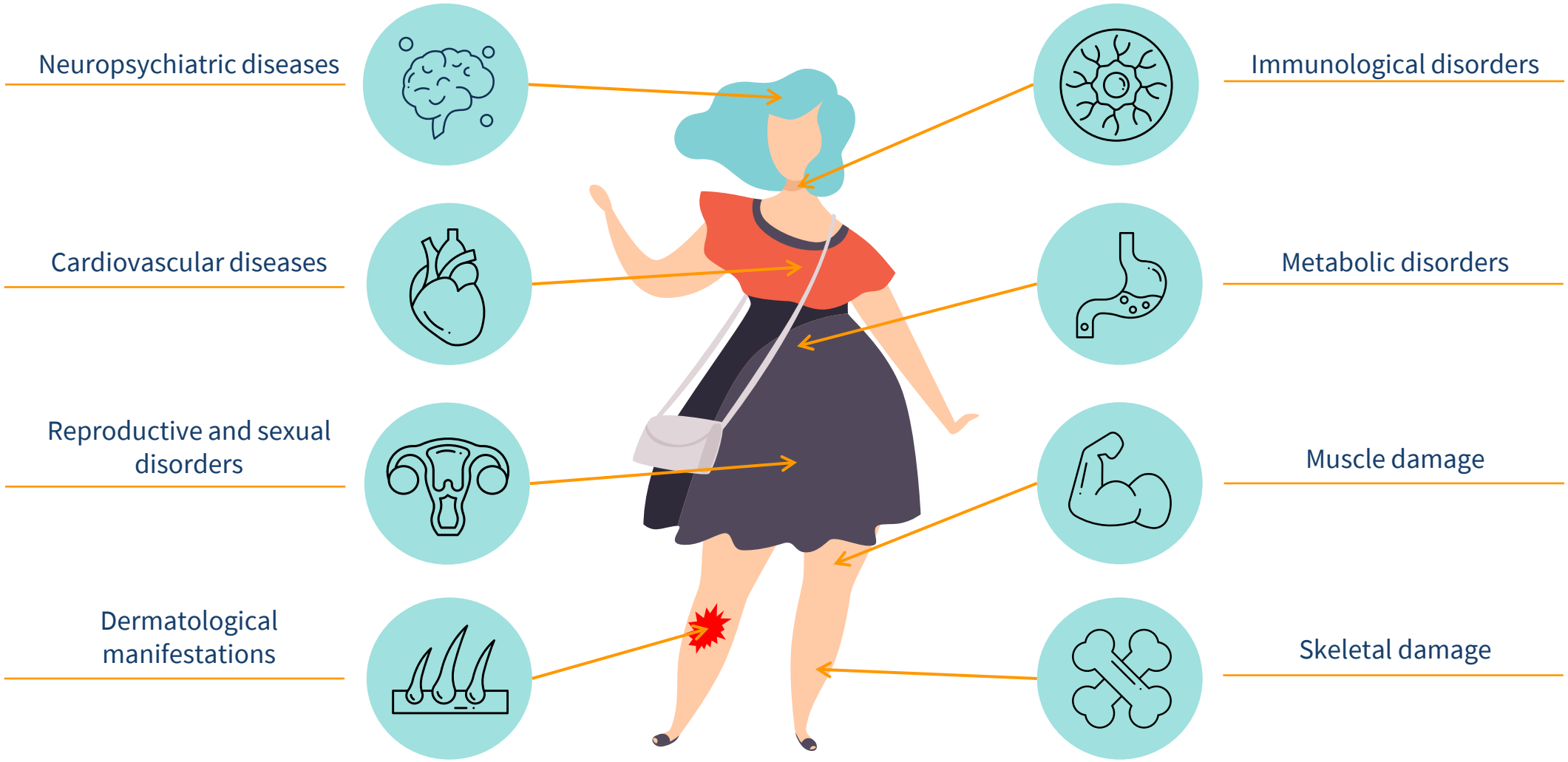
# Exogenous Cushing Syndrome



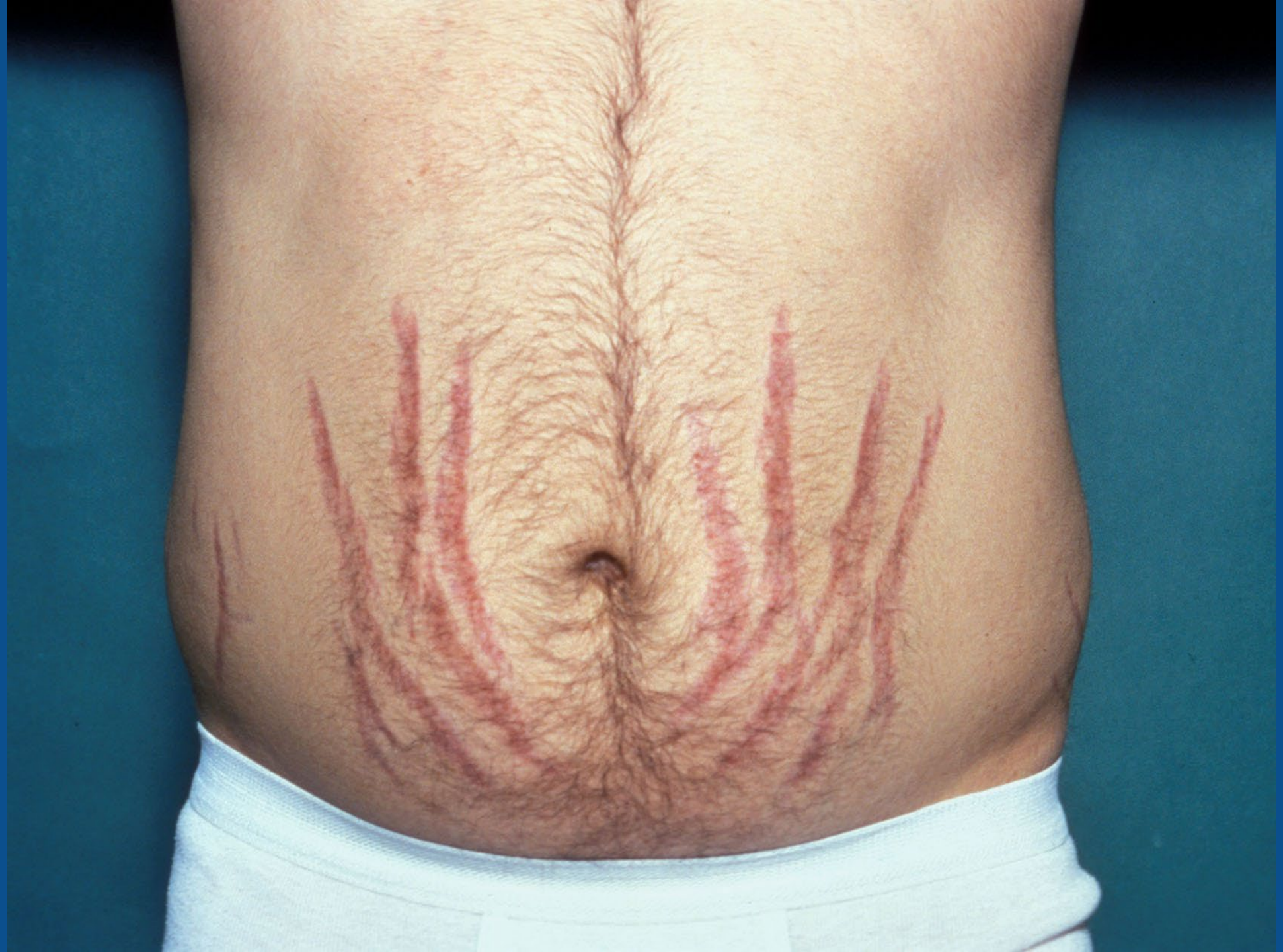
- 33-year-old Arab man was referred to the diabetes clinic
  - Extensive ophthalmologic complaints. He had used glucocorticoid eyedrops such as dexamethasone, prednisolone, and hydrocortisone preparations for 15 years.
  - The patient reported feeling unwell whenever he neglected to use the eyedrops for 1 or 2 days.
    - Cortisol <1 ug/dL, ACTH 9 pg/mL (9-54), T score -3.3 at spine
- Interactions between budesonide, fluticasone and systemic triamcinolone with:
  - Antifungal agents (Azole derivatives)
  - Ritonavir

Lipworth BJ, et al. *Arch Intern Med*. 1999; Katz HI, et al. J *Am Acad Dermatol.* 1987; Afandi B, et al. *Endo Pract*. 2003; Armstrong RD, et al. *Ann Rheum Dis*. 1981.

# Hypercortisolism and Comorbidities

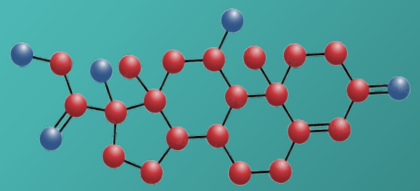



Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2016.



# Excess Cortisol and the Link to T2D and HTN

**Hypercortisolism**
**Is known to cause**



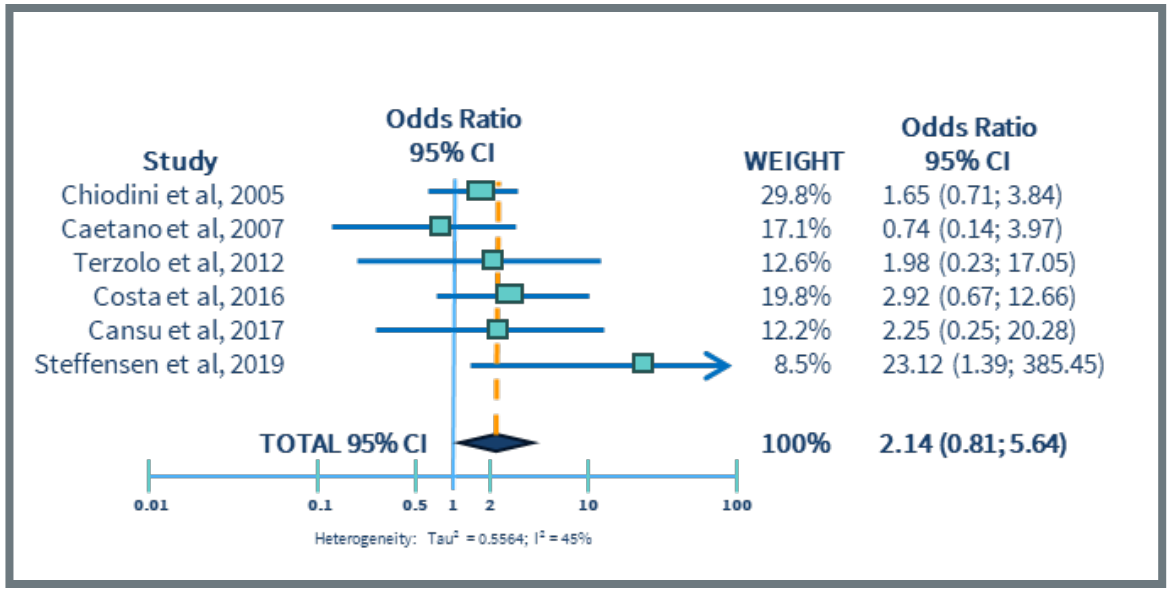
- **Hypertension**
- **Diabetes Mellitus**
- **Osteoporosis**

Previously thought prevalence of “hidden” hypercortisolism” was 0.2%-2% (up to 10% of the general population)

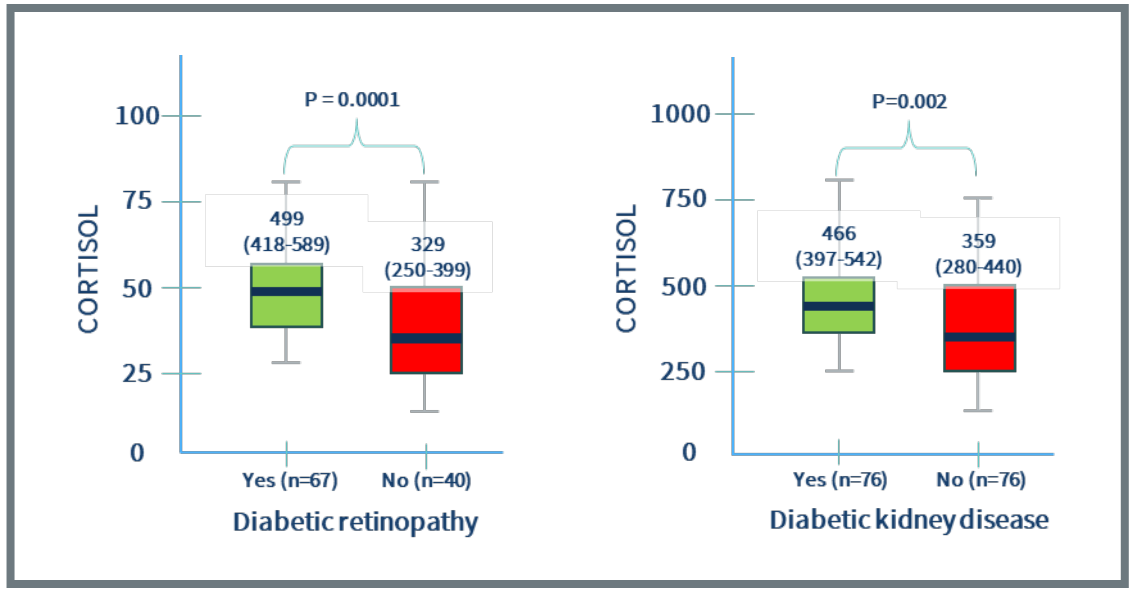
Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2016; Aresta C, et al. *Endocr Pract*. 2021; Ceccato F, et al. *Endocrinol Invest*. 2025.

# What we Know about Hypercortisolism and Comorbidities

Association of cortisol excess and high blood pressure well-known



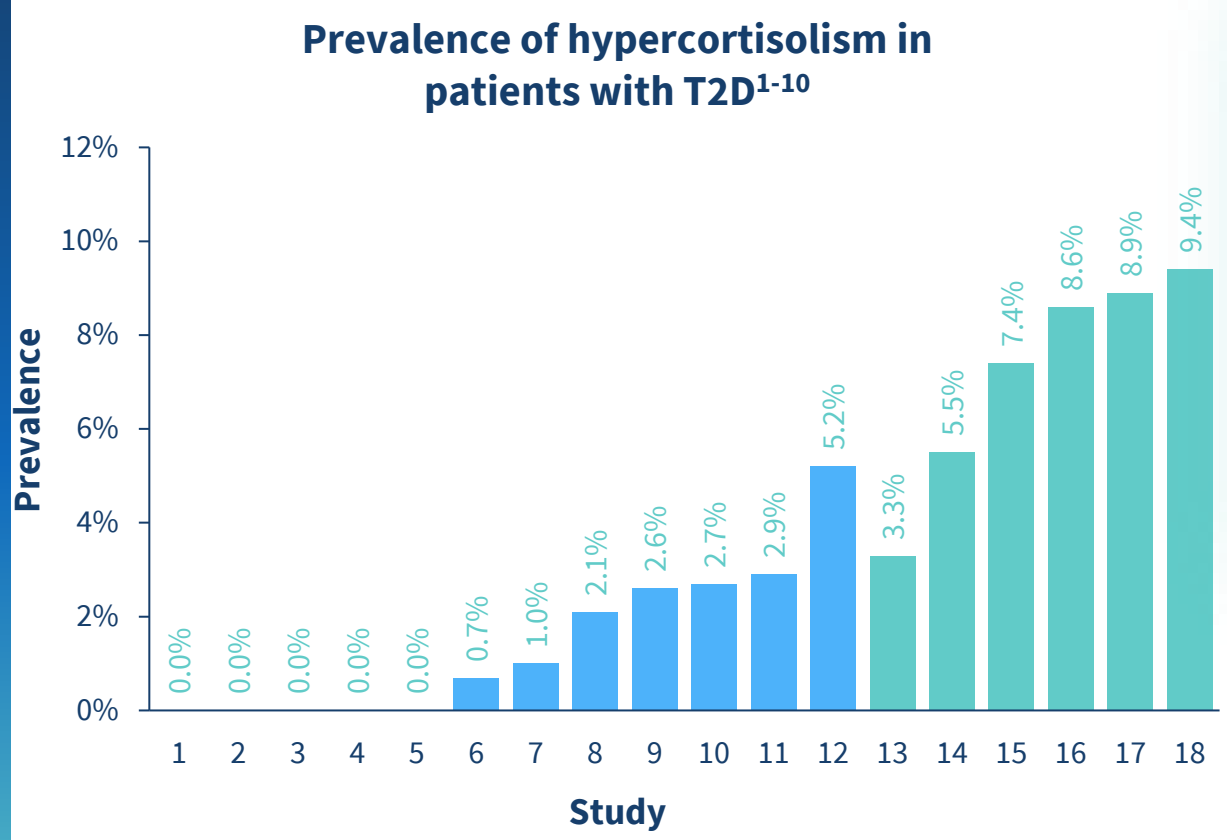

Elevated cortisol levels shows to be present especially with additional comorbidities and complications




In hypertensive patients with Cushing Syndrome, conventional antihypertensive therapy is not effective until normal cortisol levels are restored, indicating a gap in care and significant need for new therapies

Aresta C, et al. *Endocr Pract*. 2021; Jusufovic S, et al. *Clin Diabetol*. 2024; Fallo F, et al. J Int Med. 1993.

# Hypercortisolism in Patients with T2D



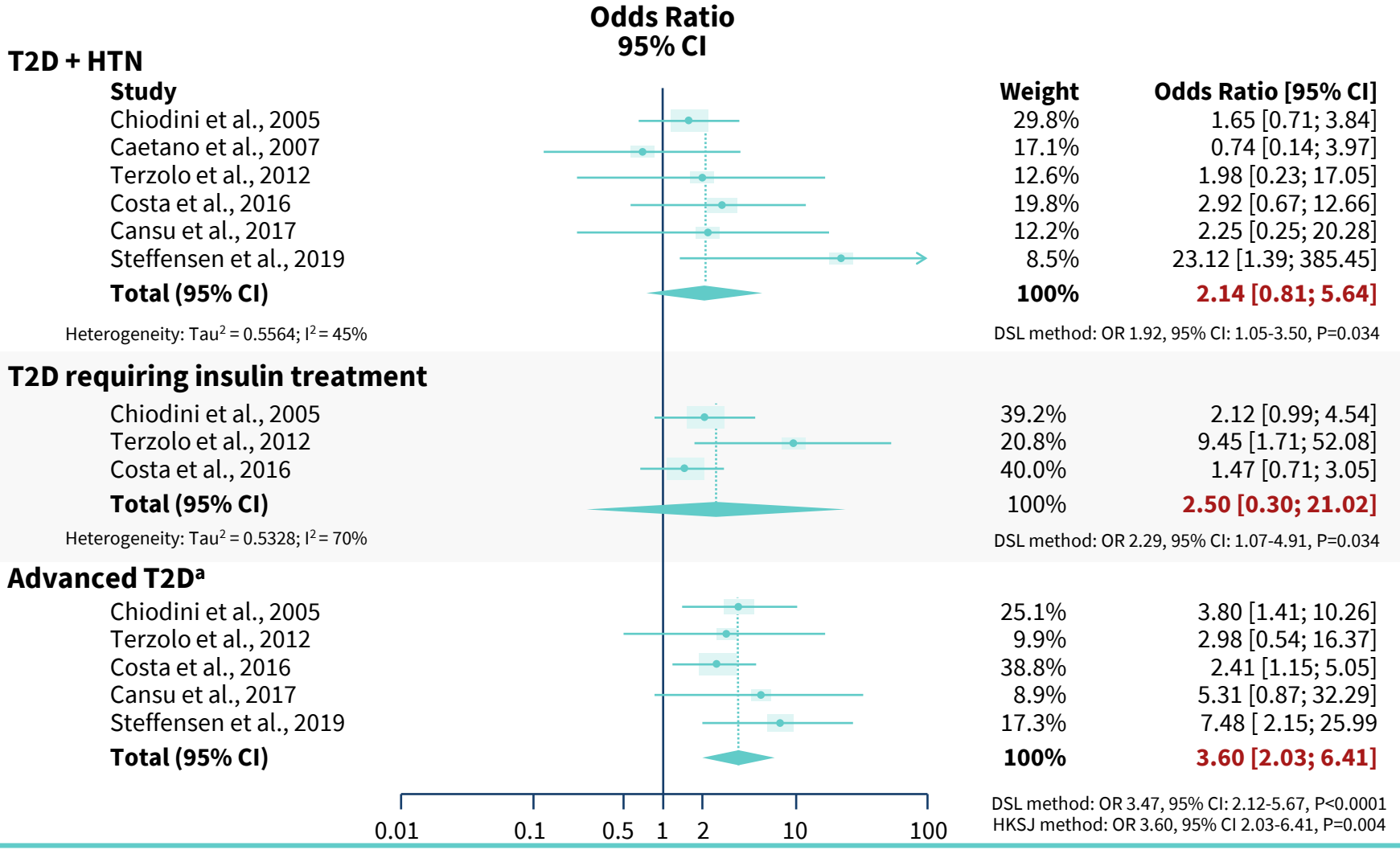

**It may be worth screening patients with poorly controlled metabolic disorders for underlying hypercortisolism**

| 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%** |
| 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%** |

[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

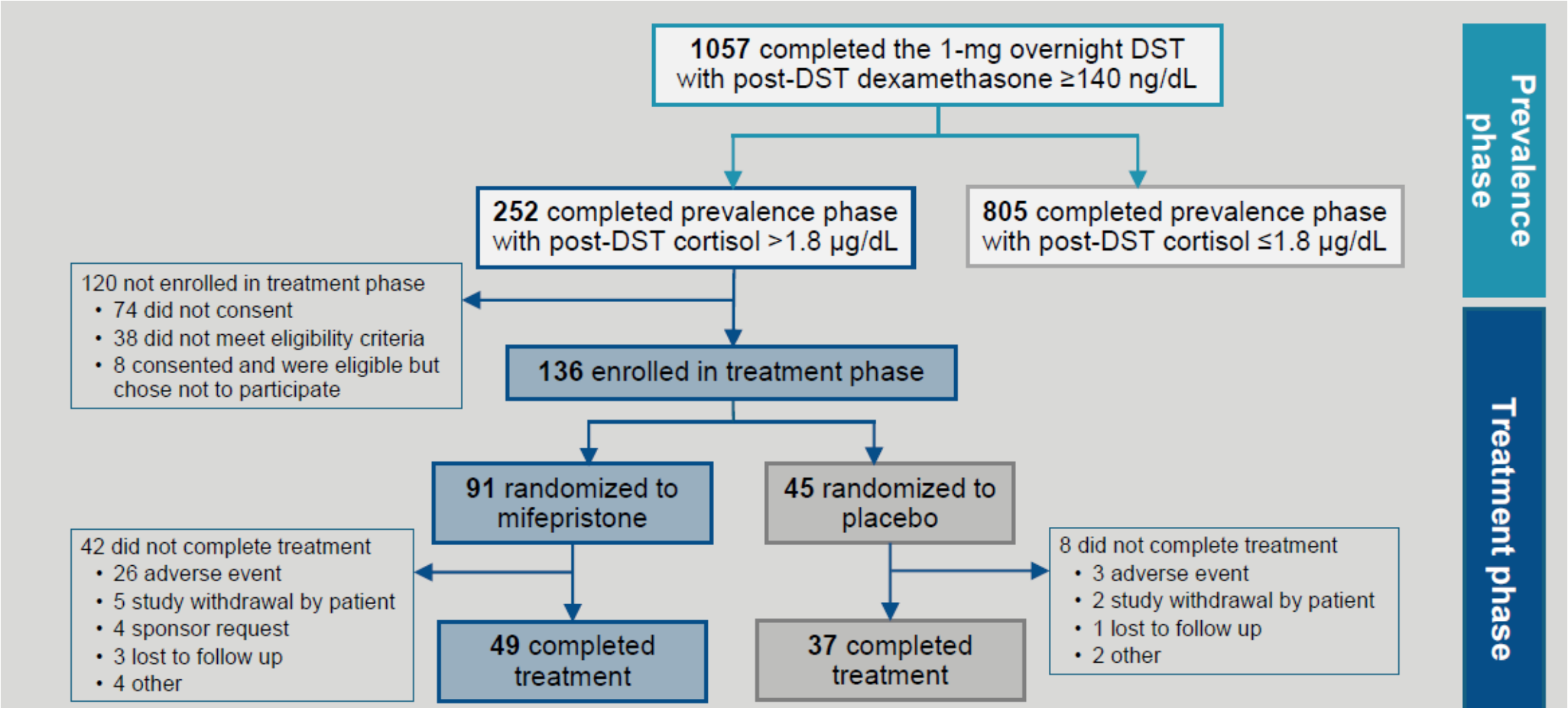



DSL=DerSimonian and Laird method; HKSJ=Hartung-Knapp-Sidik-Jonkman method.

[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.

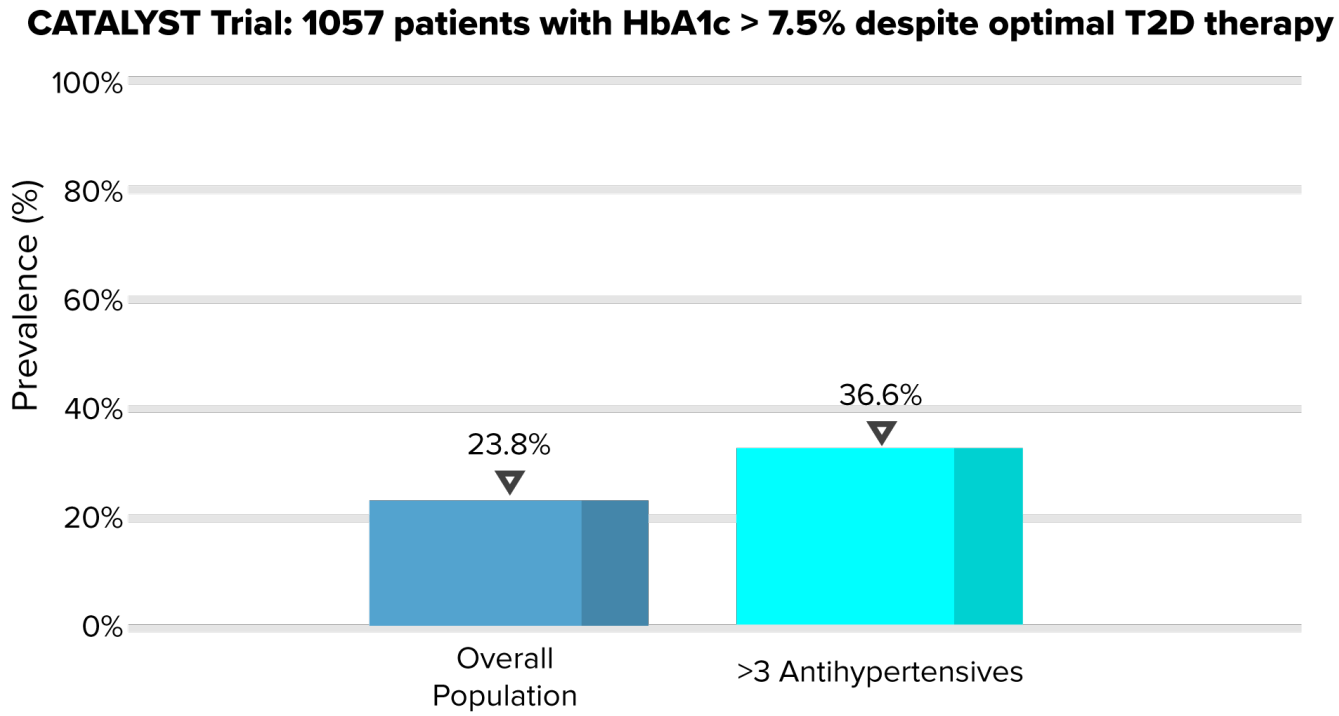
Aresta C, et al. *Endocr Pract*. 2021.

# CATALYST: Participant Flow




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

# Updated Prevalence of Hypercortisolism in T2D

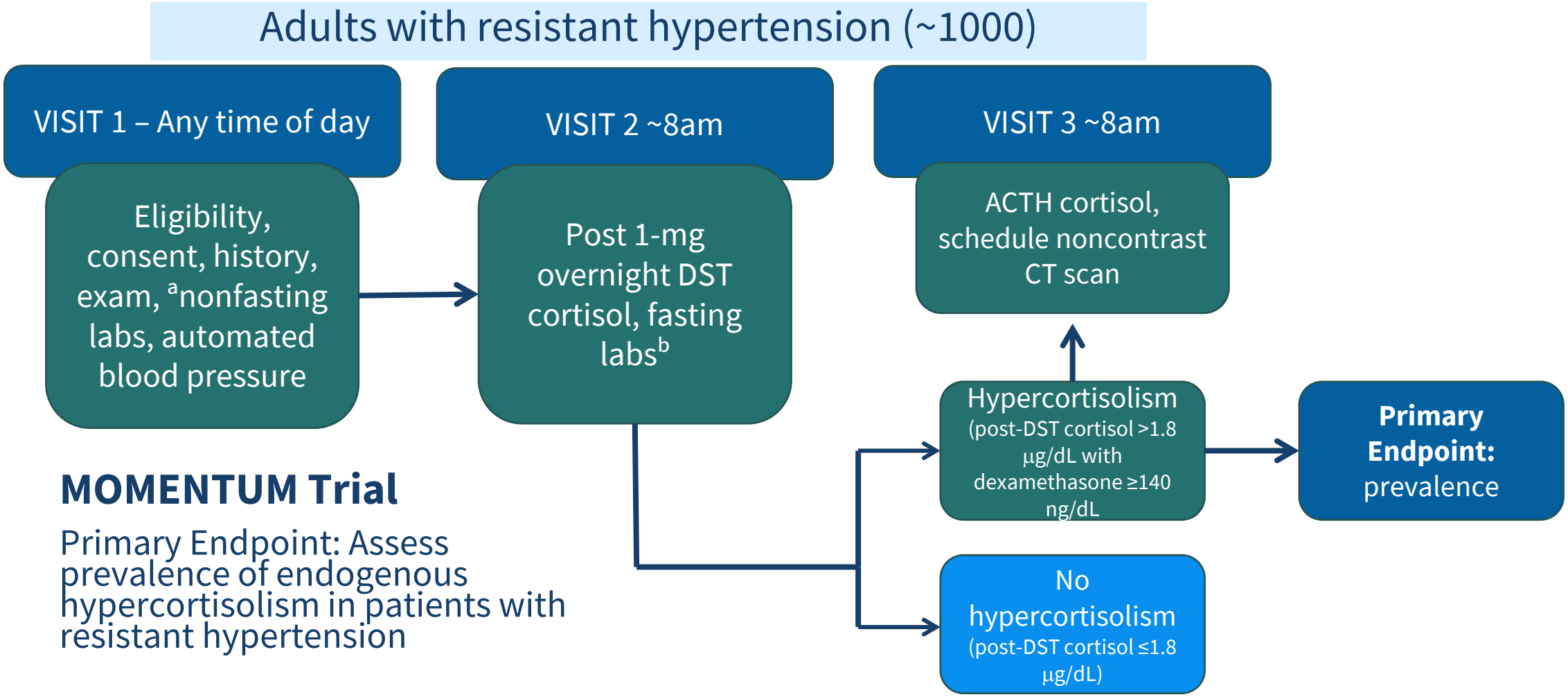



Results:

- Prevalence of hypercortisolism (Post-DST cortisol levels >1.8 µg/dL) in people with difficult-to-treat T2D was 23.8%
- Prevalence rose to 36.6% when looking at people with resistant hypertension (on 3 or more antihypertensive agents)
  - The odds of hypercortisolism was nearly 2x as high in this patient population

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

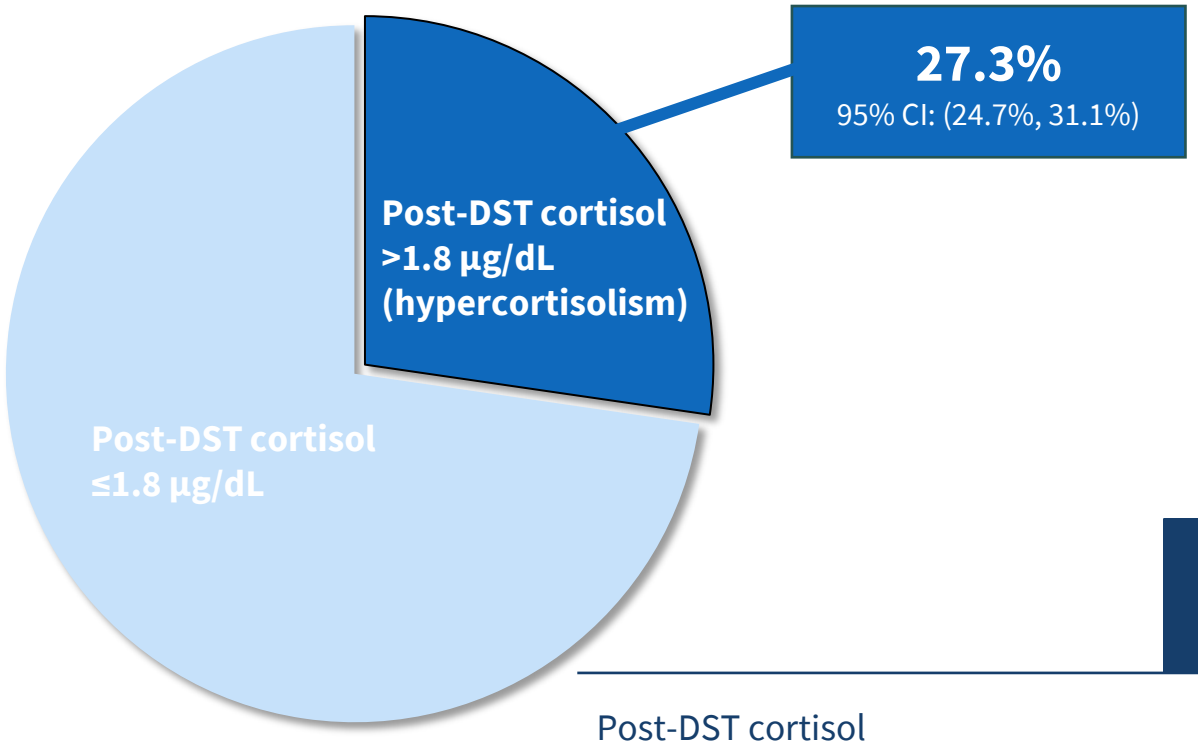
# Updated Prevalence of Hypercortisolism in Resistant HTN is Here




Plutzky J, et al. *JACC Adv*. 2026.

[a]Plasma renin activity, aldosterone, dehydroepiandrosterone sulfate, N-terminal-pro-brain-natriuretic peptide, HbA1C, Fibrosis-4, aspartate aminotransferase-to-platelet-ratio index, uric acid, high-sensitivity C-reactive protein, complete blood count, comprehensive metabolic panel, eGFR and urine-albumin-to-creatine ratio.
[b]ACTH, fasting glucose, and fasting lipids

# Updated Prevalence of Hypercortisolism in Resistant HTN is Here




| | Mean (SD) | Diagnostic Threshold for Hypercortisolism |
|---|---|---|
| Post-DST cortisol | 4.2µg/dL (3.5 µg/dL ) | ≤1.8 µg/dL |
| Dexamethasone | 484.2 ng/dL (336.8 ng/dL) | >140 ng/dL |

Bhatt DL, et al. *ACC*. 2026.

# 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

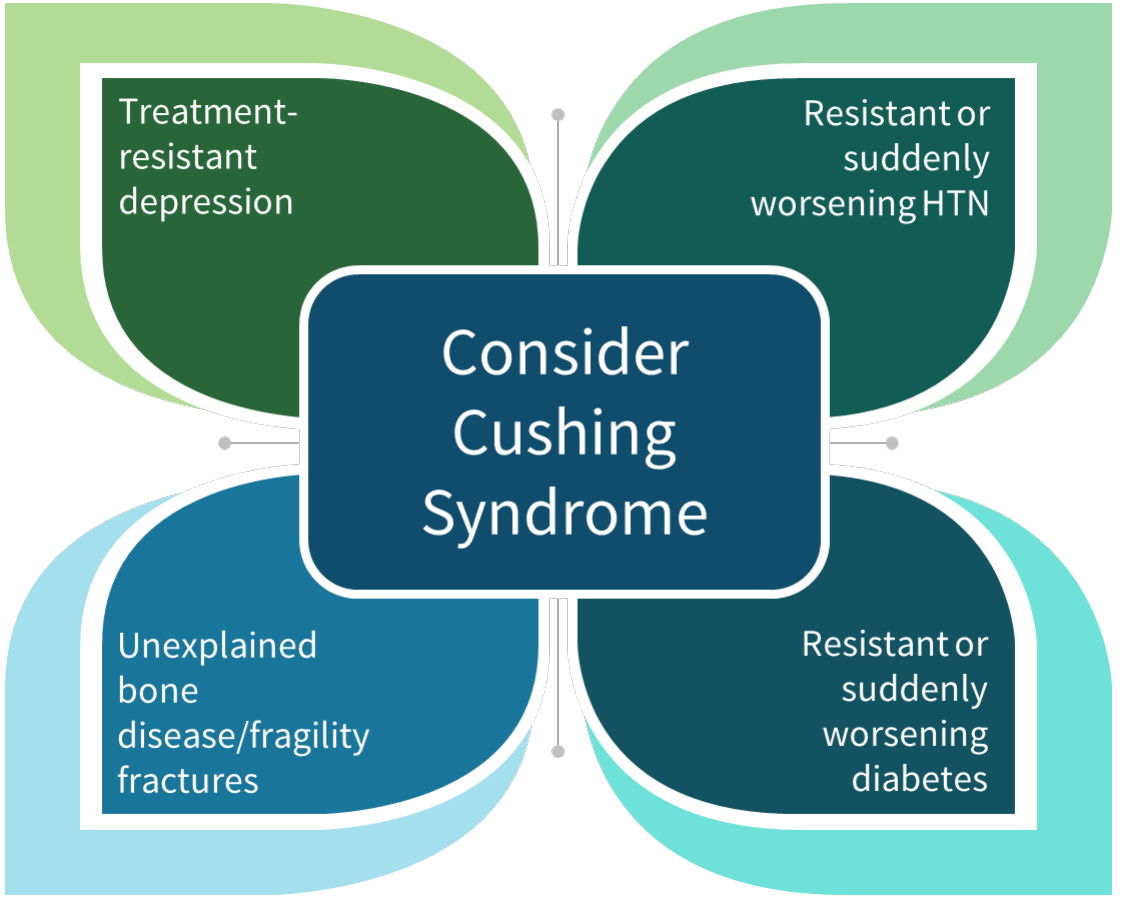
Typical severity of hypercortisolism by etiology (with exceptions):

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

Nieman LK, et al. *J Clin Endocrinol Metab.* 2015.

# The Toughest to Recognize: Non-Specific Cushing Syndrome Presentations

When to consider Hypercortisolism: Clustering of Problems from Multiple Organ Systems




Aresta C, et al. *Endocr Pract*. 2021; Nieman LK, et al. *J Clin Endocrinol Metab*. 2008; Giovanelli L, et al. *J Endocrinol Invest*. 2021.

# Recognizing the Need for Increased Screening

Consistent with the Endocrine Society Guidelines to screen for hypercortisolism as a secondary cause in patients with uncontrolled **T2D- CATALYST** was the first randomized, placebo-controlled study to demonstrate both prevalence and response to cortisol-directed treatment.

## Patients with acute worsening of hypertension and diabetes

Patients with non-neoplastic hypercortisolism respond to treatment with mifepristone

## Patients with uncontrolled hypertension and diabetes

Roughly one third will have hypercortisolism

## Patients with uncontrolled diabetes

~25% will have hypercortisolism

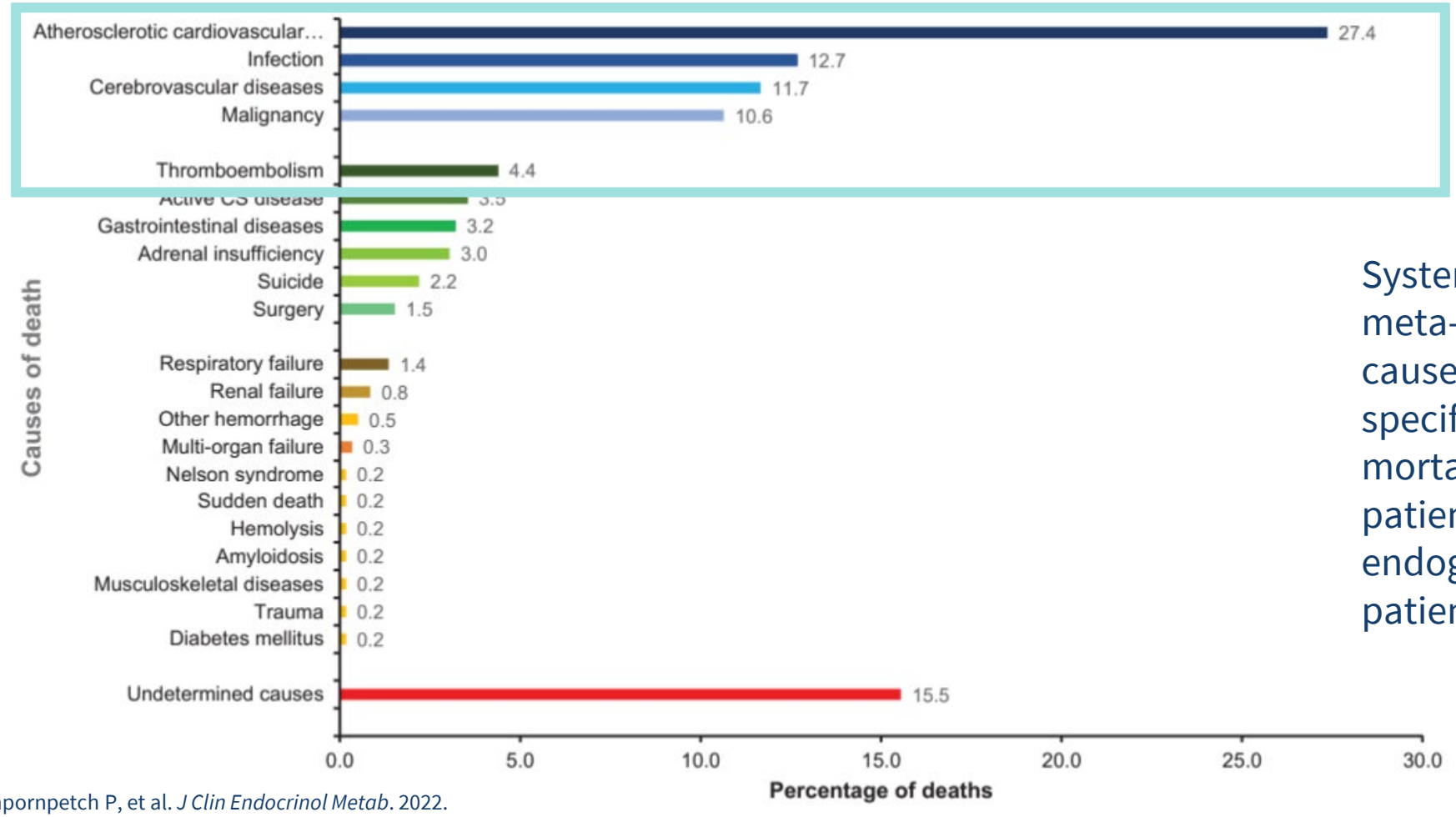
Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021; DeFronzo RA, et al. *Diabetes Care*. 2025; Buse JB, et al. *Diabetes Care*. 2025.

# New AACE Guidelines on Hypercortisolism (Other Types of Diabetes)

- DM can develop secondary to Cushing syndrome and acromegaly.
- The diagnosis and management of both endocrine conditions are complex, and suspicion should prompt referral to an endocrinologist for appropriate testing and interpretation.
- Management approaches include treatment of the primary disease (surgical removal of the culprit neoplasm and/or treatment with medical therapy), as this can result in DM remission in some cases.
- Aside from overt Cushing syndrome, in individuals with **milder forms of hypercortisolism**, such as with autonomous cortisol secretion from an adrenal nodule, the classical Cushingoid signs may not be present, while **metabolic issues predominate**.
    - Results from the CATALYST trial demonstrated that, in adults meeting the study definition of difficult-to-control T2D, there is a **high prevalence of hypercortisolism (23.8%),** as determined by a nonsuppressed morning cortisol (>1.8 mg/dL [50 nmol/L]) after 1 mg dexamethasone overnight, and this **prevalence was even higher in participants on multiple BP-lowering medications (36.6%)**.
    - Adrenal imaging abnormalities were found in 34.7% of those with an abnormal suppression test, of which 65.8% were unilateral adrenal nodules.
        - This finding is intriguing and a follow-up report showed that **treatment (24 weeks) with the glucocorticoid receptor antagonist**, mifepristone, **improved weight, waist circumference, and A1C (-1.5% or -16 mmol/mol), intimating that cortisol may be a culprit rather than a bystander**

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

# Mortality Ratio of Patients with Benign Endogenous CS

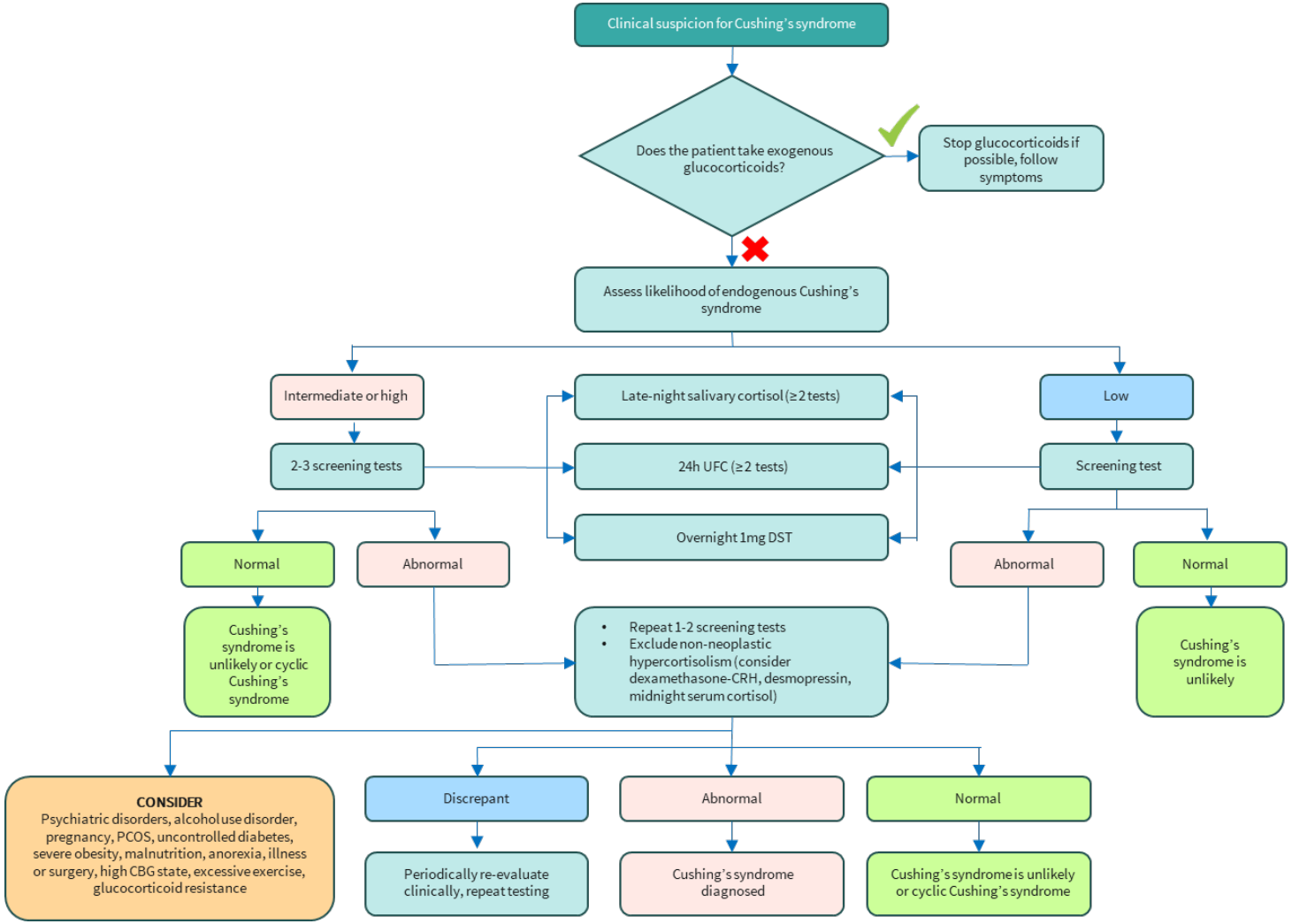



Systematic review and meta-analysis of all-cause and cause-specific standardized mortality ratio of patients with benign endogenous CS (3691 patients)

Limumpornpetch P, et al. *J Clin Endocrinol Metab*. 2022.


# Cortisol Clues: How to Screen?

# Screening for Cushing Syndrome




Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021.

# Sensitivity, Specificity, and Caveats of Screening Tests for Cushing's Syndrome

| Test | Sensitivity | Specificity | Caveat |
|---|---|---|---|
| 1 mg DST (<1.8 µg/dL) | 91-97% | 80-94% | CBG effect, Dex clearance |
| 24-hr UFC | 85-92% | 45-98% | Improper collection, high fluid intake (>5 liters), CKD |
| LNSC | 88-100% | 82-100% | Improper collection, shift workers |
| 2-day LDDST (<1.4 µg/dL) | 90-100% | 97-100% | CBG effect, Dex clearance |
| 2-day Dex/CRH Test (<1.4 µg/dL) | 98-100% | 60-100% | CBG effect, Dex clearance |

Sharma ST, et al. *Clin Epidemiol*. 2015.

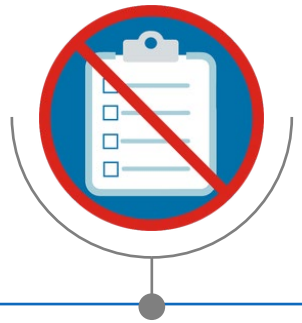
# Screening for Suspected Adrenal Cushing Syndrome

**Recommended clinically in patients with difficult-to-control T2D**


Dexamethasone suppression test (DST)

**High sensitivity**

**No longer recommended routinely**



Late-night salivary cortisol (LNSC)

**No longer recommended routinely**

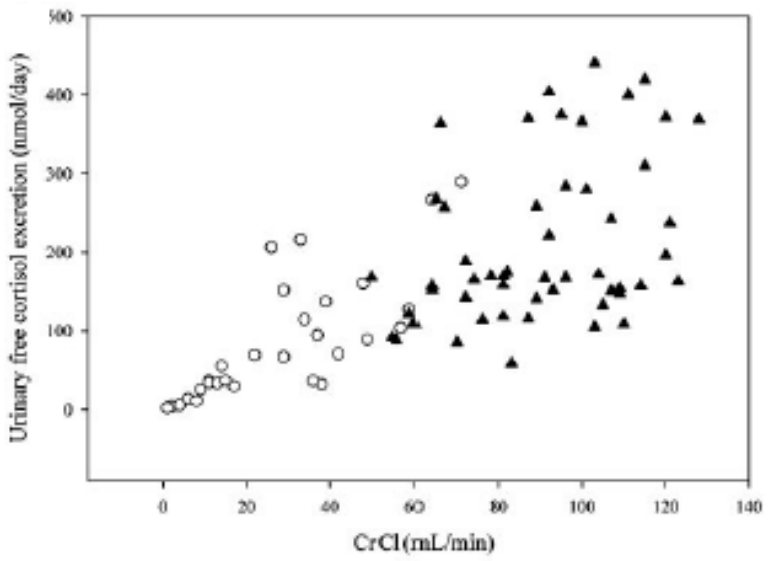
Urinary free cortisol (UFC)

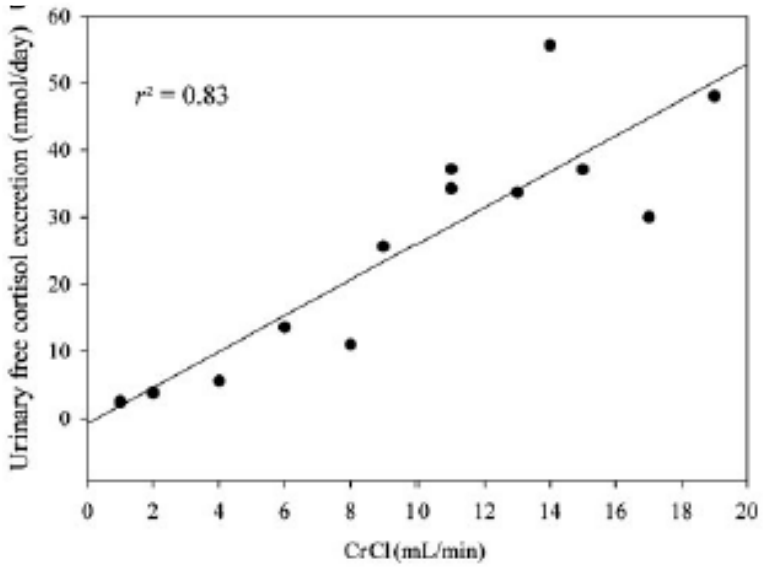
**Low sensitivity and specificity in adrenal hypercortisolism**

Nieman LK. *Endocrinol Metab (Seoul)*. 2018.

# UFC Pitfall

UFC decreases in severe renal failure and is not reliable when Cr Clearance is <20 ml/min




Chan KC, et al. *Clinical Biochemistry.* 2004.

# Potential Issues with Other Tests


## DST

False positive results possible with increased gut transit time, chronic diarrhea, or celiac disease; concomitant treatment with CYP3A4 inducers; and increased corticosteroid binding globulin (CBG) levels from oral estrogens, pregnancy, or chronic active hepatitis (measuring dexamethasone concomitantly can reduce this risk)


## 24h urine

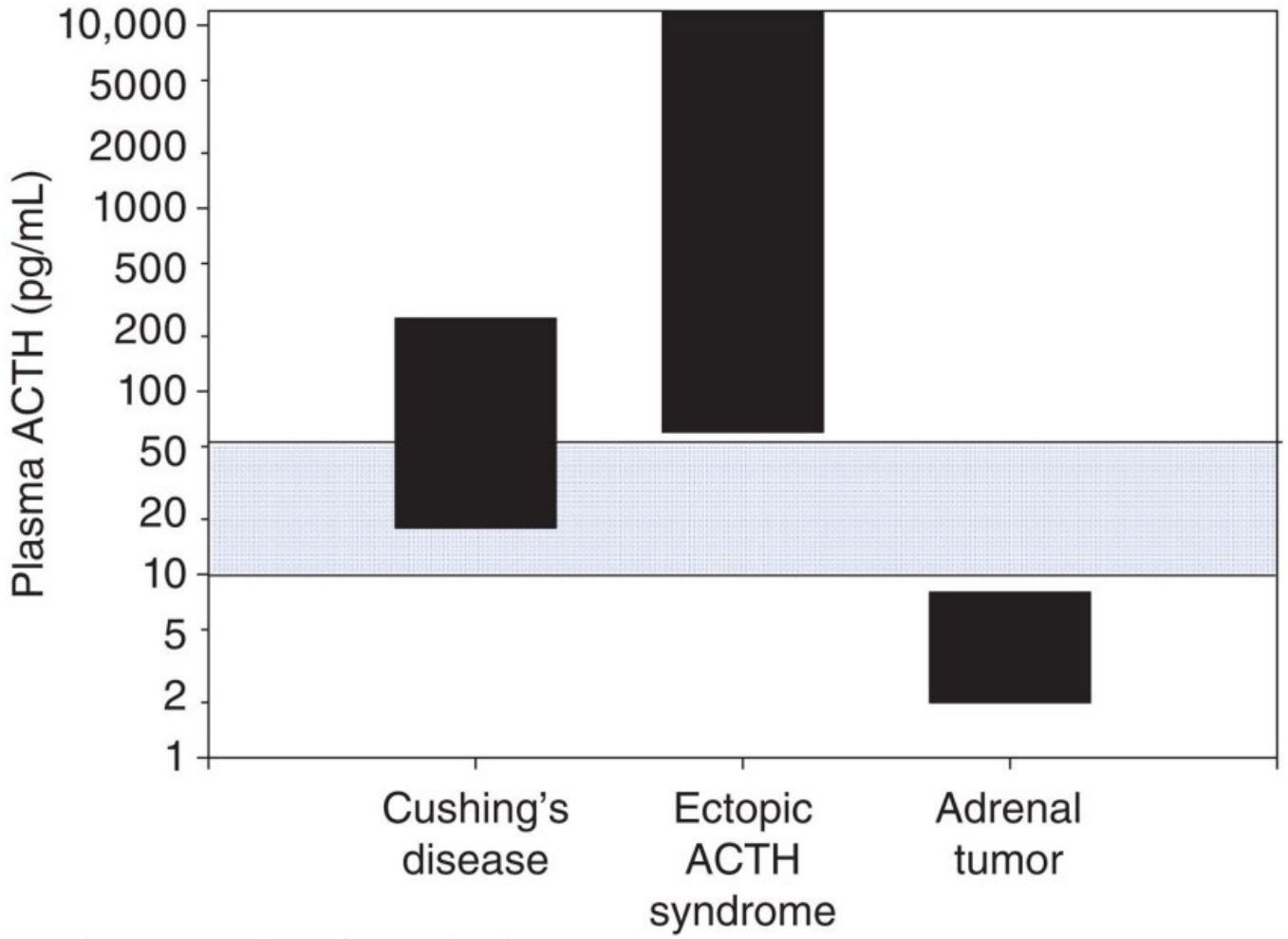
Incomplete collection, high urine volume, cyclicity of hypercortisolism, multiple confounders that increase or decrease urinary cortisol, interference from carbamazepine, cross reactivity with cortisol metabolites and synthetic glucocorticoids

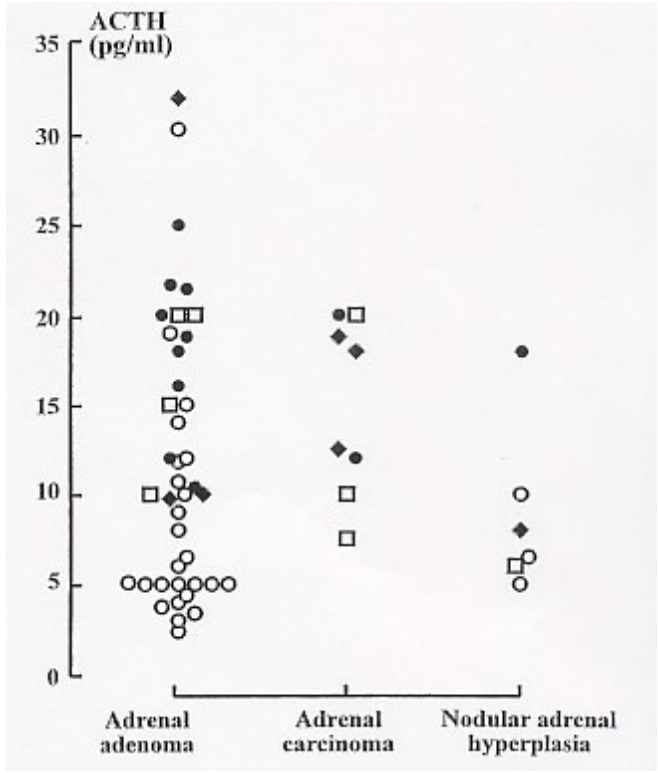
## LNSC

Stress/excitement prior to sample collection; contamination from blood- or steroid-containing products; smoking, chewing tobacco or using licorice; susceptibility of immunoassays to cross-reactivity with cortisone, other steroids, and synthetic steroids (facial lotion); susceptibility of MS-MS to interference from exogenous steroids (eg, prednisolone) and certain endogenous metabolites

Sandooja R, et al. *Endocr Pract*. 2025; Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021; Kidambi S, et al. *European J Endocrinol*. 2007; Nieman LK, et al. *J Clin Endocrinol Metab*. 2008; Cannizzaro E, et al. *Int J Environ Res Public Health*. 2020; Flowers KC, et al. *Diagnostics (Basel)*. 2023; Casals G, et al. *Ann Lab Med*. 2020; Bansal V, et al. *Neurosurg Focus*. 2015; Babic N, et al. *Endotext*. 2000.

# Screening Continued- ACTH

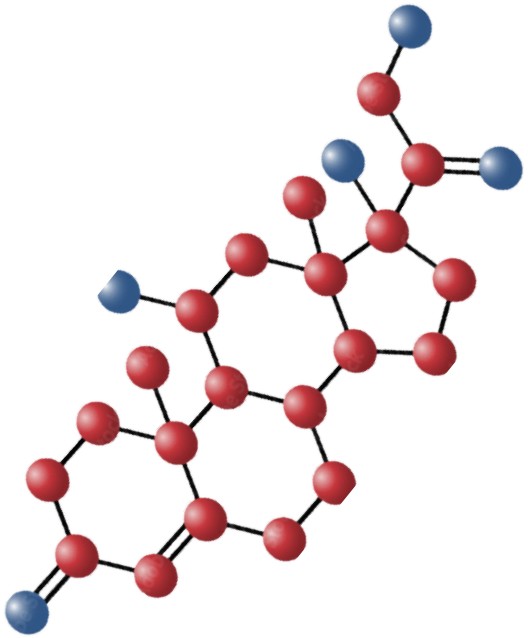



Inviti C, et al. *JCEM*. 1999; Raff H, et al. *Compr Physiol.* 2014.

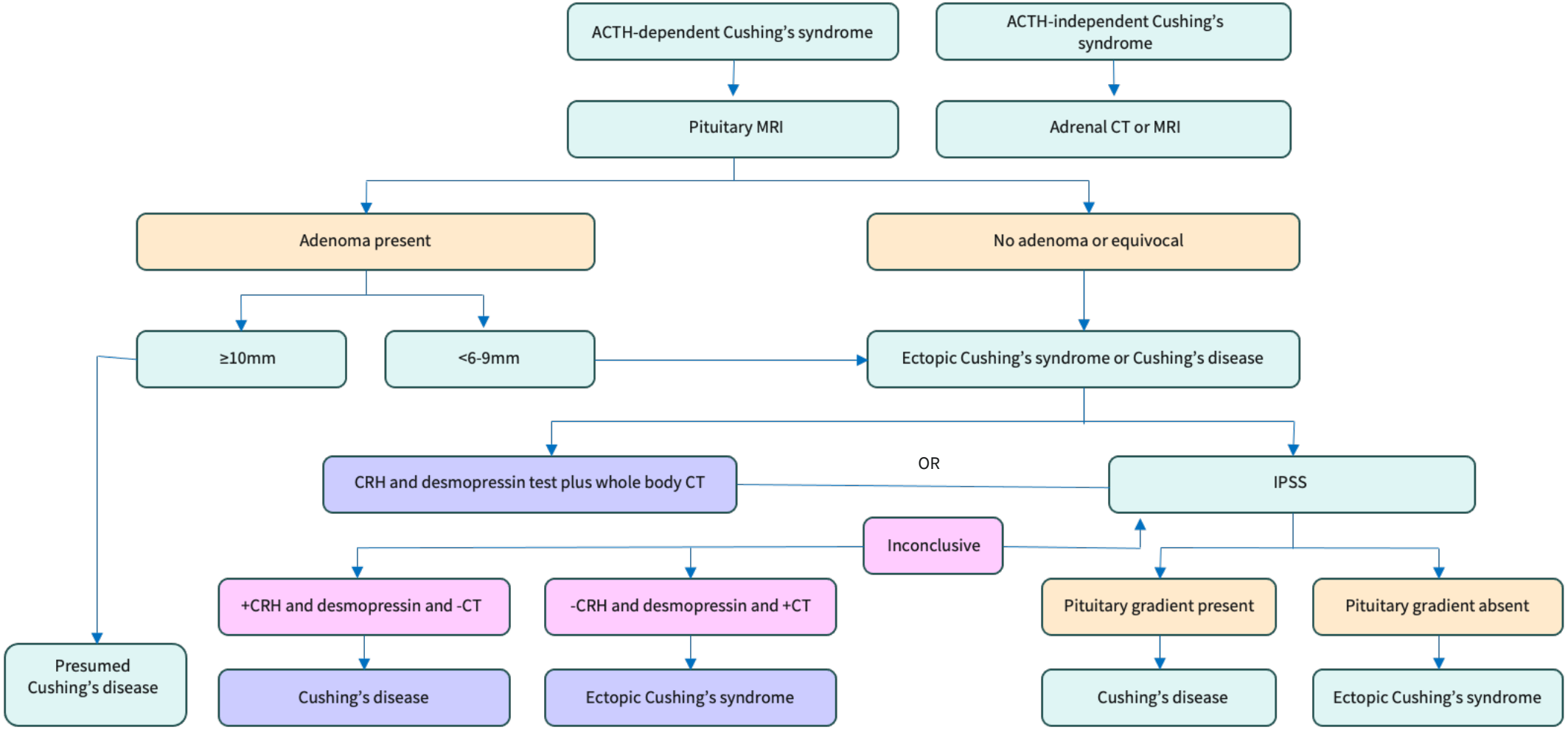
# ACTH Independent Hypercortisolism

- ACTH is usually undetectable in adrenal CS
- ACTH is usually (but not always) <15 mg/mL in MACS; DHEAS is usually low in both adrenal CS and MACS
- CT abdomen is the localization study of choice
  - If unilateral adrenal mass → unilateral adrenal hypercortisolism confirmed
  - If bilateral adrenal mass → usually bilateral adrenal hypercortisolism (though unilateral hypercortisolism is possible → adrenal vein sampling)
  - If no adrenal tumors → (very rare) → diagnosis is likely micronodular adrenal hyperplasia (always bilateral)



Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021.

# ACTH Dependent Hypercortisolism




Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021.

# Interprofessional Team Overview: What is the Role(s) of the Care Team?

***Physicians:*** Endocrinologists work with primary care, internists, neurosurgeons, endocrine surgeons, radiologists, pathologists

- Screen, diagnose, determine and oversee treatment plans

***Advanced Practice Providers:*** Nurse Practitioners, Physician Assistants

- Perform patient assessments, manage symptoms, provide follow-up care, and support treatment delivery in collaboration with physicians

***Clinical Pharmacy Specialists:***

- Optimize pharmacologic treatment plans, educate patients on medication use and side effects, and answer drug information questions

***Nurses:***

- Provide day-to-day care coordination, triage symptoms, administer treatments, and serve as key points of patient contact
- Educate patients and families about care plans and procedures

***Social Workers:***

- Address psychosocial needs, coordinate resources (transportation, financial support, counseling), and facilitate communication between patients, families, and the care team

# Practicing Motivational Interviewing



## Ask open ended questions

- Facilitates discussion
- Ask permission



## Practice active listening

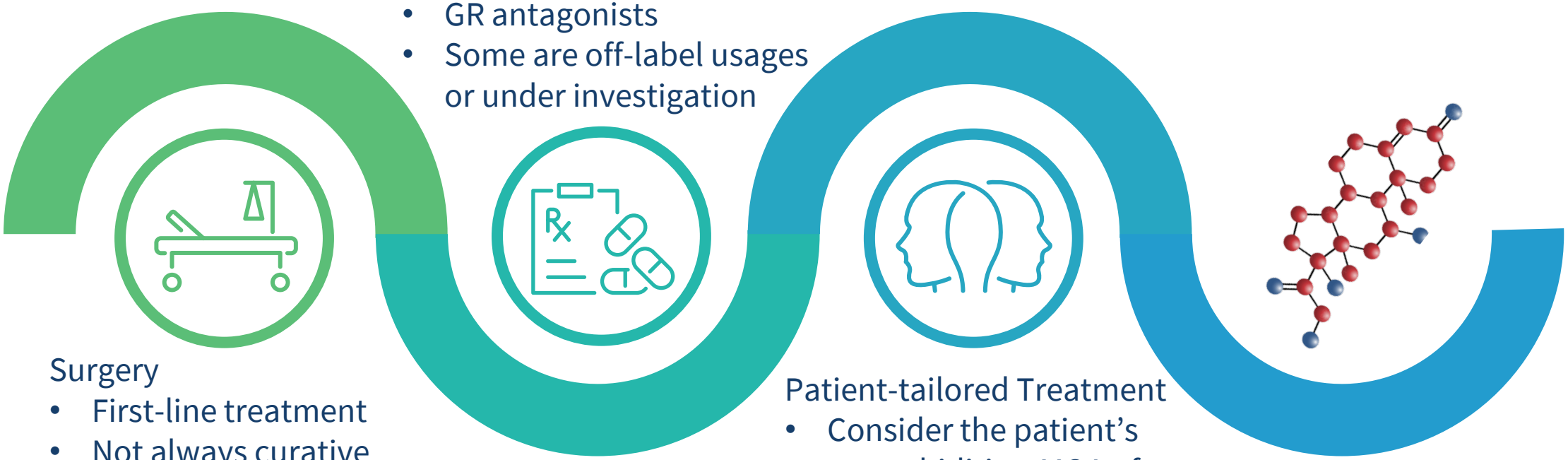
- Focus on strengths
- Celebrate small successes
- Repeat or paraphrase
- Summarize

Miller WR, et al. 2019.


# Beyond Surgery: Advances in Medical Management of Cushing Syndrome

# Treatment Options for Cushing Syndrome/ Disease

Medical Management
- Pituitary-directed agents
- Adrenal-directed agents
- GR antagonists
- Some are off-label usages or under investigation

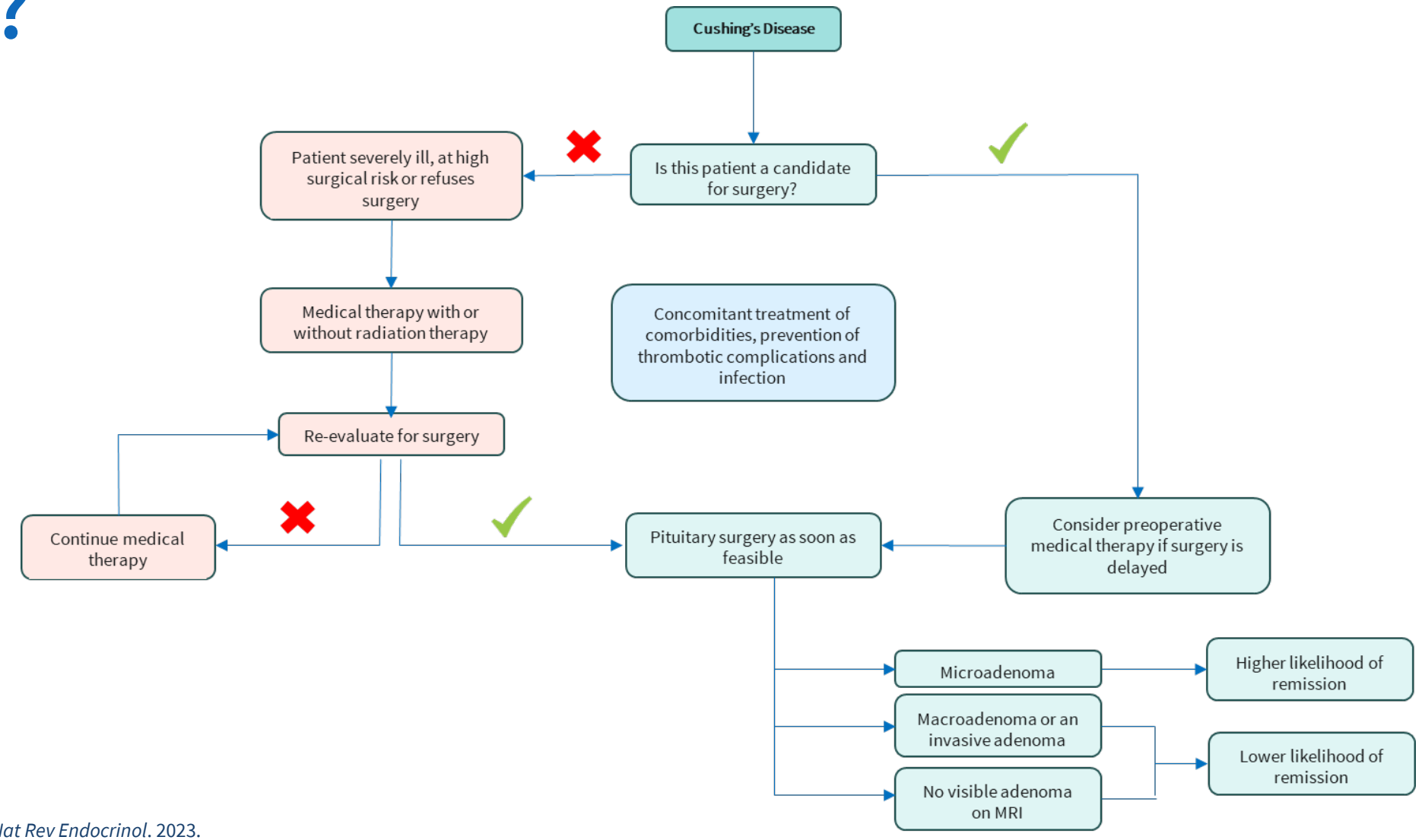


Surgery
- First-line treatment
- Not always curative
- Not always suitable

Patient-tailored Treatment
- Consider the patient's comorbidities, MOA of drug, availability and clinical scenario

Feelders RA, et al. *Lancet Diabetes Endocrinol*. 2019.

# Cushing Syndrome/Disease: Surgery or Not?




Fleseriu M, et al. *Nat Rev Endocrinol*. 2023.

# Surgical Management Overview for Cushing Syndrome/Disease

- Surgery is first-line treatment.
- Surgery achieves adequate control of Cushing Disease in 65%-90% of patients.
- Many patients have post-surgical recurrence
  - Up to 35% within 5 years
  - Up to 69% within 10 years

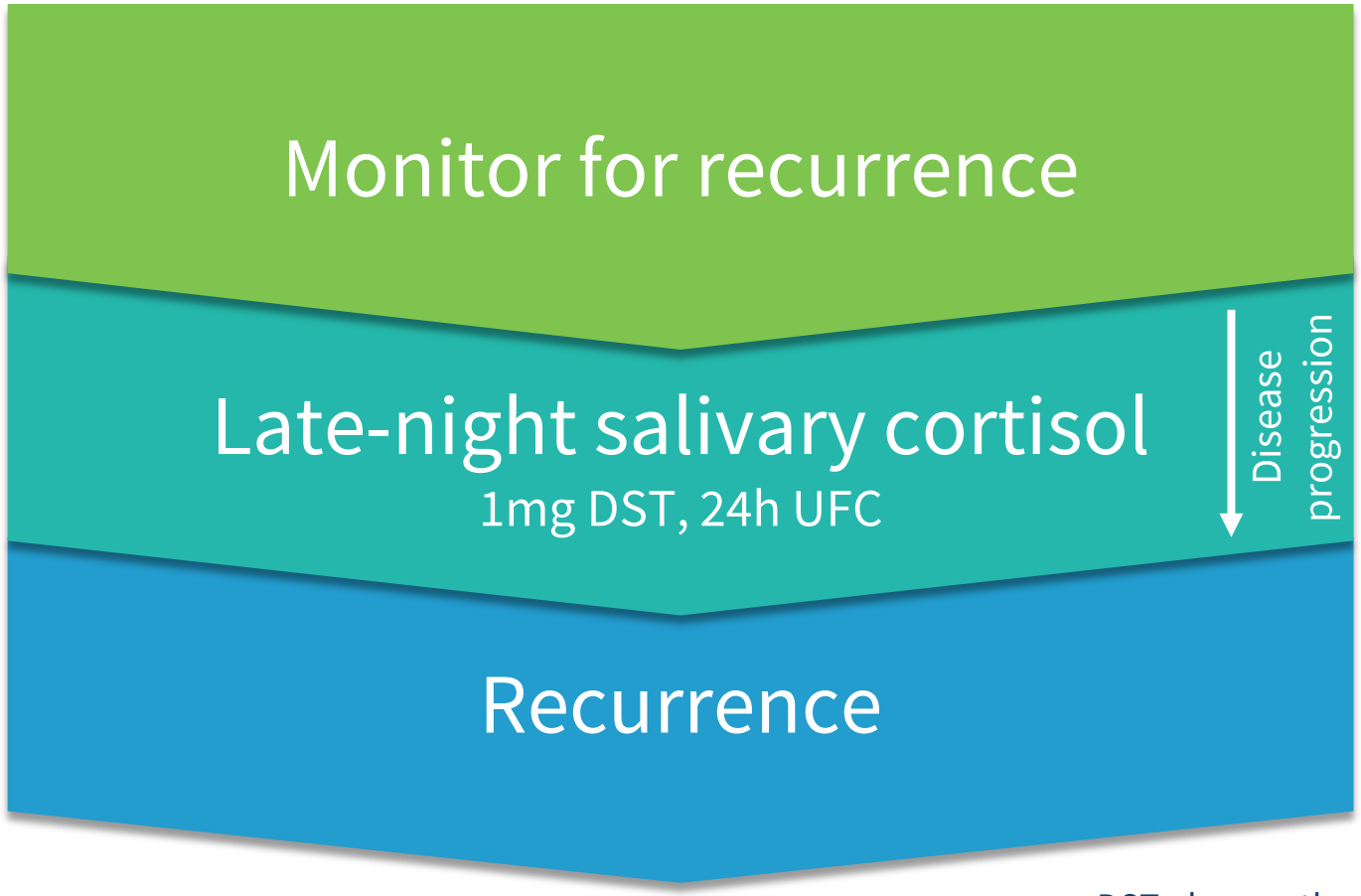
Silverstein JM. *Pituitary.* 2016; Samson SL. *Exp Clin Endocrinol Diabetes*. 2014.

# Recent Data on Surgery Treatment Success

| | All CS, n = 296 | ACS, n = 84 | ECS, n = 27 | CD, n = 185 |
|---|---|---|---|---|
| First-line surgical therapy, n (%) | 284 (96) | 83 (99)<br>ADX, unilateral adenoma: 53/54<br>BADX, MiBAH: 7/7<br>BADX, PBMAH: 4/23<br>ADX, PBMAH: 18/23<br>BADX, PBMAH: 1/23 | 21 (78)<br>Tumor resection: 16 (59)<br>BADX: 3(11)<br>Unnecessary TSS:2 (7) | 180 (97)<br>TSS: 175 (95)<br>BADX: 5 (3) |
| First-line medical therapy | 11 (4) | Osilodrostat: 1 | Metyrapone: 6 (22)<br>Additional ketoconazole: 4 (15) | Pasireotide: 2 seconds.c.(1)<br>Cabergolin:3 (2) |
| Persistence | 54 (18) | 5 (6) | 4 (15) | 45 (24) |
| Recurrence | 40 (14) | 3 (4) | 4 (15) | 33 (18) |
| Second-line therapy | | ADX li: 1<br>Metyrapone: 2<br>Osilodrostat: 1<br>No therapy: 4 (mild CS, patients' preference | Tumor resection: 2<br>BASX: 4<br>Metyrapone: 1<br>Other medications: 1 | TSS: 31<br>BADX: 10<br>Radiation: 8<br>Pasireotide: 14<br>(8 seconds.c., 6 LAR)<br>Cabergoline: 3<br>Metyrapone: 6<br>Osilodrostat: 4<br>Ketoconazole: 8<br>Other medications: 5 |
| No remission | 52 | 6 | 2 | 44 |
| Further lines of therapy | | Metyrapone: 2<br>Osilodrostat: 1<br>No therapy: 3 (mild CS, patients' preference | Tumor resection: 1<br>BASX: 2 | TSS: 10<br>BADX: 18<br>Radiation: 8<br>Pasireotide: 5<br>(2 seconds.c., 2 LAR, 1 both)<br>Cabergoline: 4<br>Metyrapone: 10<br>Osilodrostat: 4<br>Ketoconazole: 6 |
| No remission | 20 | 5 | 0 | 15 |

Ritzel K, et al. *J Clin Endocrinol Metab*. 2025.

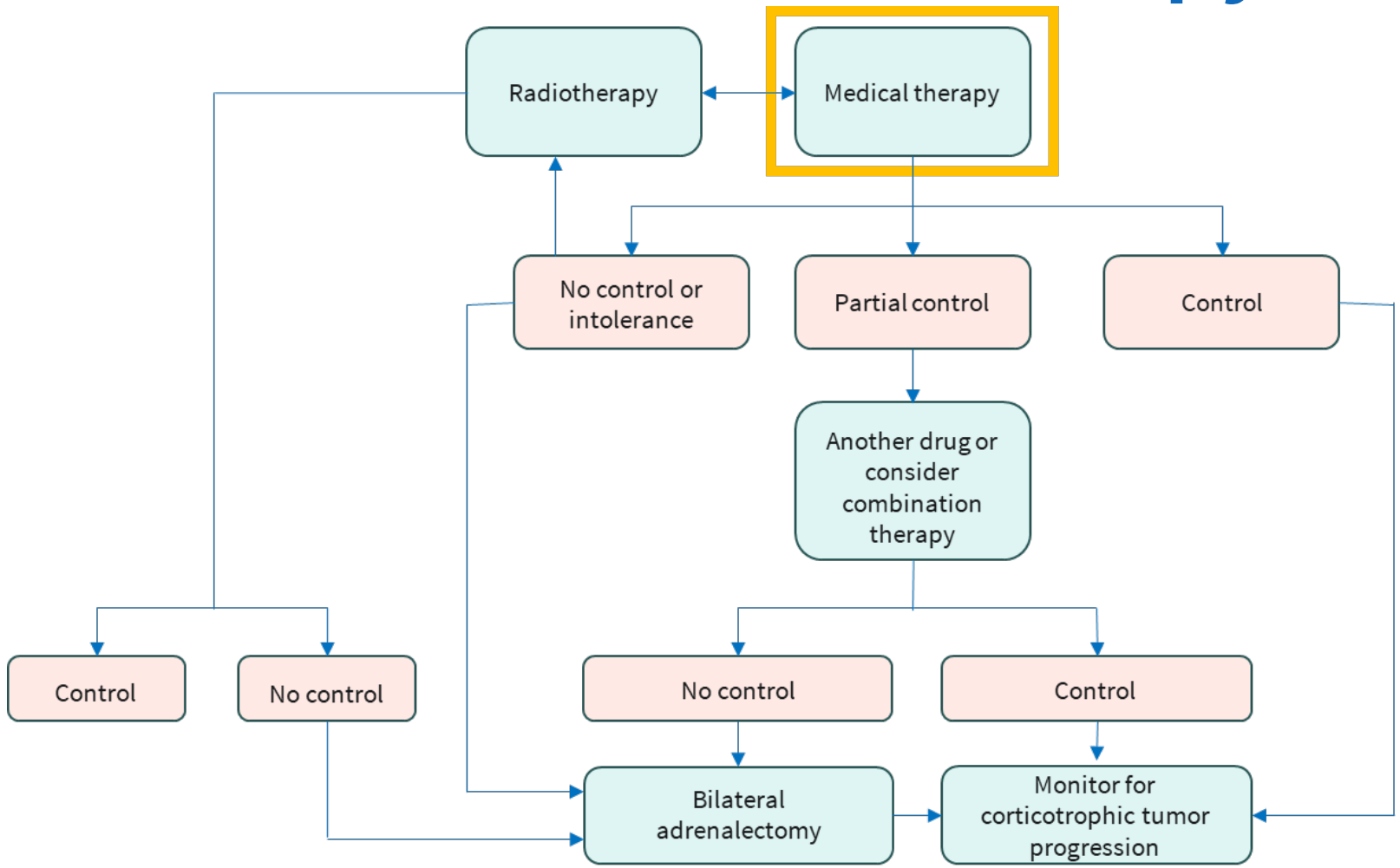
# Monitoring for Recurrence Post-Surgery




Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021.

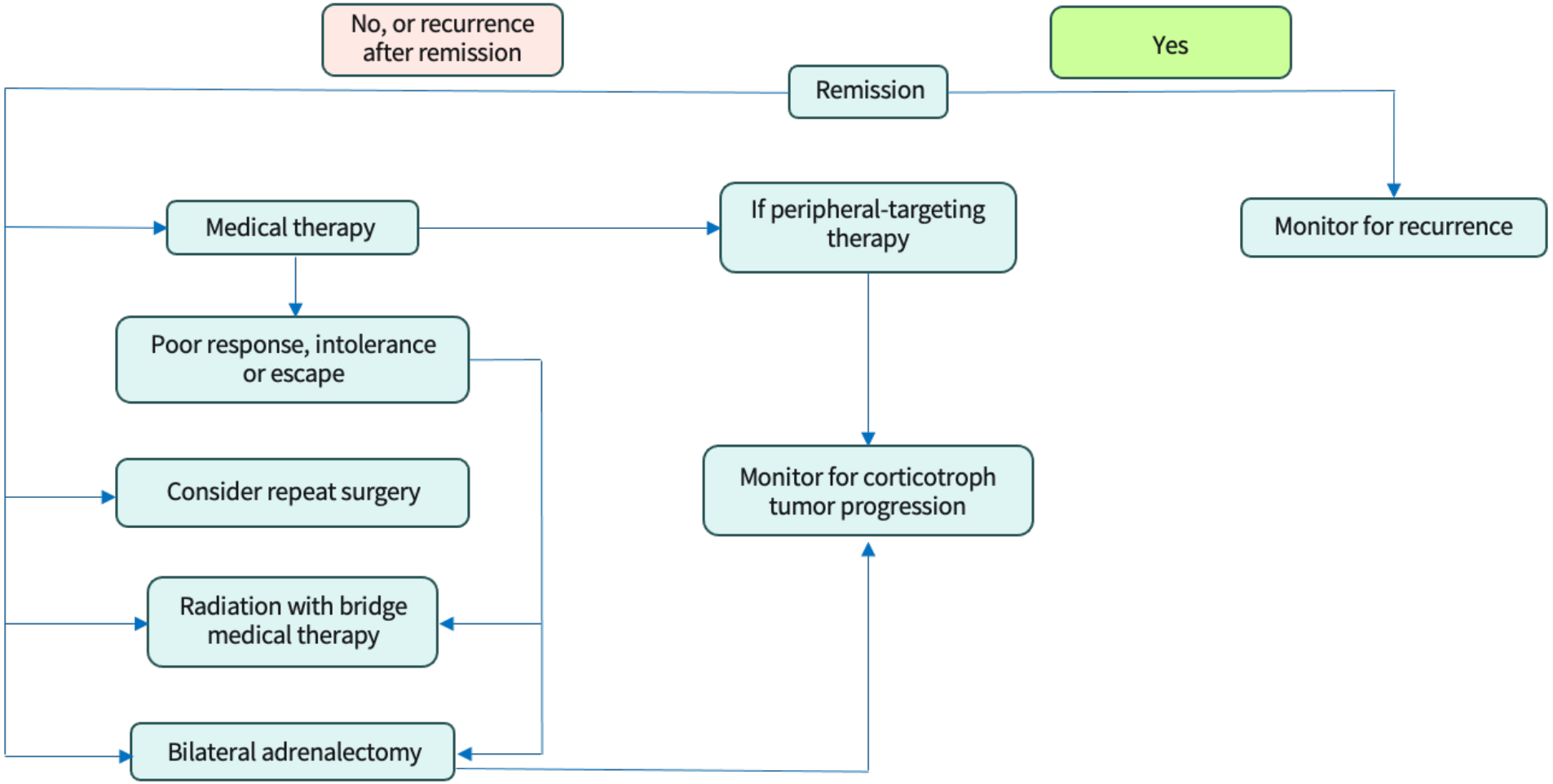
DST: dexamethasone suppression test
UFC: urinary free cortisol

# 2021 Pituitary Society Guidelines: What is the Role of Medical Therapy?



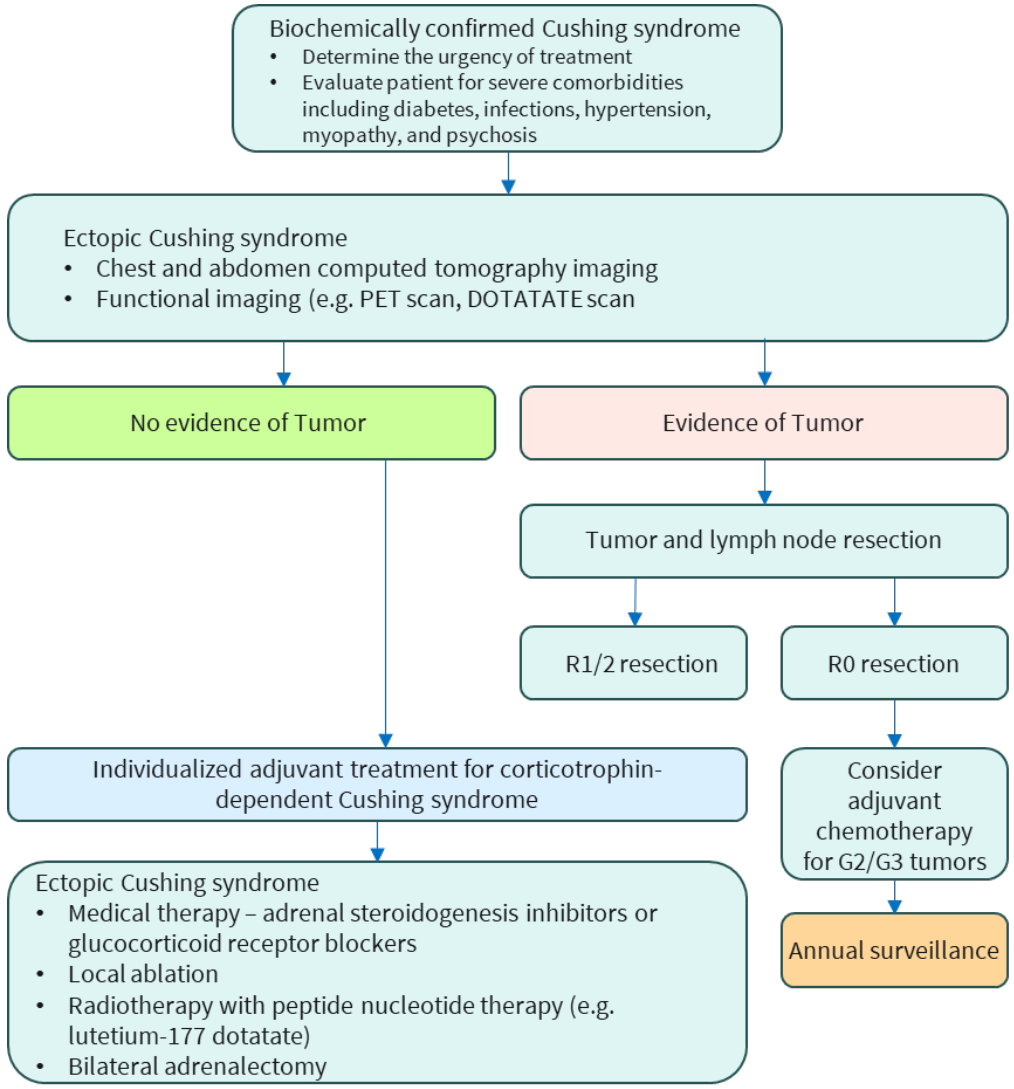

Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021.

# Cushing Syndrome/Disease: Role of Medical Management Post-Surgery




Fleseriu M, et al. *Nat Rev Endocrinol*. 2023.

# Ectopic Cushing's Syndrome Management




Fleseriu M, et al. *Nat Rev Endocrinol*. 2023.

# When Medical Management is Indicated

- When surgery is not an option or is refused
- When disease persists after surgery
- When disease recurs after successful surgery
- When severe symptoms present and emergency treatment is needed
- While awaiting surgery or radiation therapy

Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2021; Gadelha M, et al. *Lancet*. 2023; Nieman LK, et al. *J Clin Endocrinol Metab*. 2015.

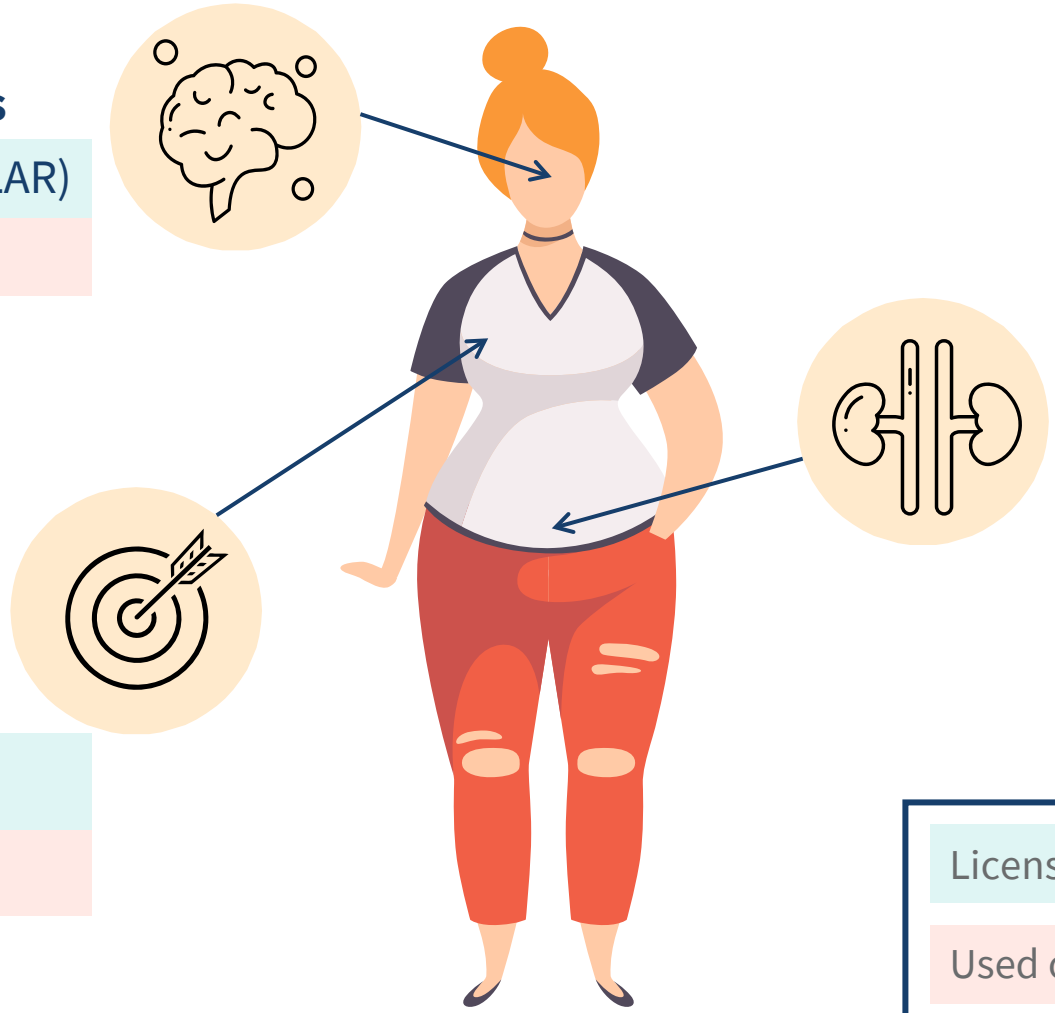
# Medical Therapies for Cushing's Syndrome

### Pituitary-Directed Agents

- Pasireotide (subQ and LAR)
- Cabergoline

### Glucocorticoid Receptor Blocker/Modulator

- Mifepristone
- Relacorilant



### Adrenal-Directed Agents: Steroidogenesis Inhibitors

- Osilodrostat
- Levoketoconazole
- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate

Licensed in US for Cushing's indications

Used off-label/Not approved in US

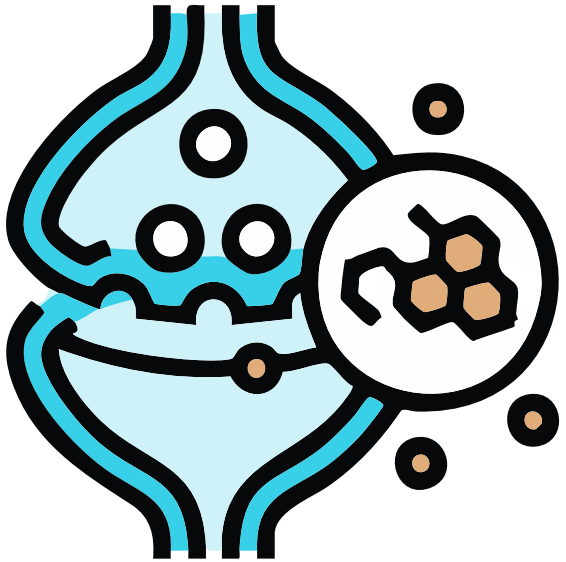
LAR-long-acting release; sq, subcutaneous.

Gadelha M, et al. *Lancet*. 2023; Reincke M, et al. *JAMA*. 2023; Fleseriu M, et al. *Nat Rev Endocrinol*. 2023.


# Glucocorticoid Receptor-Directed Agents (Glucocorticoid Receptor Modulator)

# Mechanism of Action

- Glucocorticoid Receptor (GR)-Directed Agents work by blocking binding of cortisol to the GR receptor
- Mifepristone is a GR antagonist, but also a progesterone receptor antagonist
  - May causes vaginal bleeding and endometrial hypertrophy
- Relacorilant is a selective glucocorticoid receptor modulator antagonizes only the GRs and NOT progesterone receptors
  - Mild side effect profile
  - Increased selectivity may overcome side effects related to mechanism of action of mifepristone

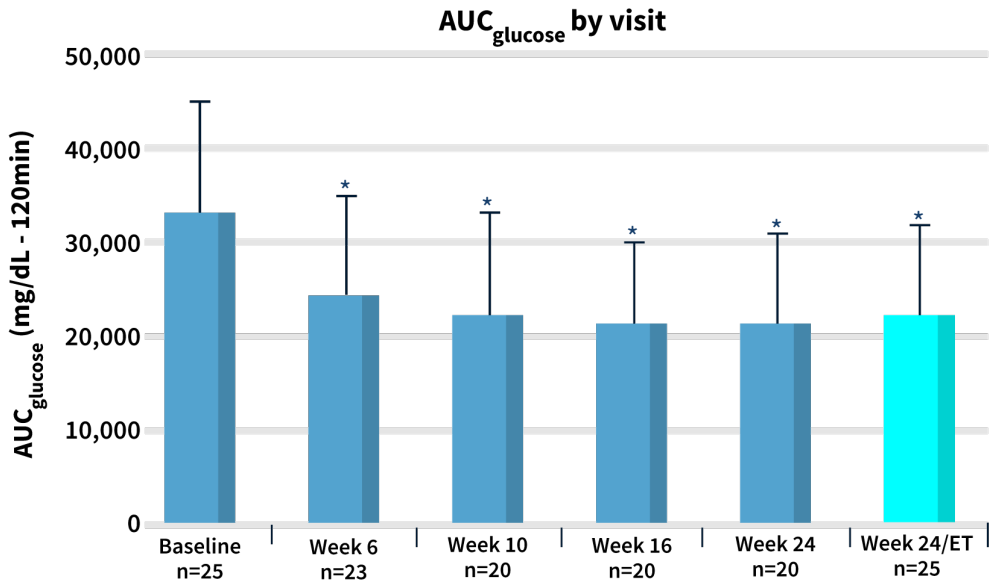


Hinojosa-Amaya JM, et al. *Drugs*. 2019; Pivonello R, et al. *Front Endocrinol*. 2021.

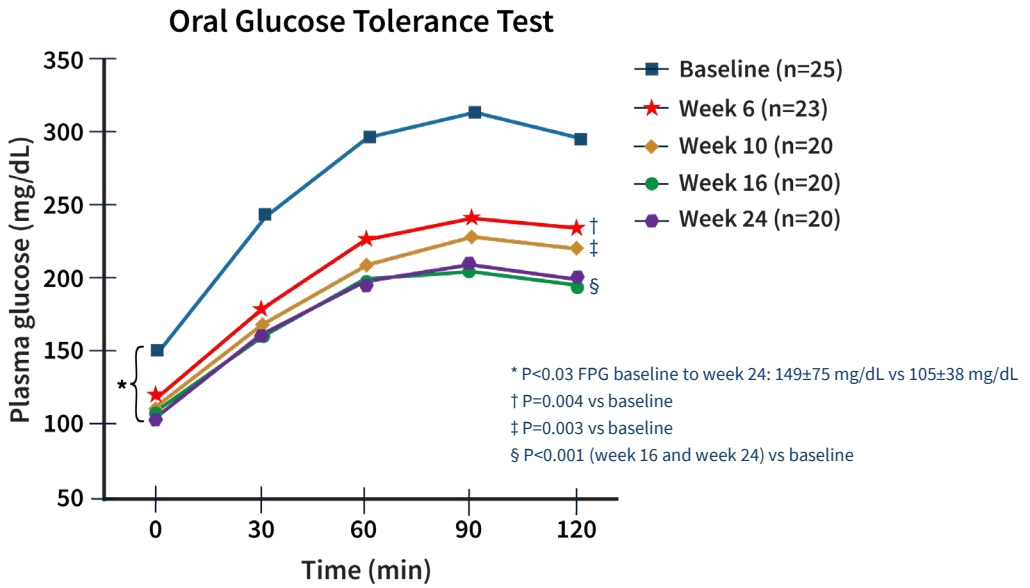
# Mifepristone

- SEISMIC Study: Efficacy and Safety in Endogenous CS
- 24-wk multicenter, open-label trial after failed multimodality therapy
- Participants: 50 adults with endogenous CS associated with T2DM/impaired glucose tolerance (C-DM) or a diagnosis of hypertension alone (C-HT)
- Primary Endpoints:
  - C-DM: change in area under the curve for glucose from baseline to wk 24
  - C-HT: change in DBP from baseline to wk 24

## Changes in glycemic parameters



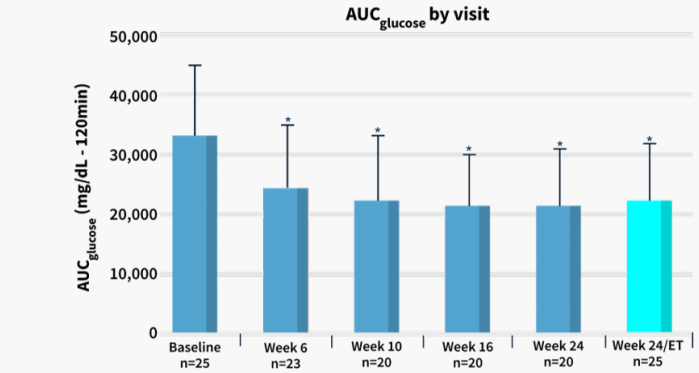

Error bars in graph are SD * P<0.001 vs baseline

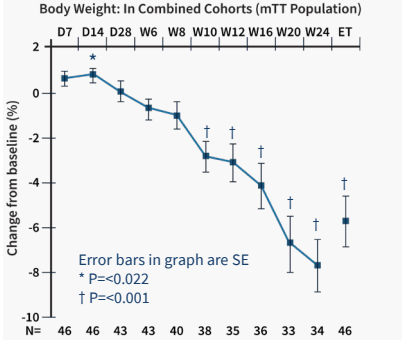



Fleseriu M, et al. *J Clin Endocrinol Metab*. 2012.

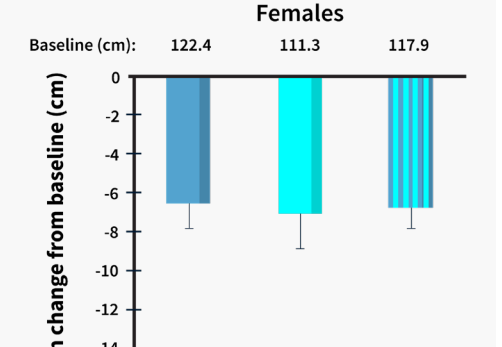
# Mifepristone

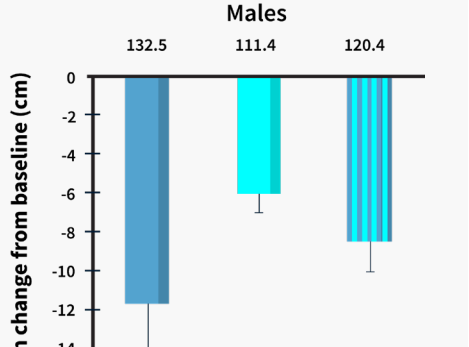
- SEISMIC Study: Efficacy and Safety in Endogenous CS

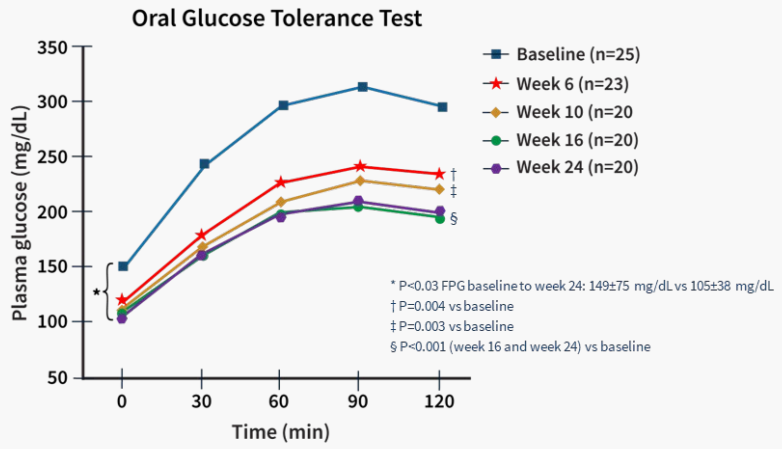


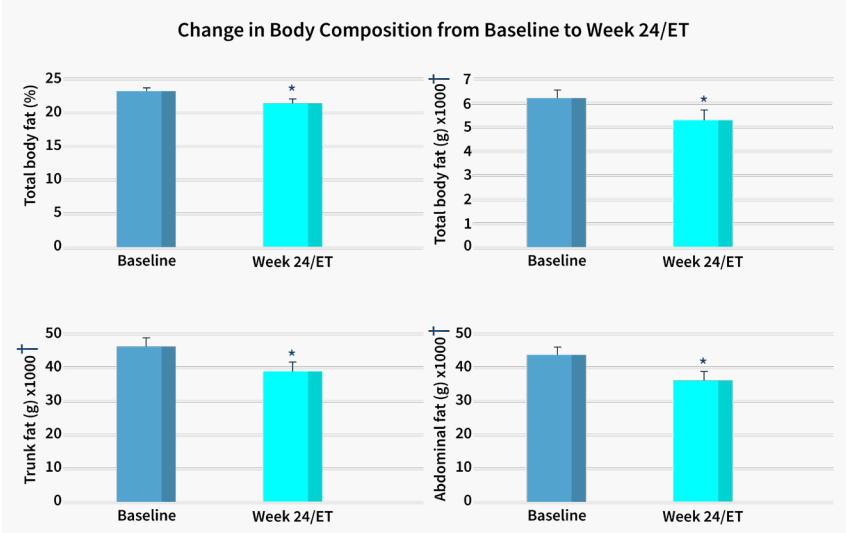




| Weight | Overall mean ± SE |
|---|---|
| Baseline (kg) | 99.5 ± 4.4) |
| Week 24/ET (kg) | 6.3 ± 1.3 (P<0.001 |
| % Change from D1 to Week 24/ET | -5.7 ± 1.1 (P<0.001) |
| % Change from D1 to Week 24 | -7.7 ± 1.2 (P<0.001) |




Fleseriu M, et al. *J Clin Endocrinol Metab*. 2012.

# Mifepristone

- SEISMIC Study: Efficacy and Safety in Endogenous CS
- Common AEs were:
  - Nausea (48%)
  - Fatigue (48%)
  - Headache (44%)
  - Decreased blood $K^+$ (34%)
  - Arthralgia (30%)
  - Vomiting (26%)
  - Peripheral edema (26%)
  - HTN (24%)
  - Dizziness (22%)
  - Decreased appetite (20%)
  - Endometrial thickening (20%)

**Table 3. Summary of responders analyses (mITT population)**

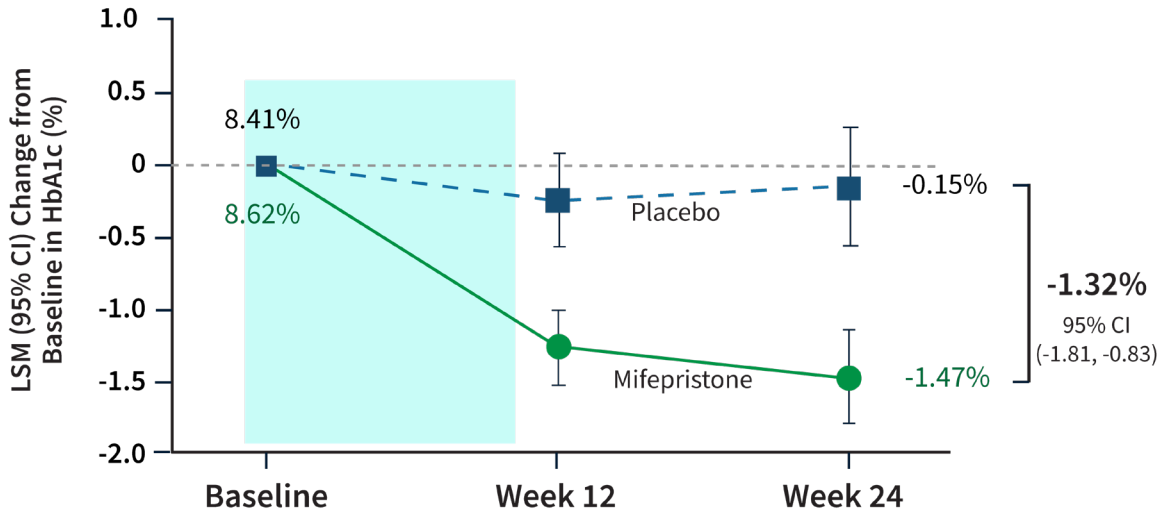
| Statistics (mITT population) | Responder [n (%)] | Nonresponder [n (%)] | Lower bound one-sided 95% exact binomial CI (95%) | *P* value |
|---|---|---|---|---|
| C-DM (n=25) | | | | |
| • Participants with or without a 25% reduction from baseline in $AUC_{glucose}$ at wk 24/ET | 15 (60) | 10 (40) | 41.7 | <0.0001 |
| C-HT (n=21) | | | | |
| • Participants who had ≥5 Hg reduction from baseline in DBP at wk 24/ET | 8 (38.1) | 13 (61.9) | 20.6 | <0.05 |
| C-HT and C-DM with HTN at screening (n=40) | | | | |
| • Participants who had ≥5 Hg reduction from baseline in DBP at wk 24/ET | 17 (42.5) | 23 (57.5) | | |
| • Participants who had a reduction in antihypertensive meds at wk24/ET | 11 (27.5) | 29 (72.5) | | |
| • Participants who either had ≥5 Hg reduction from baseline in DBP or had a reduction in antihypertensive meds at wk24/ET | 21 (52.5)[a] | 19 (47.5) | | |
| Median clinical improvement score of +1 at any reviewed visit[b] | | | | |
| • Combined cohorts (n=46) | 40 (87.0) | 6 (13.0) | 75.9 | <0.0001 |
| • C-DM (n=25) | 23 (92.0) | 2 (8.0) | 76.9 | |
| • C-HT (n=21) | 17 (81.0) | 4 (19.0) | 61.6 | |

Fleseriu M, et al. *J Clin Endocrinol Metab*. 2012.

# Mifepristone

## CATALYST Part 2: Treatment Phase

- A Randomized, Placebo-Controlled Study
- Adults with inadequately controlled T2D and hypercortisolism (based on DST)- N=136
- Primary endpoint: change in HbA1c from baseline to week 25




**Number of participants**

| | | | |
|---|---|---|---|
| Mifepristone | 86 | 74 | 62 |
| Placebo | 44 | 40 | 38 |
| **P-value** | | **<0.001** | **<0.001** |

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

# Mifepristone

## CATALYST Part 2: Other Findings

- Improvements in glycemic control were accompanied by reductions in:
  - Glucose-lowering medications
  - Body weight (-4.4 kg)
  - BMI and waist circumference (-1.5 kg/m2 and -5.2 cm)

| No. (%) | Placebo | Mifepristone |
|---|---|---|
| Long-acting insulin | 3 (13.0) | 32 (49.2) |
| Fast-acting insulin | 2 (10.5) | 10 (30.3) |
| Sulfonylureas | 2 (10.5) | 4 (22.2) |
| GLP-1 RAs | 0 | 4 (12.1) |
| Tirzepitide | 0 | 2 (10.5) |
| Metformin | 0 | 1 (1.5) |
| SGLT2 Inhibitors | 1 (3.7) | 0 |
| Total, No. | 8 | 53 |

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

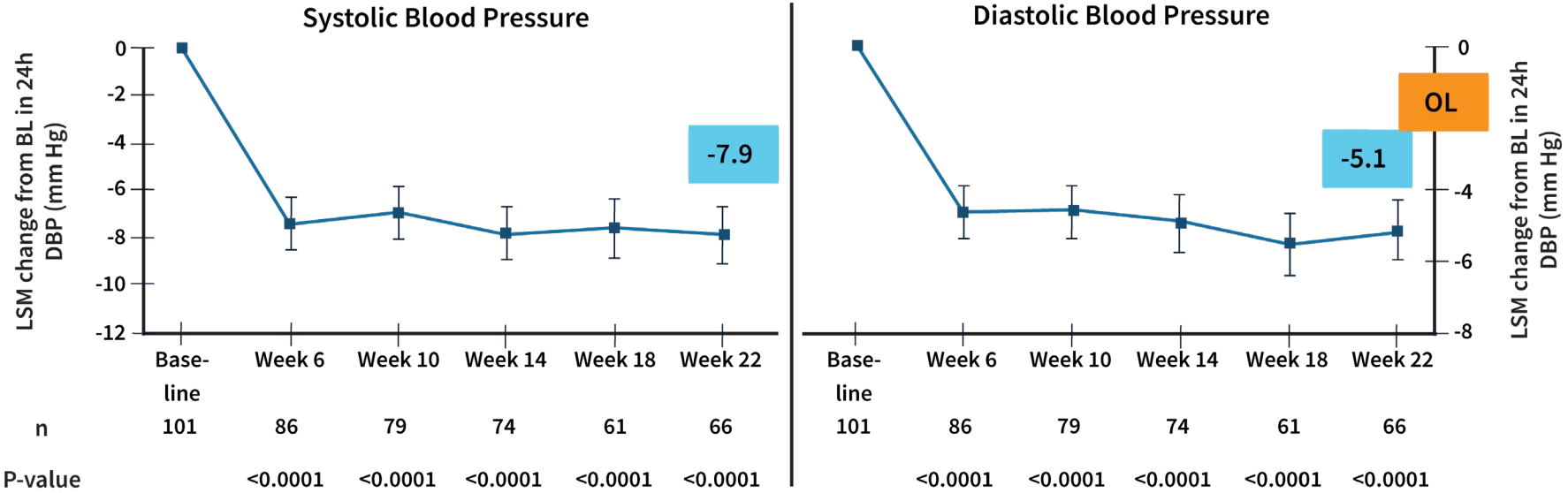
# Relacorilant

- Relacorilant is an investigational selective glucocorticoid receptor (GR) modulator designed to modulate excess cortisol activity at the GR to treat the manifestations of endogenous hypercortisolism.
  - Highly selective for the GR, with no activity at the progesterone, mineralocorticoid, or androgen receptors; structurally different from the nonselective GR antagonist mifepristone
  - Avoids unwanted off-target progesterone receptor effects (eg, endometrial hypertrophy, vaginal bleeding)
  - Because of a lack of increase in ACTH, it does induce hypokalemia and is not associated with adrenal insufficiency or QT interval prolongation

Jabbour S, et al. *Heart in Diabetes*. 2025.

# Relacorilant

- GRACE Study: Efficacy and Safety in Cushing Syndrome (CS)
- Phase 3 open-label (OL) trial followed by 12 week double-blind, placebo-controlled random withdrawal (RW) phase
- Participants: 152 adults with CS and uncontrolled HTN and/or hyperglycemia (DM/IGT)
  - N=31 with HTN, n=50 with DM/IGT, n=71 with both
- OL Phase Results (relacorilant 100mg daily, up to 400 mg daily, as tolerated): rapid and sustained improvements in blood pressure (ambulatory blood pressure monitoring)




Pivonello R, et al. *J Endocr Soc*. 2024; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

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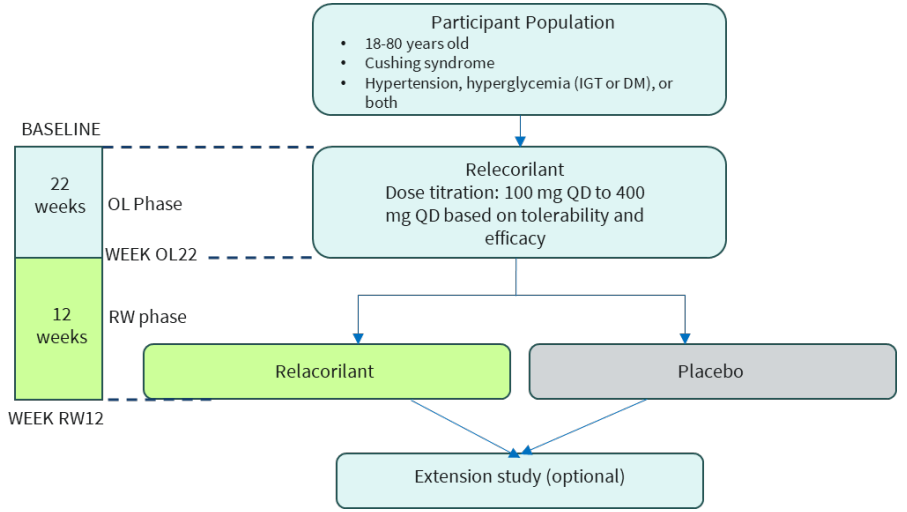
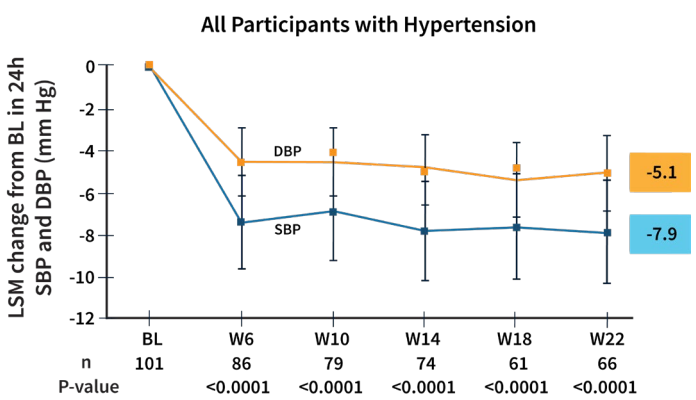
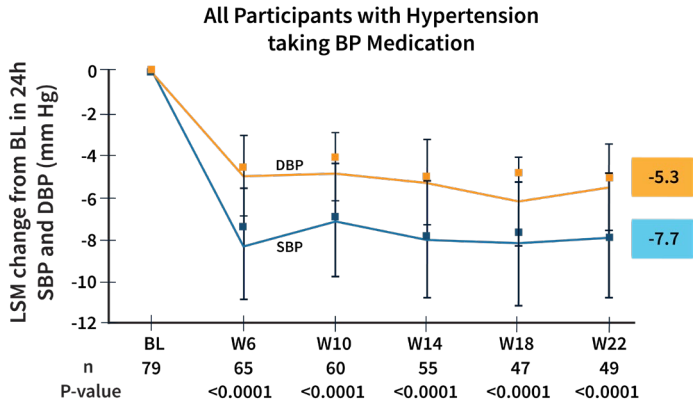
# GRACE Trial Results: OL Phase

| | Participants (n=102) |
|---|---|
| Age, years, mean (SD) | 48.6 (12.7) |
| Female, n (%) | 85 (83.3) |
| Weight, kg, mean (SD) | 95.1 (26.1) |
| BMI, kg/m2, mean (SD) | 34.7 (9.0) |
| Waist circumference, cm, mean (SD) | 115.1 (19.5) |
| HbA1c, mean (%) | 6.7 (1.6) |
| 24-h SBP, mm Hg, mean (SD) [n] | 140.6 (10.6) [101] |
| 24-h DBP, mm Hg, mean (SD) [n] | 88.9 (7.2) [101] |



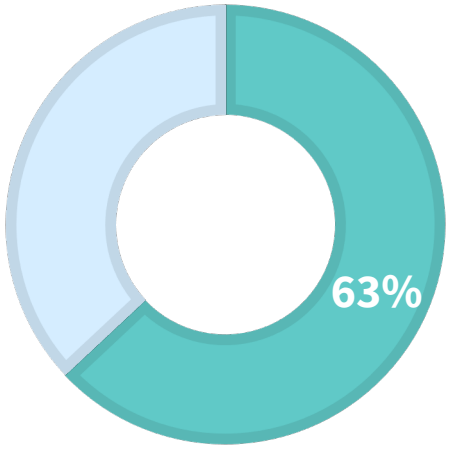




Jabbour S, et al. *Heart in Diabetes*. 2025; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

# Additional GRACE Trial Results: OL Phase

Patients with DM/IGT with or without HTN(n=121) mean change (SD)

- AUC (glucose): -3.3 (6.7) h*mmol/L; P<.0001
- HbA1c: -0.3% (1.0%); P<.001)




Patients who achieved HTN and/or hyperglycemia control

Pivonello R, et al. *J Endocr Soc*. 2024; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

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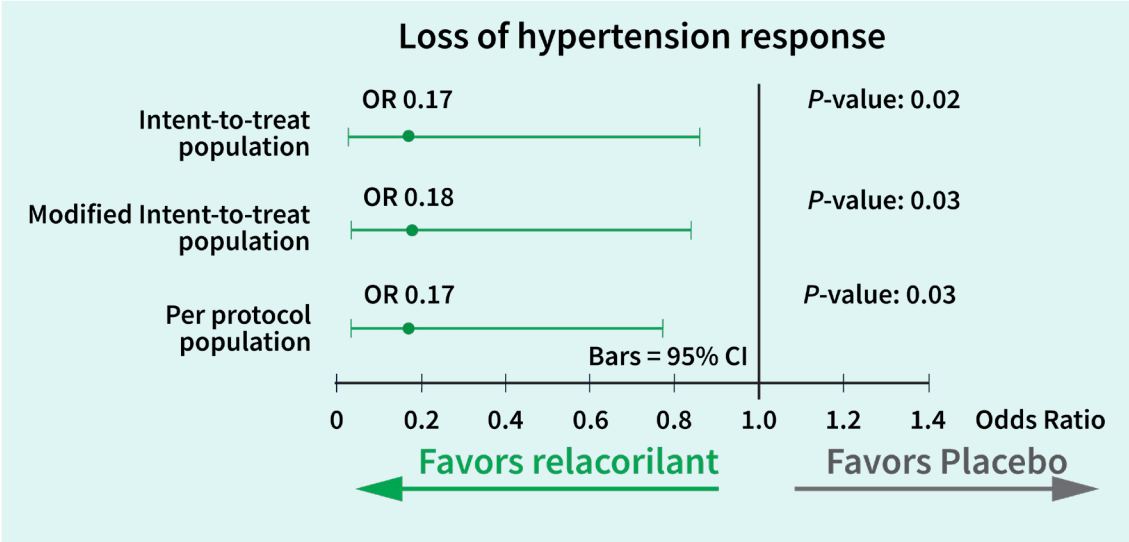
# Relacorilant

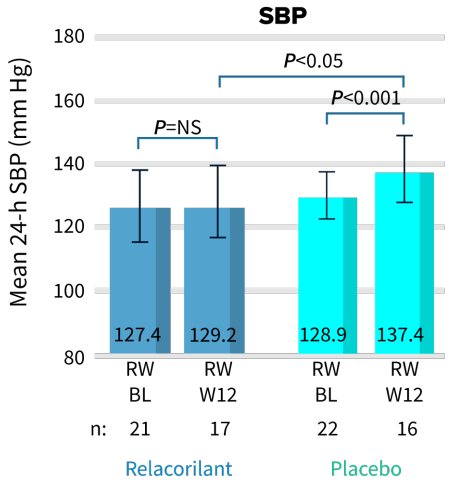
GRACE Study Continued: Efficacy during RW phase

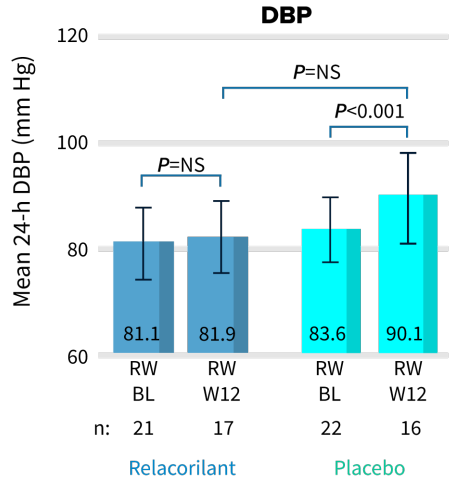
- 65% of patients who completed the OL phase continued to the RW phase
- N=32 receiving placebo; n=30 continued with relacorilant
- RW Phase Results
  - Blood Pressure: patients taking placebo more likely to lose control of HTN and patients receiving relicorilant were 6x more likely to maintain HTN response
    - Systolic Blood Pressure: -12.6 (6.5) mm Hg; P<.0001
    - Diastolic Blood Pressure : -8.3 (4.9) mm Hg; P<.001)
  - Glycemic Control:
    - AUC (glucose): -6.2 (6.5) h*mmol/L; P<.0001
    - HbA1c: -0.7% (1.1%); P<.001)
  - Other Metabolic Parameters:
    - Weight Loss: -3.3 (5.9) kg, P<.0001
    - Waist Circumference: -2.8 (6.2) cm, P<.0001
  - Improvements in Quality of Life (QoL):
    - +7.4 (14.6) points on Cushing QoL normalized total score, P<.0001




Pivonello R, et al. *J Endocr Soc*. 2024; Pivonello R, et al. *Endocrine Abstracts*. 2025; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

# GRACE Trial Results: Withdrawal Phase




| | Relacorilant (n=21) | Placebo (n=22) |
|---|---|---|
| Age, years, mean (SD) | 46.1 (11.4) | 49.0 (13.3) |
| Female, n (%) | 15 (71.4) | 20.0 (90.9) |
| Weight, kg, mean (SD) | 93.7 (32.0) | 85.0 (21.4) |
| BMI, kg/m², mean (SD) | 32.5 (8.4) | 31.6 (6.8) |
| Waist circumference, cm, mean (SD) | 113.1 (20.5) | 105.9 (16.7) |
| 24-h SBP, mm Hg, mean (SD) | 137.9 (11.0) | 140.8 (10.6) |
| 24-h DBP, mm Hg, mean (SD) | 89.2 (7.0) | 90.6 (5.5) |

Pivonello R, et al. *Endocrine Abstracts*. 2025; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

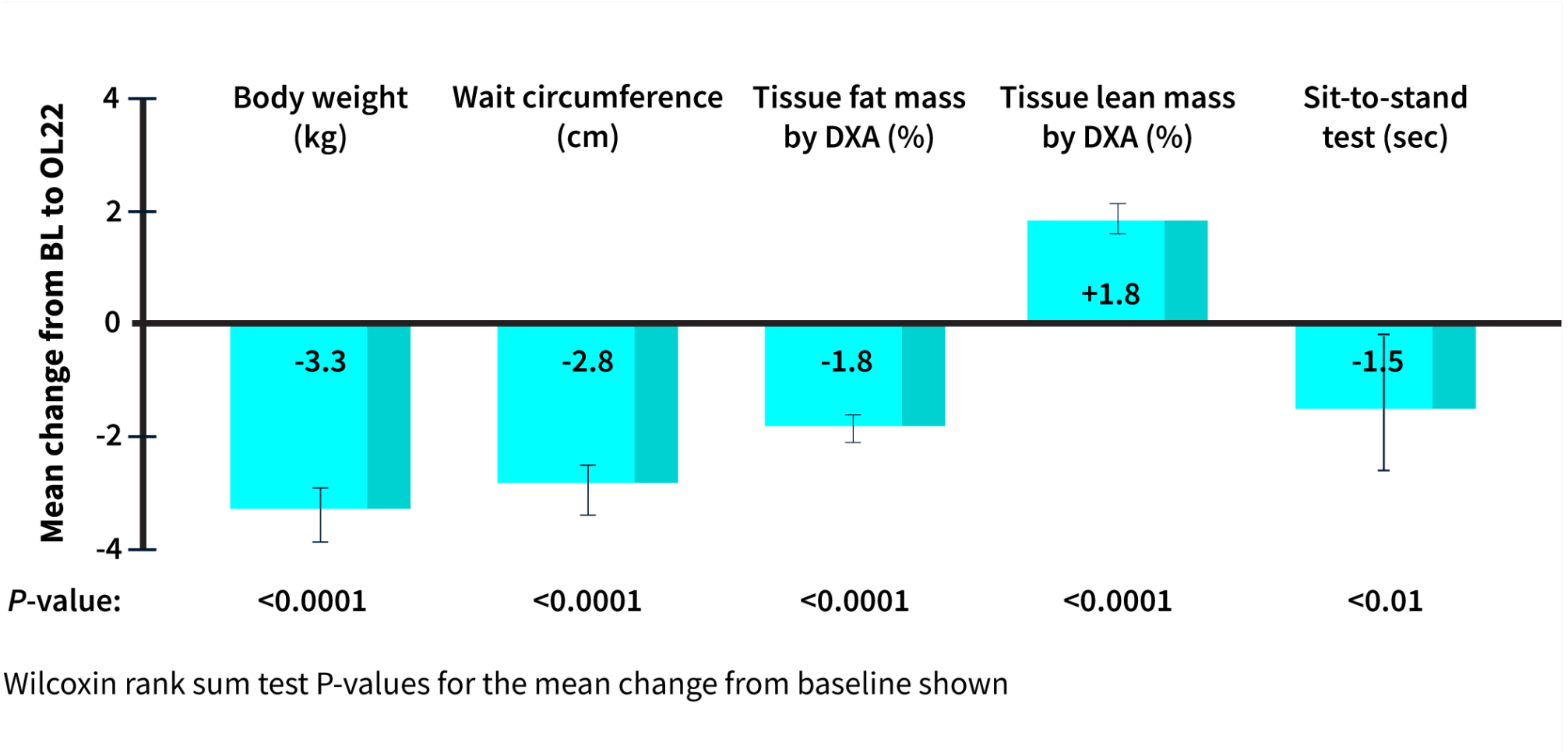
# GRACE Trial Results: Withdrawal Phase, Impact on Glycemic Measures

| | Relacorilant (n=30) | Placebo (n=32) |
|---|---|---|
| Change from RW baseline to week RW12 in **$AUC_{glucose}$** (in patients with hyperglycemia at study entry), h*mmol/L | | |
| • N | 15 | 19 |
| • Mean (SD) | +1.1 (4.7) | +4.9 (6.1) |
| • Wilcoxon signed rank sum P-value[a] | ns | 0.0003 |
| Change from RW baseline to week RW12 in **HbA1c** (in patients with hyperglycemia at study entry), % | | |
| • N | 16 | 19 |
| • Mean (SD) | +0.1 (0.8) | +0.3 (0.6) |
| • Wilcoxon signed rank sum P-value[a] | ns | 0.03 |
| Change from RW baseline to week RW12 in **HbA1c** (in patients with diabetes at study entry), % | | |
| • N | 13 | 13 |
| • Mean (SD) | +0.1 (0.8) | +0.4 (0.6) |
| • Wilcoxon signed rank sum P-value[a] | ns | 0.04 |

[a]Wilcoxin signed-rank test P-values within each treatment arm

Pivonello R, et al. *Endocrine Abstracts*. 2025; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

# GRACE Trial Results: Impact of Relacorilant on Body Composition




Wilcoxin rank sum test P-values for the mean change from baseline shown

Pivonello R, et al. *Endocrine Abstracts*. 2025; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

# Relacorilant

## GRACE Study Continued: Safety Profile

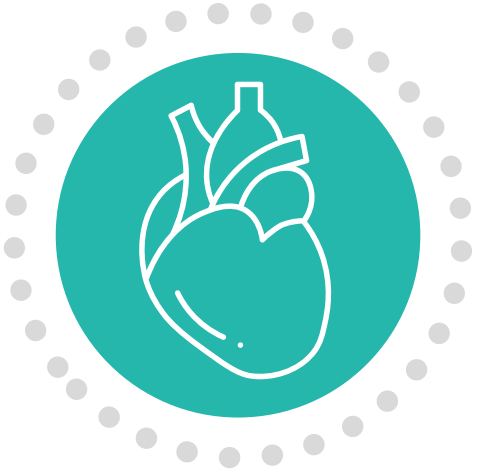
- Overall: efficacy observed without serious side effects

Metabolic Side Effects:

- No increase in cortisol concentrations
- No hypokalemia associated with excess cortisol

Gynecologic Side Effects:

- No excess vaginal bleeding
- No endometrial hyperplasia



Cardiac Side Effects:

- No confirmed QT interval prolongation

Common adverse events:

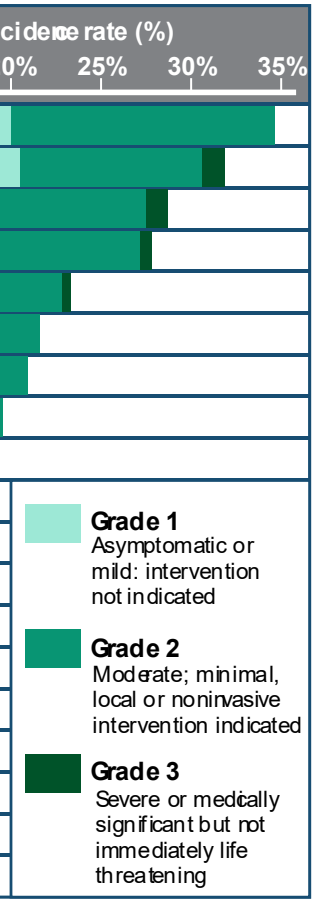
- Nausea, peripheral edema, pain in extremity, back pain, and fatigue (≥ 20%)

Pivonello R, et al. *J Endocr Soc*. 2024; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

# GRACE Trial Results: Safety

## Adverse events occurring in ≥10% of patients

| Adverse event, n (%) | Relacorilant (n=152) |
|---|---|
| Nausea | 52 (34.2) |
| Edema peripheral | 50 (32.9) |
| Extremity pain | 43 (28.3) |
| Backpain | 41 (27.0) |
| Fatigue | 34 (22.4) |
| Headache | 31 (20.4) |
| Arthralgia | 30 (19.7) |
| Diarrhea | 28 (18.4) |
| Skin hyperpigmentation | 24 (15.8) |
| Upper abdominal pain | 23 (15.1) |
| Constipation | 23 (15.1) |
| Dizziness | 23 (15.1) |
| Paresthesia | 21 (13.8) |
| Myalgia | 21 (13.8) |
| Asthenia | 19 (12.5) |
| Vomiting | 19 (12.5) |
| Abdominal pain | 17 (11.2) |
| Decreased appetite | 17 (11.2) |
| Muscular weakness | 17 (11.2) |




Data updated based on database lock: analysis date 5 July 2024, TEAE's and CTCAE grade shown.

Pivonello R, et al. *Endocrine Abstracts*. 2025; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

# Relacorilant NDA Submission

- Corcept submitted an NDA for Relacorilant as a treatment for hypertension secondary to hypercortisolism based on the Phase 3 GRACE trial (primary endpoint met) and supporting GRADIENT trial data.
- The FDA issued a complete response letter stating that while GRACE met its primary endpoint and GRADIENT provided confirmatory evidence, additional evidence of effectiveness is required for a favorable benefit-risk assessment.
- Corcept plans to meet with the FDA as soon as possible to determine the path forward.

# Why Does QT Interval Matter in Cushing Syndrome Management?

QT interval may be influenced by medical therapies, therefore monitoring before and during treatment is crucial, especially in those patients who:

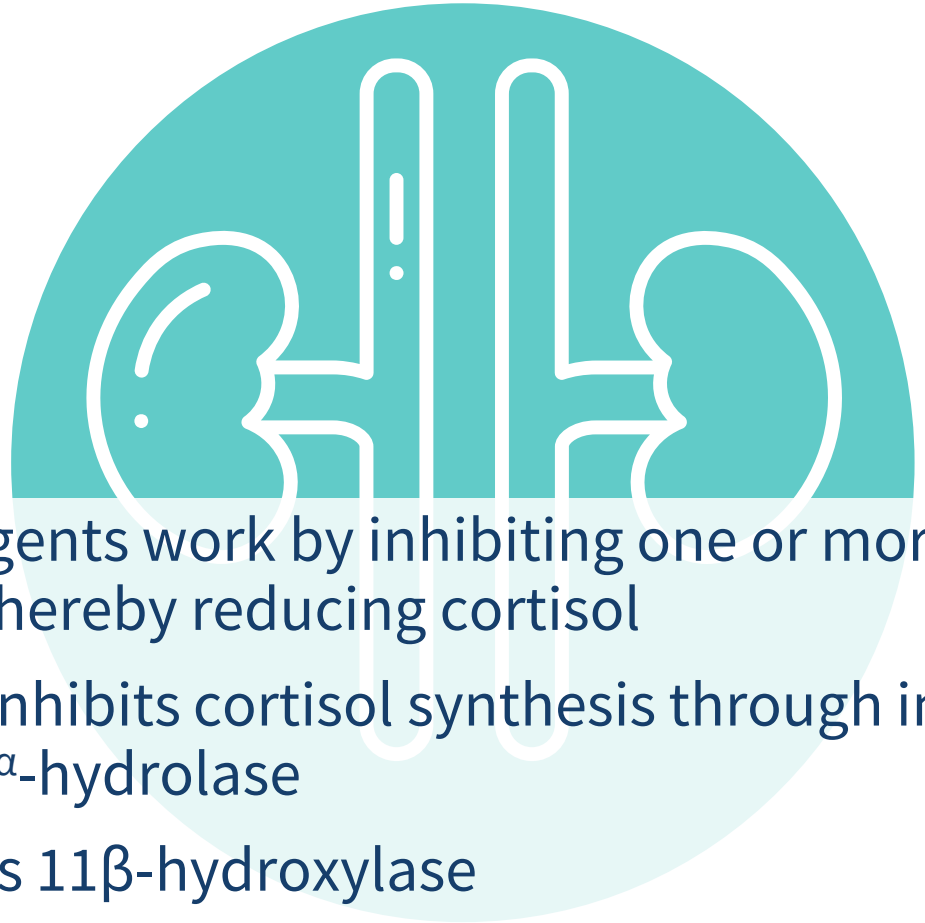
- Use other drugs influencing QT or inducing hypokalemia
- Use a combination of different medications for CS both inducing longer QT intervals

| Medication | Study | QT Prolongation, (%) |
|---|---|---|
| Pasireotide SC | SOM230B2305 | 2.0 |
| Pasireotide LAR | SOM230G2304 | 3.0 |
| Osilodrostat | LINC 3 | 4.0 |
| Levoketoconazole | SONICS; LOGICS | 5.3; 10.7 |

Colao A, et al. *N Engl J Med*. 2012; Lacroix A, et al. *Lancet Diabetes Endocrinol*. 2018; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2020; Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2019; Pivonello R, et al. *Pituitary*. 2022.


# Adrenal-Directed Agents: Steroidogenesis Inhibitors

# Mechanism of Action



- Adrenal-Directed Agents work by inhibiting one or more enzymes necessary for cortisol synthesis, thereby reducing cortisol
- Levoketoconazole inhibits cortisol synthesis through inhibition of 11β-hydroxylase and 17$^{\alpha}$-hydrolase
- Osilodrostat inhibits 11β-hydroxylase
- Other agents used off-label: ketoconazole, etomidate, metyrapone, mitotane

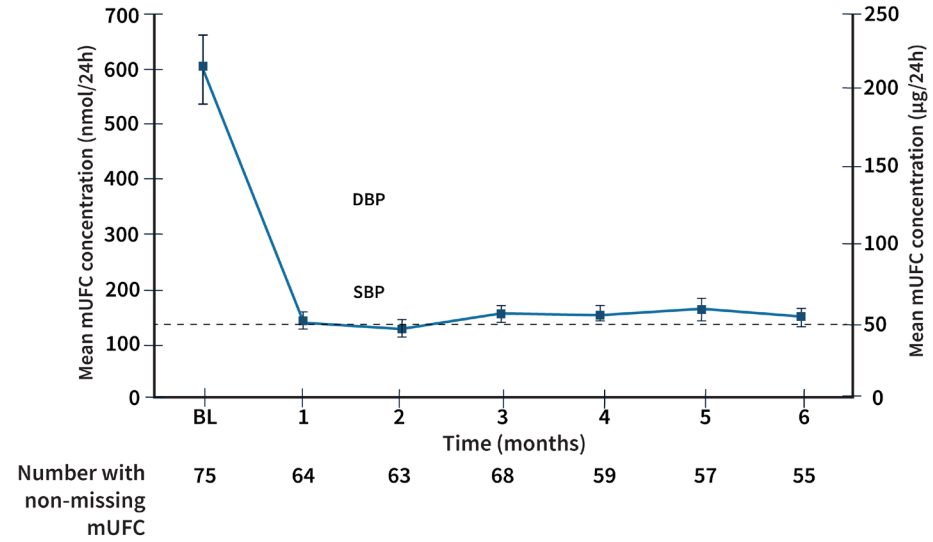
Pivonello R, et al. *Front Endocrinol (Lausanne)*. 2020; Martino M, et al. *Expert Opin Pharmacother*. 2023; Cohan P, et al. *Endocr Pract*. 2014.

# Levoketoconazole

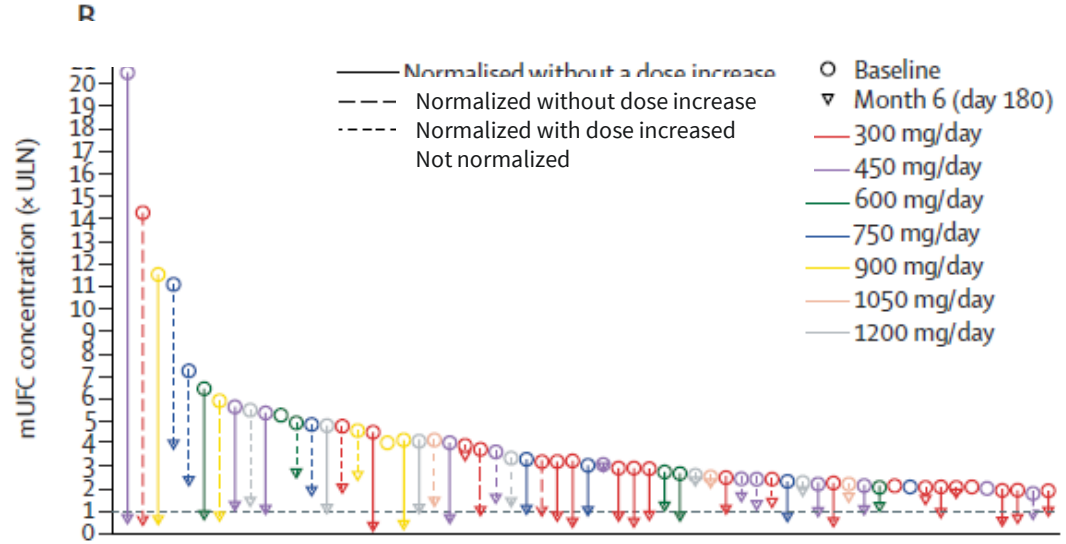
## SONICS Study: Efficacy

- Primary outcome: proportion of patients with mUFC normalization at end of maintenance, without dose increase during the maintenance

### mUFC Concentration From Baseline of the Dose Titration Phase Through the End of the Maintenance Phase (Month 6)




### Change in Individual mUFC Concentrations From Baseline of the Dose Titration Phase to the End of Maintenance Phase (Month 6)




Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2019.

# Levoketoconazole

## SONICS Study: Safety

| | Patients (n=94) |
|---|---|
| Any adverse event | 92 (98%) |
| • Serious adverse event | 14 (15%) |
| • Drug-related adverse event | 40 (43%) |
| • Adverse event leading to discontinuation | 12 (13%) |
| Intensity of adverse events | |
| • Mild | 21 (22%) |
| • Moderate | 54 (57%) |
| • Severe | 15 (16%) |
| • Life threatening | 1 (1%) |
| • Death | 1 (1%) |
| Most common adverse events | |
| • Nausea | 30 (32%) |
| • Headache | 26 (28%) |
| • Peripheral edema | 18 (19%) |
| • Hypertension | 16 (17%) |
| • Fatigue | 15 (16%) |
| • Diarrhea | 14 (15%) |
| • ALT increase | 14 (15%) |
| • GGT increase | 12 (13%) |
| • AST increase | 11 (12%) |

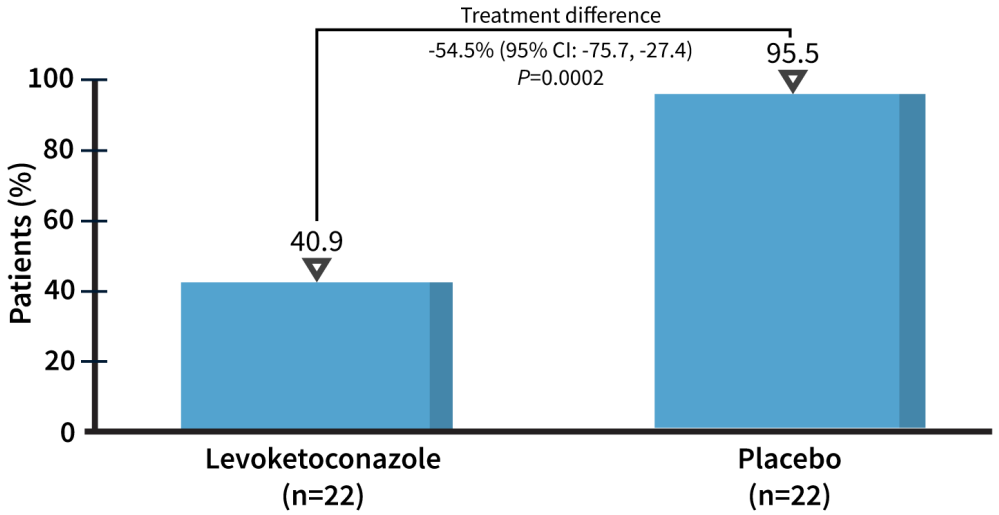
Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2019.

# Levoketoconazole

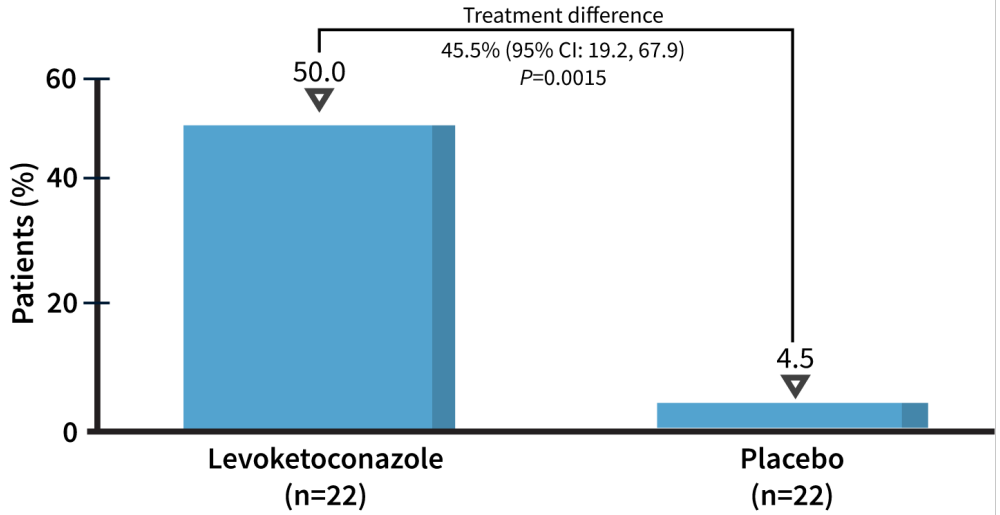
## LOGICS Study

- Phase 3, placebo-controlled, randomized-withdrawal study with open-label titration-maintenance (14–19 weeks) followed by double-blind, randomized-withdrawal (~ 8 weeks), and restoration (~ 8 weeks) phases

**Primary endpoint: rate of loss of therapeutic response**




**mUFC normalization rate**

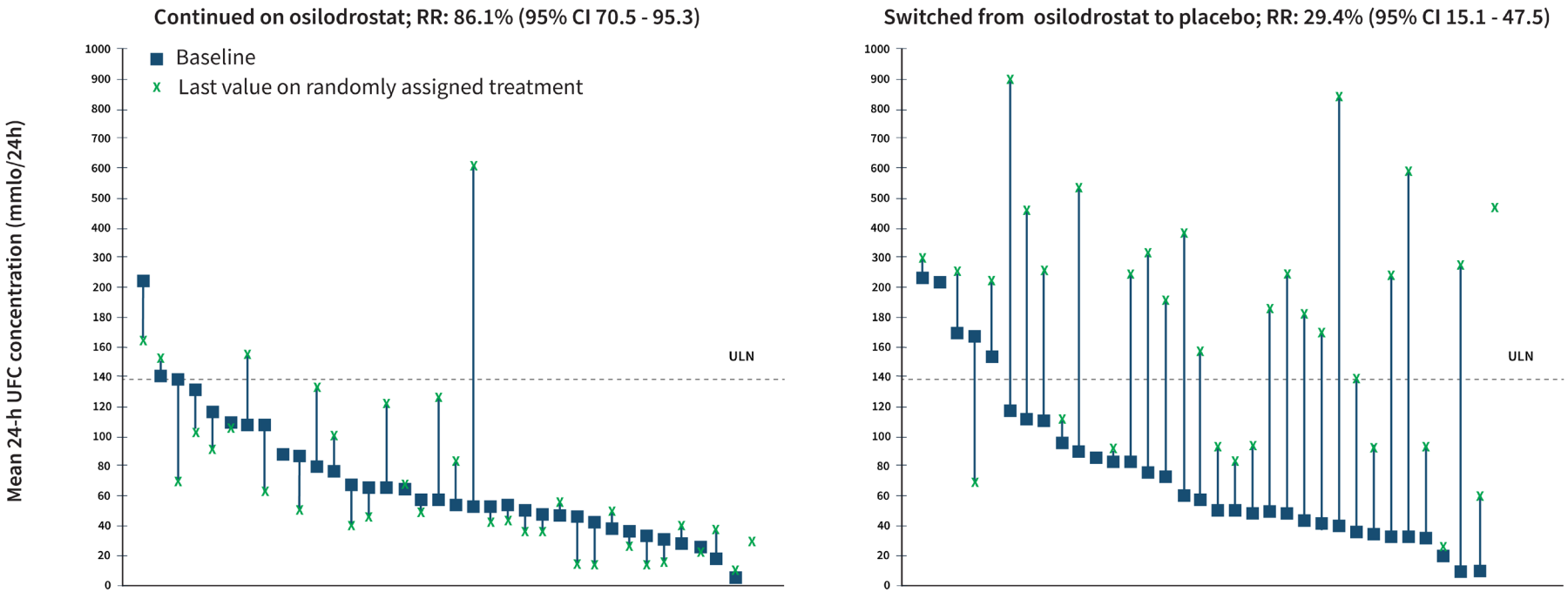



Pivonello R, et al *Pituitary*. 2022.

# Osilodrostat

LINC-3 Study: Phase 3 Safety and Efficacy in Cushing Disease

- Primary endpoint: Proportion of participants with a complete response (ie, mean 24-h UFC concentration of ≤ULN) at the end of the randomized withdrawal period (week 34), without up-titration during this period (N=137)
- Hypocortisolism occurred in 51% patients and AEs related to adrenal hormone precursors occurred in 42% patients
- Most common adverse events (ie, occurred in >25% of participants) were:
  - nausea (42%)
  - headache (34%)
  - fatigue (28%)
  - adrenal insufficiency (28%)

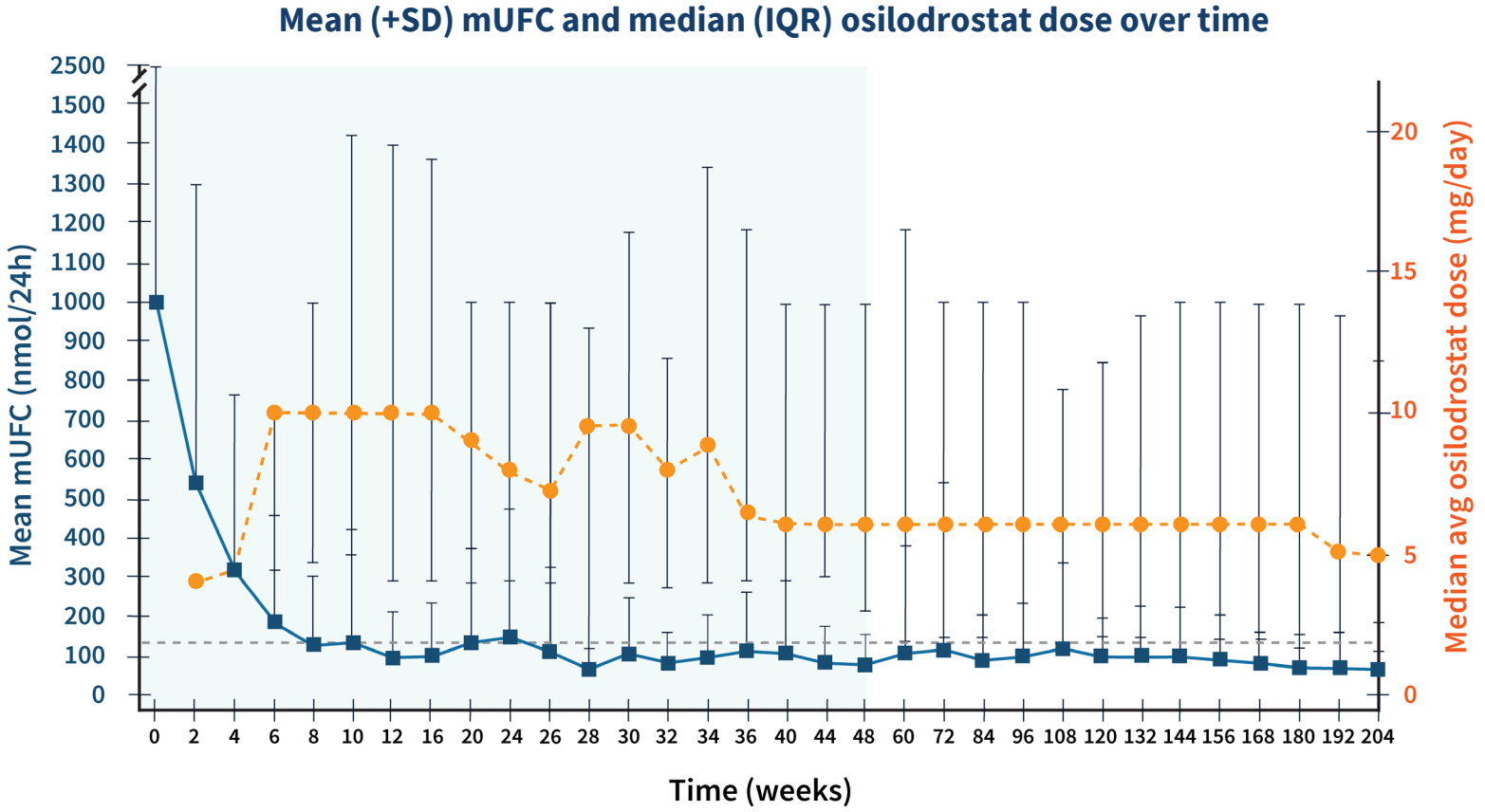



Pivonello R, et al. *Lancet Diabetes Endocrinol.* 2020.

# Osilodrostat

LINC-3 Extension Study: Long-Term Outcomes in Cushing Disease

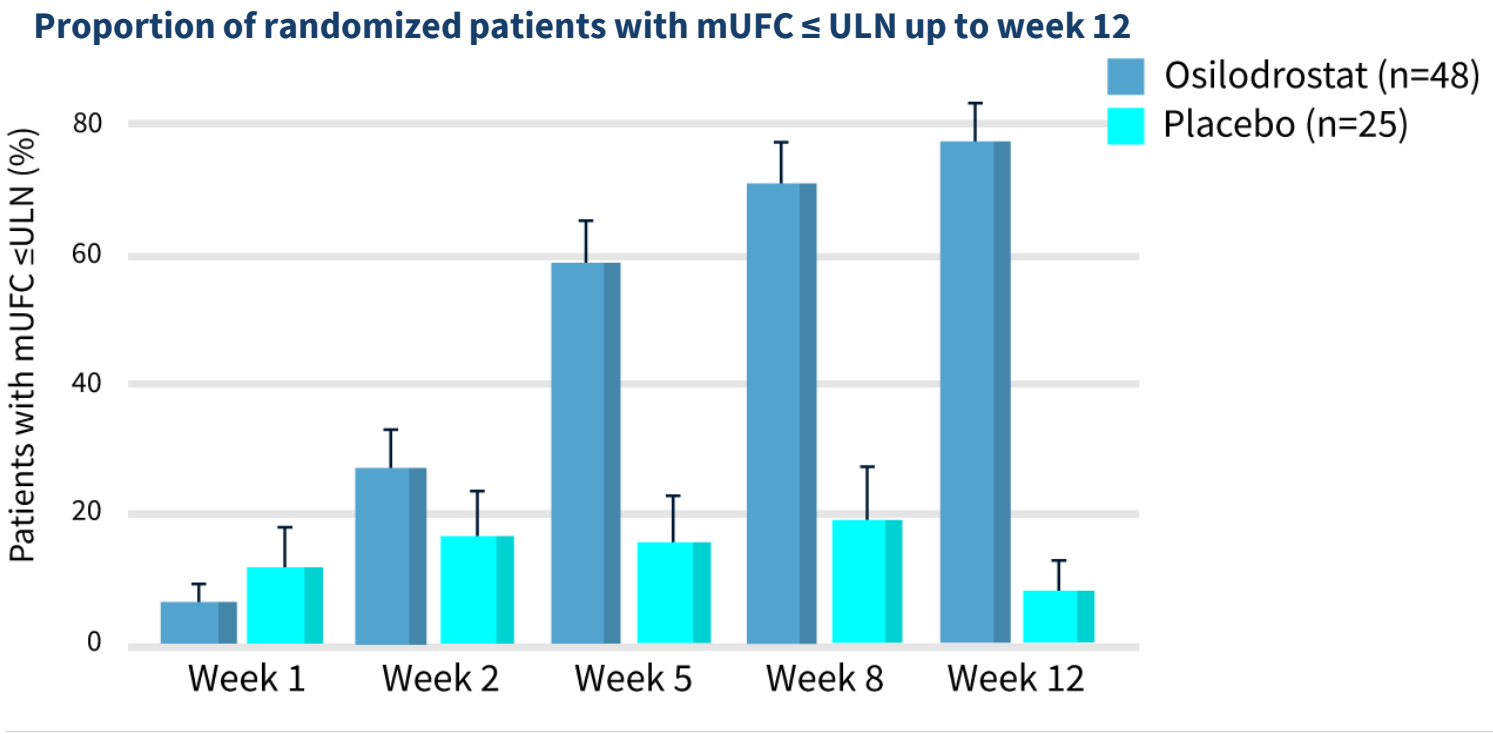
- Rates of mUFC normalization: 66.4% at week 48; 81.1% at week 60; 81.1% at week 72
- Improvements in cardiovascular/metabolic-related parameters, physical manifestations of hypercortisolism, and quality of life were maintained or improved further during the extension
- No new safety signals were reported: 10.9% (core) and 11.3% (extension) patients discontinued for adverse events




Fleseriu M, et al. *Eur J Endocrinol*. 2022.

# Osilodrostat

LINC-4: Osilodrostat in the Treatment of Cushing Disease




The most common AEs during the placebo-controlled period included decreased appetite (37%), arthralgia (35%), and nausea (31%).

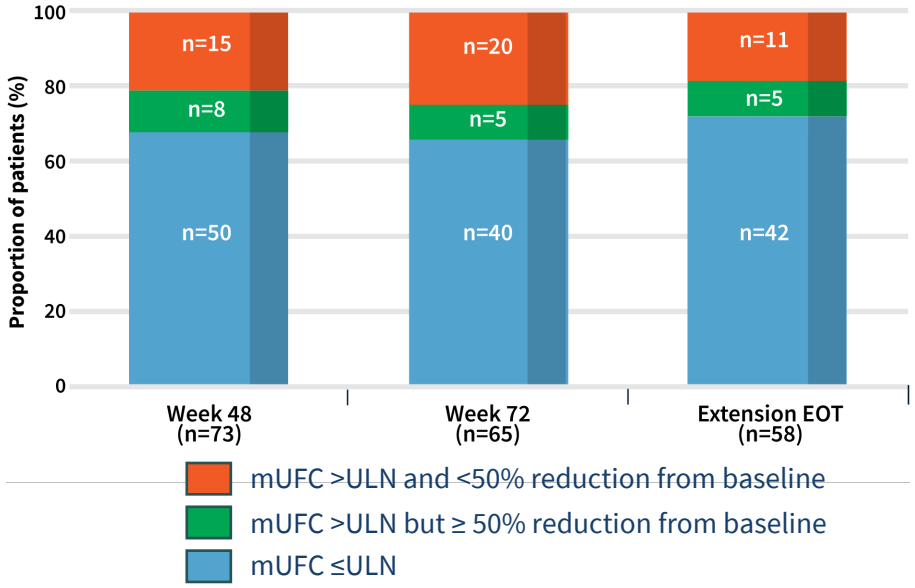
Gadelha M, et al. *J Clin Endocrinol Metab*. 2022

# Osilodrostat

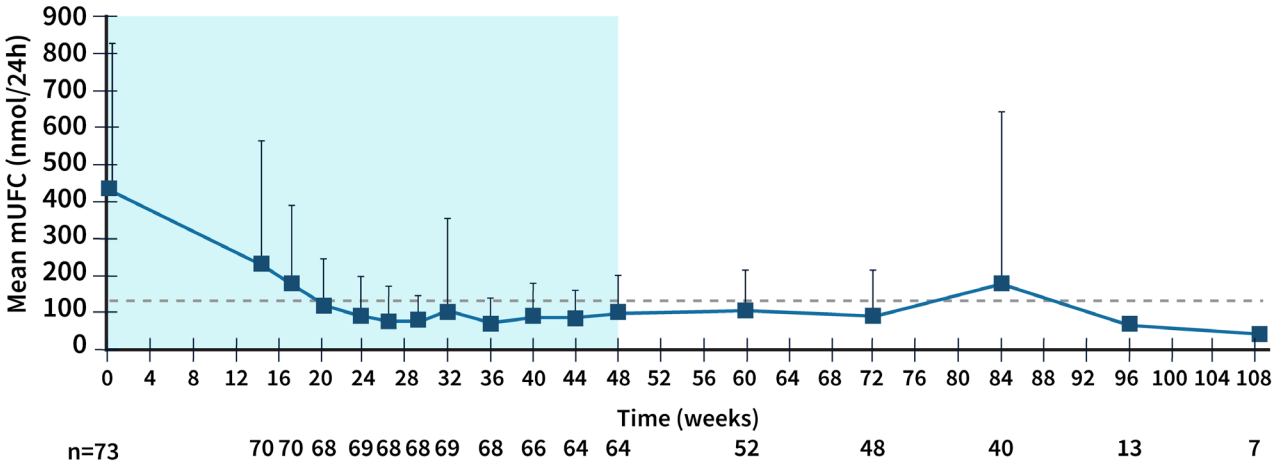
LINC-4 Extension Study:

Long-Term Efficacy and Safety of Osilodrostat in the Treatment of Cushing Disease

**Proportion of patients with mUFC response over time**




**Mean mUFC over time**



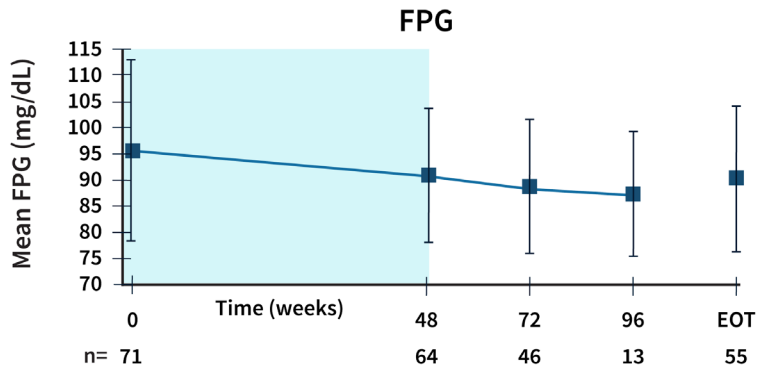

Gadelha M, et al. *Front Endocrinol (Lausanne).* 2023.

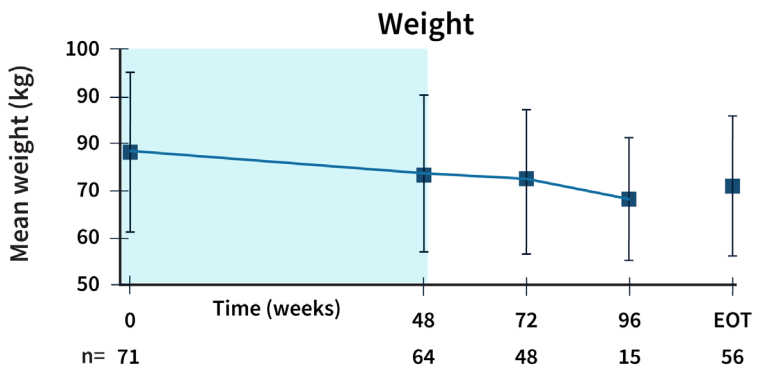
# Osilodrostat

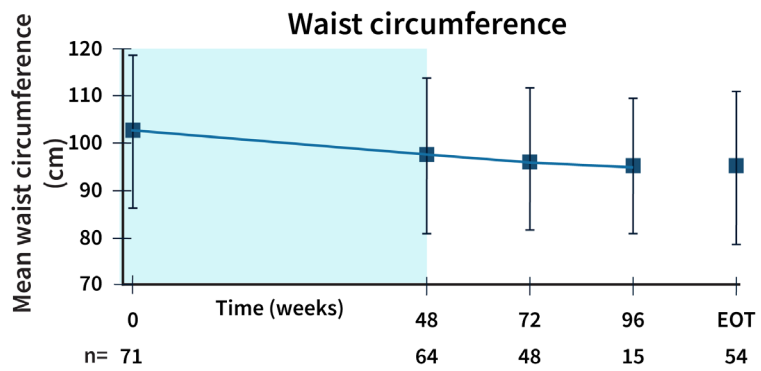
LINC-4 Extension Study:

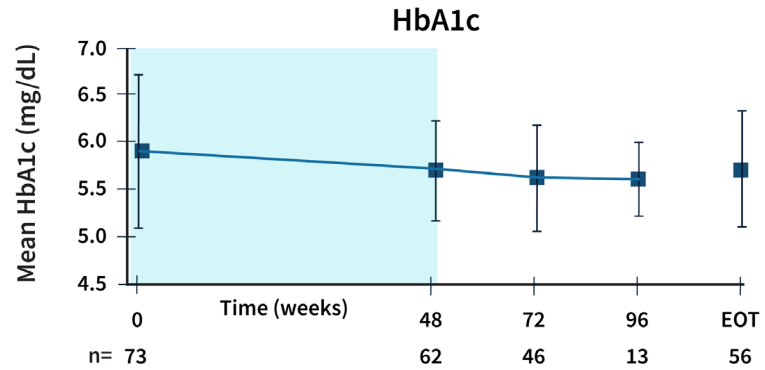
Long-Term Efficacy and Safety of Osilodrostat in the Treatment of Cushing Disease

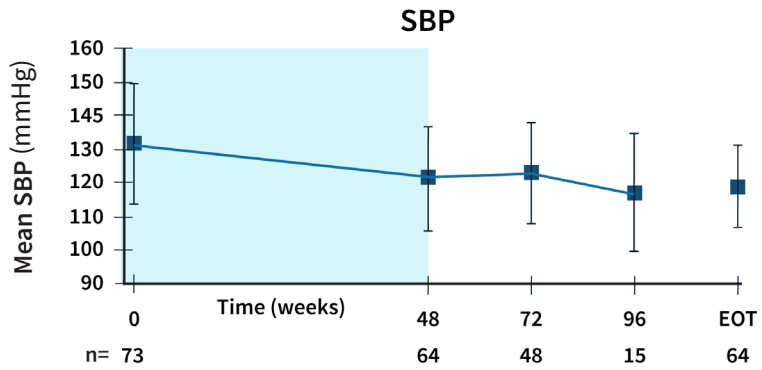
**Changes in cardiovascular-related metabolic**

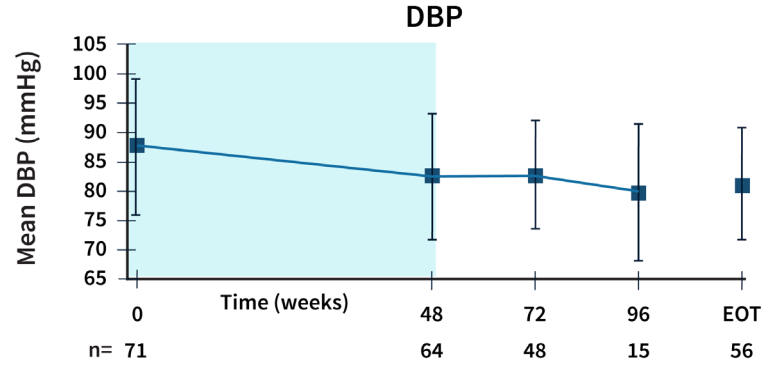



Gadelha M, et al. *Front Endocrinol (Lausanne)*. 2023.

# Osilodrostat

Dose Increases and Hypocortisolism-Related Adverse Events

Osilodrostat: initiated at a low dose, with incremental dose increases based on individual response/tolerability

- Monitor for:
  - Adrenal insufficiency
  - Hypo/Hyperkalemia
  - Pituitary tumor changes in CD

**Dose titration schedule**

**LINC3**

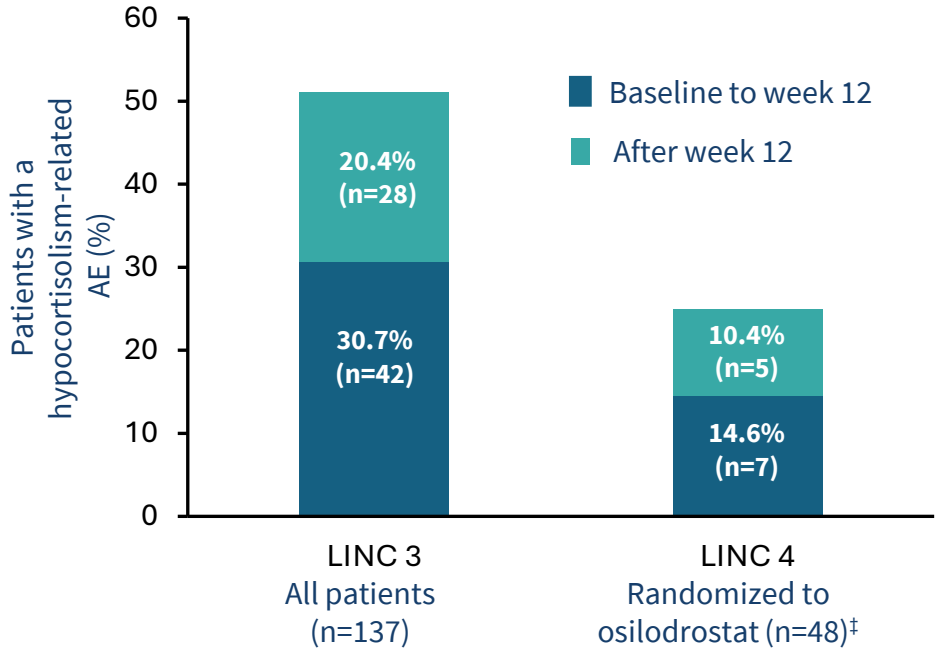
Increased every **2 weeks** if mUFC ≥ULN*

2 → 5 → 10 → 20 → **30 mg bid**

**LINC4**

Increased every **3 weeks** if mUFC ≥ULN*†

2 → 5 → 10 → **20 mg bid**



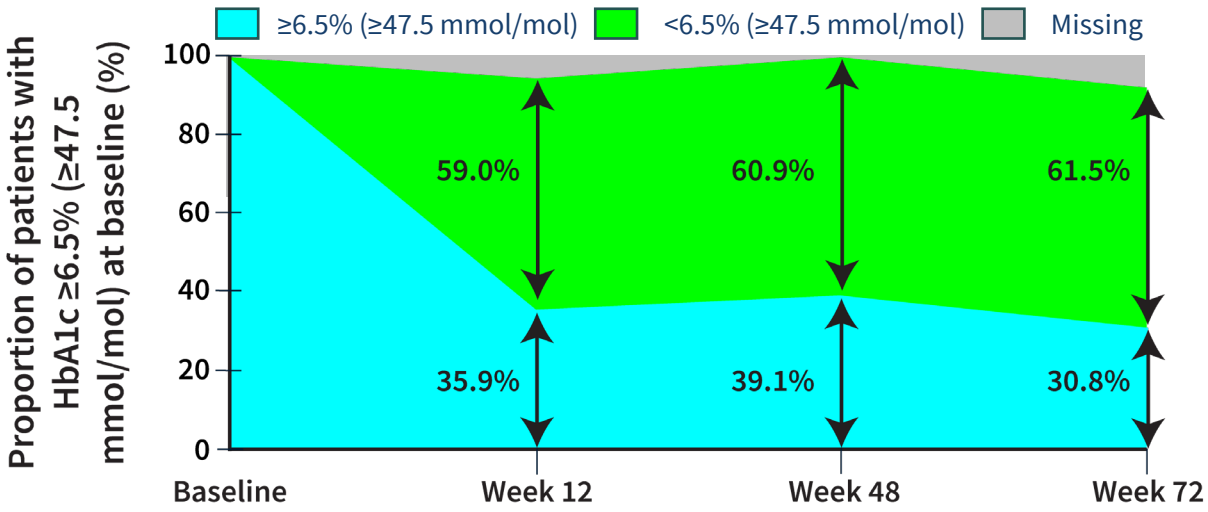

*Provided no tolerability issues; †In LINC 4, dose titration decisions were made by independent non-blinded endocrinologists until week 12; ‡Patients randomized to osilodrostat during the initial 12-week randomized, double-blind, placebo-controlled period; 8 patients who were initially randomized to placebo also experienced a hypocortisolism-related AE after switching to open-label osilodrostat

Fleseriu M, et al. *AACE*. 2021.

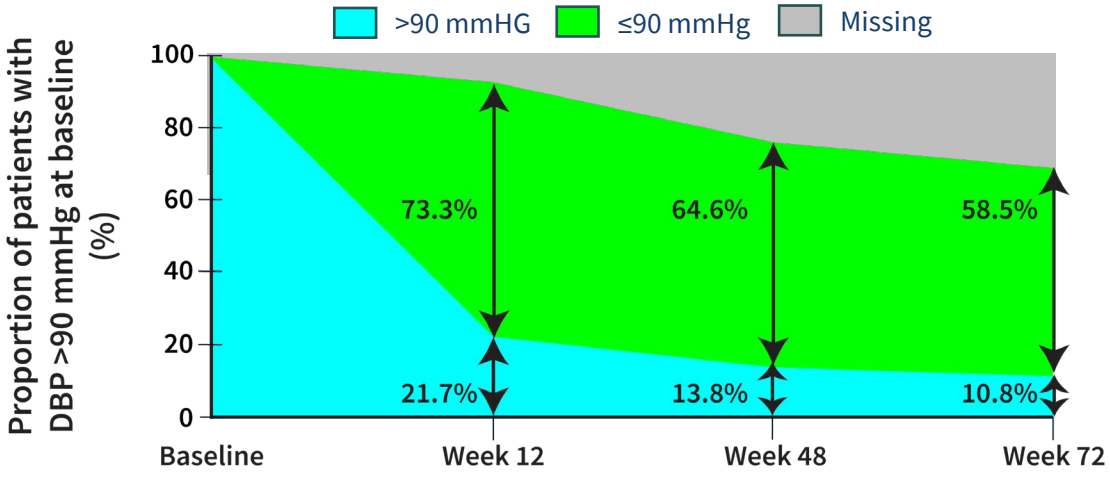
# Osilodrostat

Linc Studies (N=210)- Effect on metabolic parameters

## Effect on Glucose




## Effect on Blood Pressure




Fleseriu M, et al. *Pituitary*. 2025.

# Osilodrostat: LINC 6

- Long-Term, Real-World, Safety and Effectiveness of Osilodrostat In Patients With Pituitary and Non-Pituitary Cushing's Syndrome: 2-Year Interim Data From LINC 6
- Primary objective: long-term safety and tolerability of osilodrostat with a focus on hypocortisolism, adrenal hormone precursor accumulation, arrhythmia/QT prolongation, and pituitary tumor enlargement-related adverse events.
- Effectiveness endpoints: change in mean urinary free cortisol (mUFC) and late-night salivary cortisol (LNSC).
- 205 patients, 75.6% female, age 53.0 ± 14.4 years.
  - 161 pts had CD, and 44 had non-PCS.
  - Osilodrostat exposure: 8.3 months (0.0-20.8) and 5.0 mg/day (0.5-80.0).

Bancos I, et al. *J Endocr Soc*. 2025.

# Osilodrostat Safety- LINC 6 study

- About 20% of patients reported treatment-related AEs
  - Most were mild or moderate. The most common AEs were adrenal insufficiency, diarrhea, dizziness, fatigue, hirsutism, joint stiffness, nausea, hypokalemia, and nervous system disorders.
  - 17 (10.6%) CD and 10 (22.7%) non-PCS pts reported 29 and 16 SAEs (7 and 4 were considered treatment related), respectively.
  - 5 (3.1%) CD and 2 (4.5%) non-PCS pts discontinued because of treatment-related AEs.
  - There were 22 adrenal hormone precursor accumulation-related AEs, and 3 arrhythmogenic potential/QT interval prolongation.
- There were 3 pituitary tumor enlargements in patients with CD.

Bancos I, et al. *J Endocr Soc*. 2025.

# Osilodrostat Efficacy- LINC 6 study

- Month 3: mUFC and LNSC were normal in 73.9% (n=34/46) and 56.3% (n=18/32) of pts.
- Month 6: mUFC and LNSC were normal in 63.0% (n=29/46) and 30.4% (n=7/23) of pts.

- Authors' Conclusion:
  - The LINC 6, 2-year interim data show that osilodrostat is effective for the management of different etiologies of CS.
  - AEs were mostly mild or moderate, with few leading to treatment discontinuation.

Bancos I, et al. *J Endocr Soc*. 2025.

# Osilodrostat Expanded Indication to Cushing Syndrome

- Interim data already supported FDA label expansion from CD to all endogenous CS.
  - In April 2025, the FDA approved an expanded indication for ISTURISA® (osilodrostat) for the treatment of endogenous hypercortisolemia in adults with Cushing syndrome.


# Reduce Cortisol in Peripheral Tissues

# 11β-HSD1 inhibitors

- 11β-HSD1 inhibitors work by blocking the enzyme that reactivates glucocorticoids in peripheral tissues (liver, muscle, adipose tissue), allowing local tissue cortisol levels to be reduced while maintaining systemic cortisol necessary for homeostasis.
  - **Clofutriben** developed by Sparrow Pharmaceuticals, is in Phase 2 development for adrenocortical hyperfunction, RESCUE Trial
  - **S-707106** An 11β-HSD1 inhibitor evaluated in a Phase I/IIa open-label Japanese trial
  - **AZD4017** by AstraZeneca, a selective 11β-HSD1 inhibitor, was evaluated in the TICSI trial

# Clofutriben for endogenous Cushing Syndrome - Phase 2 Rescue Trial

- **>60% of patients normalized urinary free cortisol (UFC)** without suppressing serum cortisol to levels indicating adrenal insufficiency risk
  - Morning serum cortisol levels remained >10 ug/dL, demonstrating no signs of adrenal insufficiency
- Metabolic and cardiovascular improvement:
  - **HbA1c decreased by 0.6%** (vs. 0.2% with placebo)
  - **Systolic blood pressure decreased by 8 mmHg** (vs. 3 mmHg with placebo)
  - **LDL cholesterol decreased by 25 mg/dL** (vs. increased by 29 mg/dL with placebo)
  - **Concomitant antidiabetic and antihypertensive medications** were reduced in 4 clofutriben-treated patients

Fleseriu M, et al. *J Endocr Soc.* 2025.


# Pituitary-Directed Agents

# Mechanism of Action

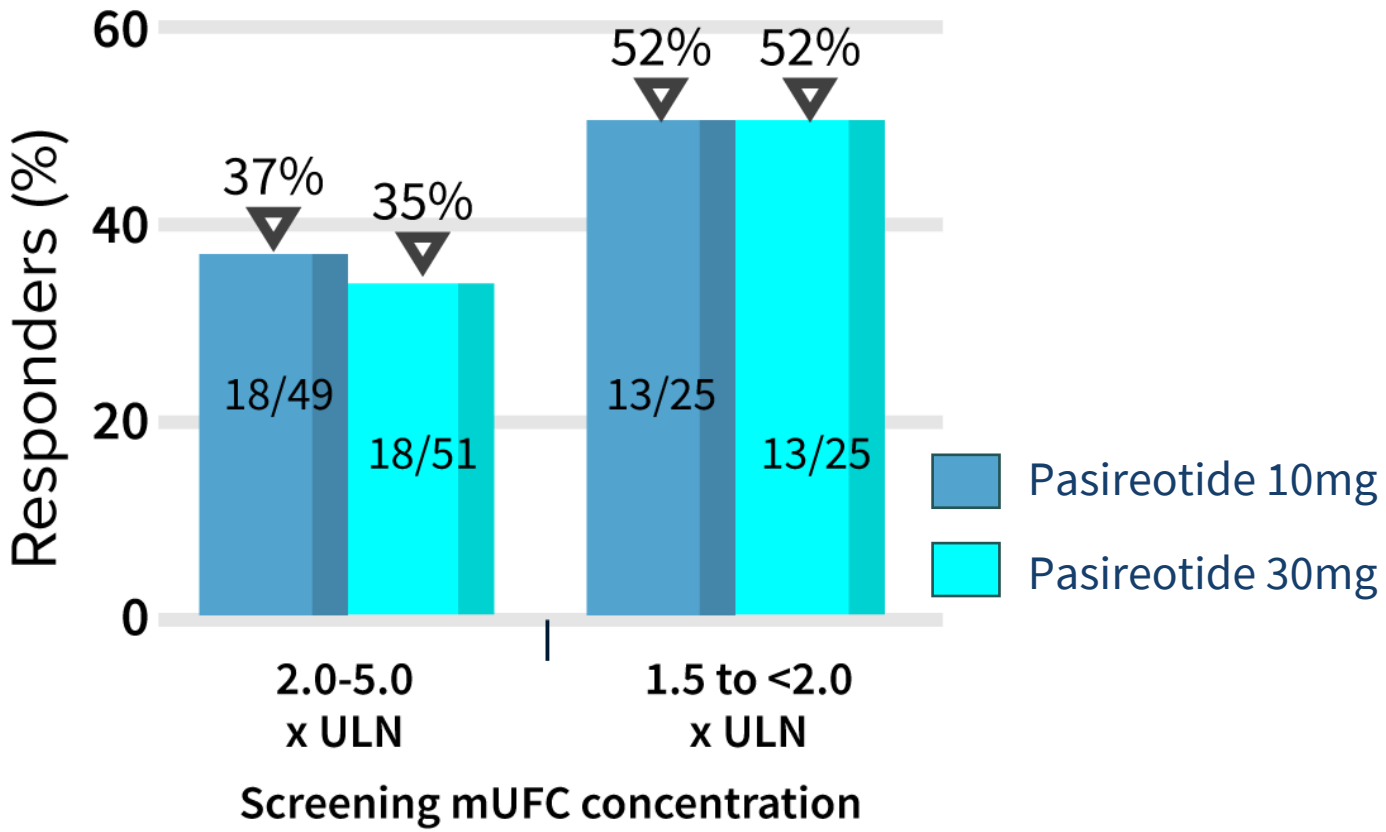
- Pituitary-Directed Agents work by blocking release of ACTH, therefore ONLY work for Cushing's Disease (pituitary cause), not ectopic Cushing or adrenal Cushing's Syndrome
- Pasireotide is a somatostatin analog, which binds to the somatostatin receptor to block the release of ACTH from corticotrophs
- Cabergoline is a dopamine receptor agonist that is used off-label

Pivonello R, et al. *Front Endocrinol (Lausanne)*. 2020.

# Pasireotide LAR

## Phase 3 study in Cushing Disease

Primary endpoint: Proportion of patients with an mUFC concentration ≤ULN at month 7 (N=150)




Lacroix A, et al. *Lancet Diabetes Endocrinol*. 2018.

# Pasireotide LAR Safety Profile

Phase 3 study in Cushing Disease

- The most common AEs were:
  - Hyperglycaemia (49% in the 10 mg group and 47% in the 30 mg group)
  - Diarrhea (35% and 43%)
  - Cholelithiasis (20% and 45%)
  - Diabetes mellitus (19% and 24%)
  - Nausea (20% and 21%)

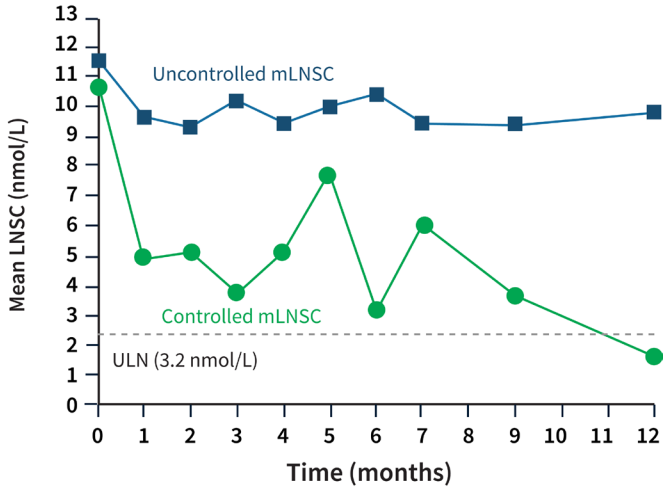
Lacroix A, et al. *Lancet Diabetes Endocrinol*. 2018.

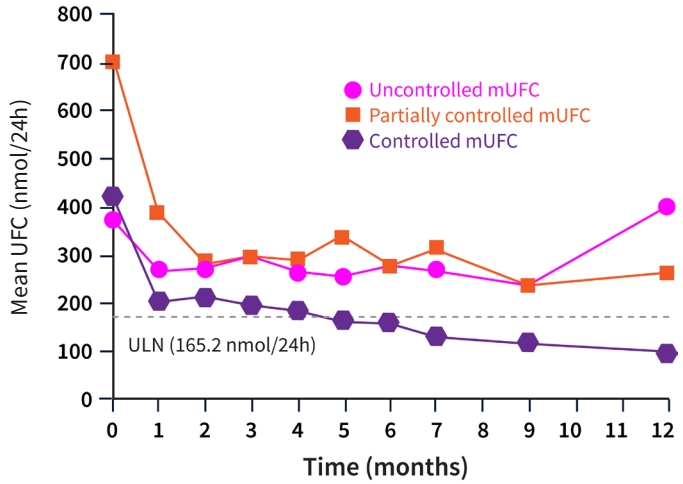
# Pasireotide LAR

Phase 3 study in Cushing Disease: Clinical Improvement

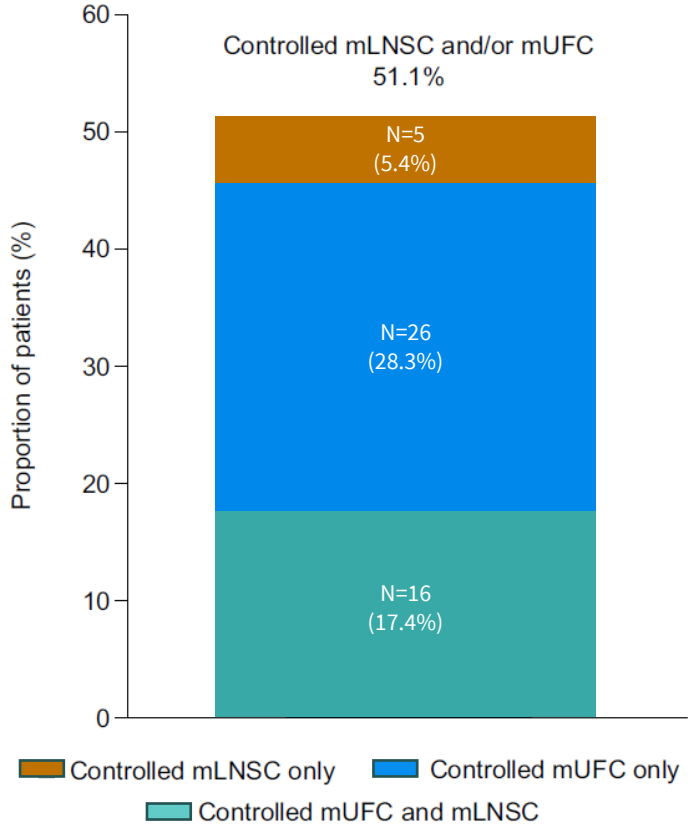
- Exploratory analysis evaluating LNSC of long-acting pasireotide in Cushing's disease (N=137)

**mLNSC and mUFC levels at baseline and during LAR pasireotide treatment according to mLNSC and mUFC response status respectively at month 12**



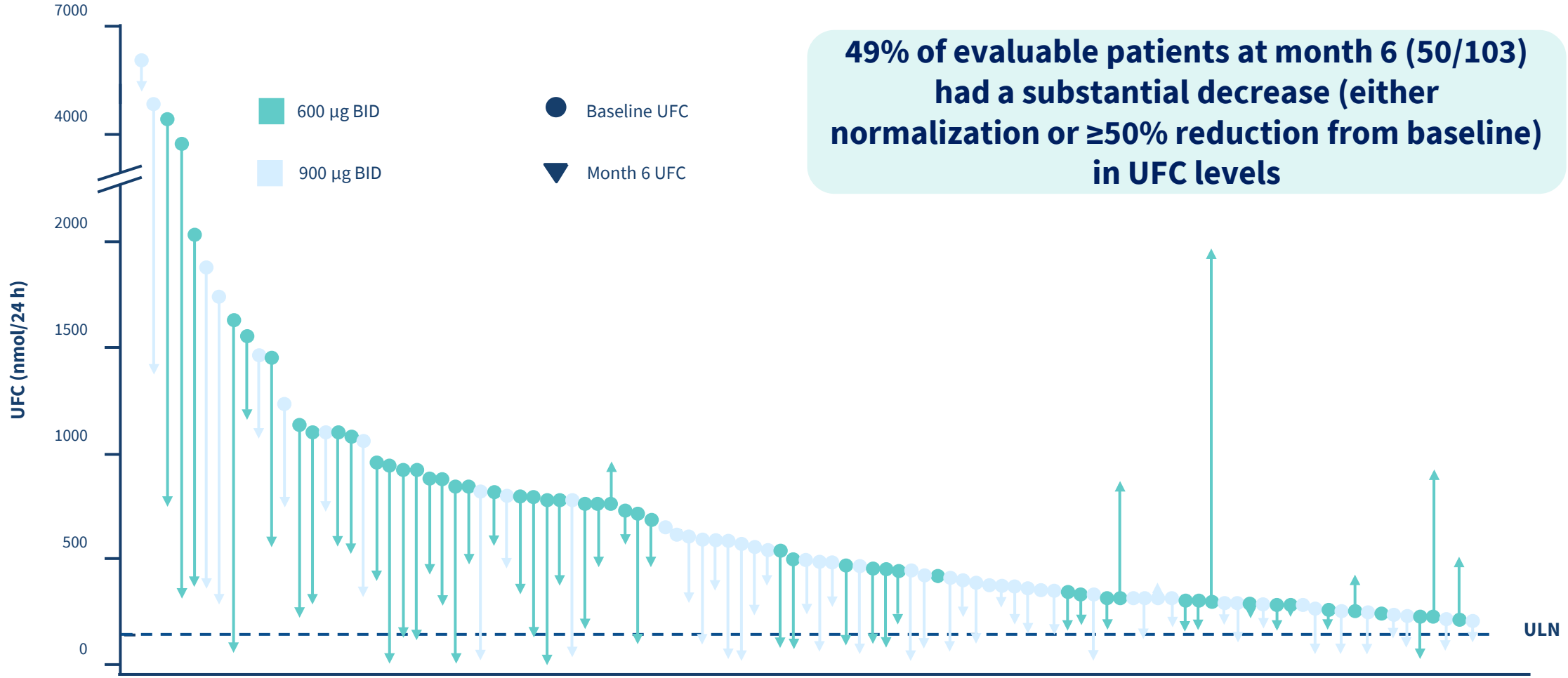

**Proportion of patients with controlled mLNSC and/or mUFC at month 12**




Newell-Price J, et al. *Eur J Endocrinol*. 2020.

# Pasireotide Efficacy in Reducing UFC Levels

**49% of evaluable patients at month 6 (50/103) had a substantial decrease (either normalization or ≥50% reduction from baseline) in UFC levels**




Single patients mUFC variation during pasireotide treatment

UFC, urinary free cortisol; ULN, upper limit of normal.

Colao A, et al. *N Engl J Med.* 2012.

# Safety Profile: Most Common AEs at 12 Months

| | Overall (N=162) | |
|---|---|---|
| **AE** | All grades n (%) | Grades 3 or 4 n (%) |
| Hyperglycaemia related | 118 (72.8) | 40 (24.7) |
| Diarrhoea related | 95 (58.6) | 5 (3.1) |
| Nausea related | 85 (52.5) | 4 (2.5) |
| Gallbladder and biliary related | 54 (33.3) | 4 (2.5) |
| Liver chemistry related | 26 (16.0) | 7 (4.3) |
| Bradycardia related | 23 (14.2) | 3 (1.9) |
| Hypocortisolism related | 13 (8.0) | 4 (2.5) |
| QT prolongation related | 13 (8.0) | 4 (2.5) |
| Hypothyroidism related | 7 (4.3) | 0 |

Grading (1–4) of AEs follows the US HHS Common Terminology Criteria for Adverse Events (CTCAE) 2009. Common AE terms were pooled.

Colao A, et al. *N Engl J Med.* 2012.

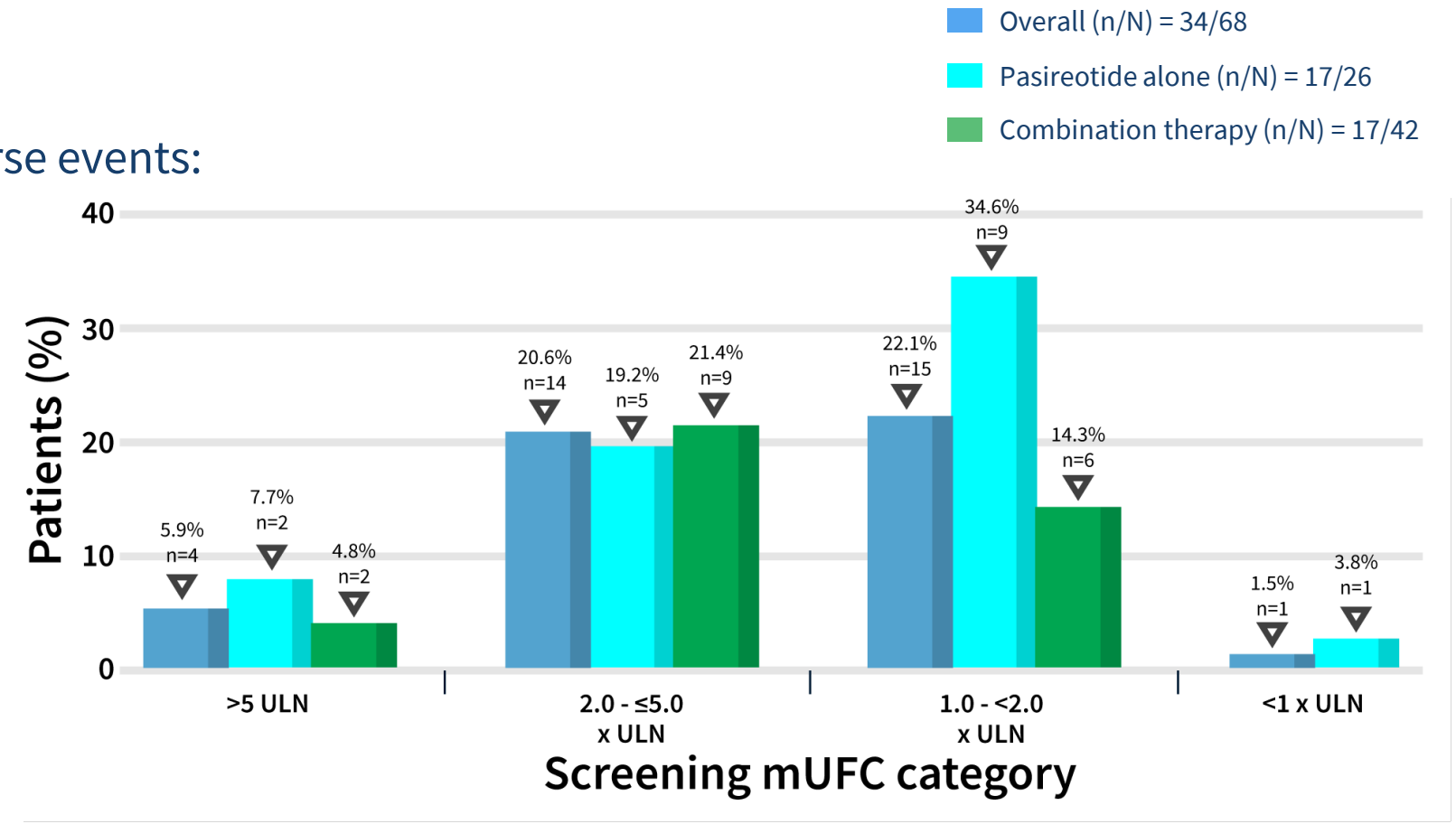
**6% of patients discontinued due to hyperglycaemia-related AEs**

# Combination Pasireotide LAR and Cabergoline

Primary endpoint: Proportion of patients with a mUFC level not exceeding the ULN at week 35 (N=68)

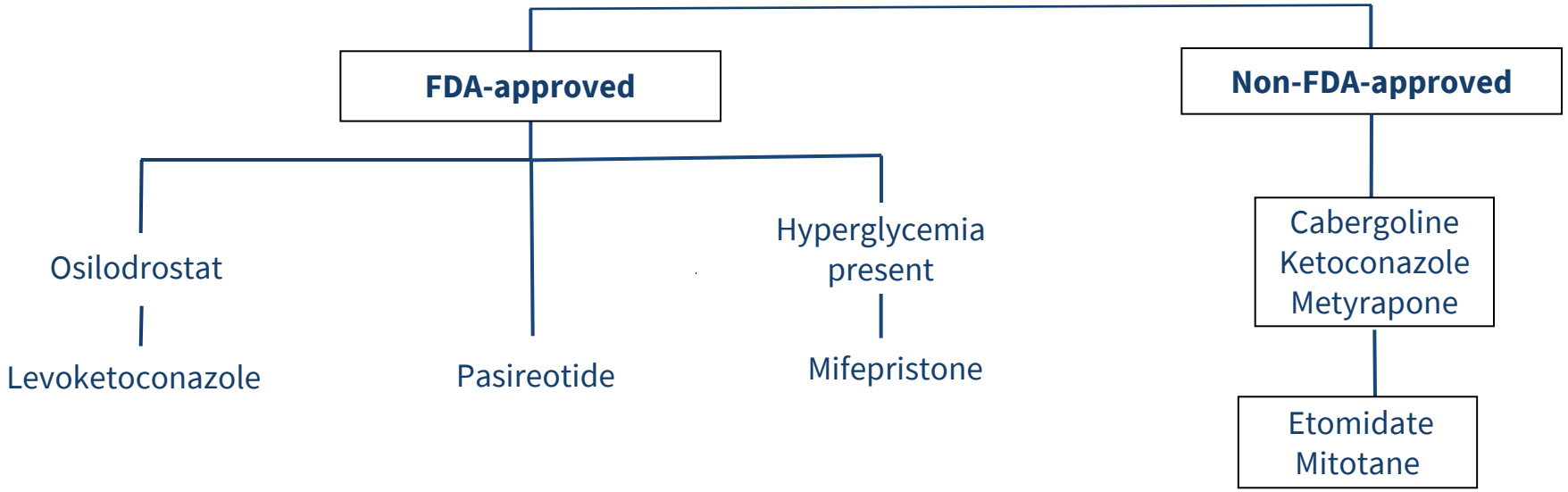
Safety: most common adverse events:

- Hyperglycemia (51.5%)
- Nausea (51.5%)
- Diarrhea (44.1%)
- Cholelithiasis (33.8%)




Feelders RA, et al. *Front Endocrinol (Lausanne).* 2023.

# Medical Management of Cushing Syndrome




## Special circumstances

- Etomidate for parenteral usage in severe hypercortisolism
- Metyrapone and cabergoline during pregnancy
- Pasireotide in patients with large tumors
- Combination therapies in patients with severe hypercortisolism
- Cabergoline or ketoconazole may be considered as first-line drug therapy when the cost is an issue
- Temozolomide in patients with aggressive or metastatic disease


# Medical Management Monitoring

# Monitoring Medical Therapy for Cushing Syndrome: Expert Recommendations

## 1 Monitor biochemical response

- Not applicable to mifepristone
- Serial urinary free cortisol and late-night salivary cortisol
- Morning serum cortisol as needed to assess adrenal insufficiency

## 2 Monitor clinical response

- Weight, blood pressure, skin condition, muscle strength, glycaemic control

## 3 Monitor for adverse effect or intolerance

- Metabolic parameters prior to any new drug therapy
- Liver enzymes with ketoconazole, levoketokonazole, mitotane and pasireotide
- Electrocardiogram (QT interval) prior to ketoconazole, levoketokonazole, osilodrostat, metyrapone, mitotane, mifepristone and pasireotide

## 4 Close monitoring

- Hypertension and oedema with osilodrostat, metyrapone and mifepristone
- Acne and hirsutism with metyrapone and osilodrostat
- Male hypogonadism with ketoconazole and levoketoconazole
- Hyperglycaemia with pasireotide
- Impulse control disorders with cabergoline

## 5 Monitor for corticotroph tumour mass progression

- Adrenocorticotrophic hormone levels and MRI every 6-12 months with adrenal steroidogenesis inhibitors and mifepristone
- MRI as needed with pituitary-targeted therapy based on initial tumour mass size

## 6 Periodic assessments during treatment

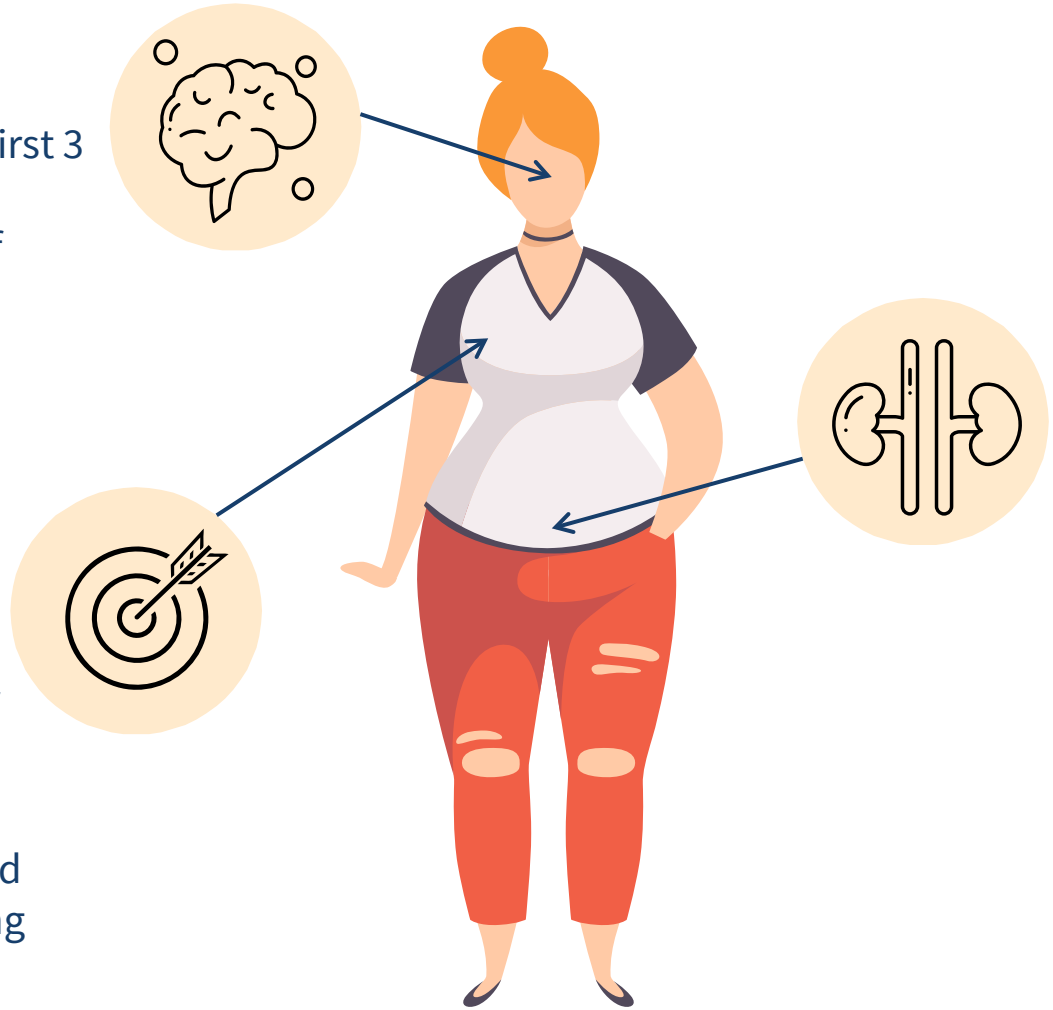
- Potassium & magnesium with ketoconazole, levoketokonazole, osilodrostat, metyrapone, mifepristone & pasireotide
- Liver enzymes w/ ketoconazole, levoketokonazole, metyrapone & pasireotide
- Electrocardiogram w/ ketoconazole, levoketokonazole, metyrapone, mifepristone & pasireotide
- Consider adrenal insufficiency or glucocorticoid withdrawal with all meds. If adrenal insufficiency is present: dexamethasone (2-4mg) w/ mifepristone, hydrocortisone for all other therapies

Fleseriu M, et al. *Nat Rev Endocrinol*. 2023.

# Safety Comparison of Classes

**Pituitary-Directed Agents**

- Hyperglycemia common in first 3 months
- Works for pituitary causes of Cushing Disease ONLY



**Glucocorticoid Receptor Blocker/Modulator**

- Need to titrate dose slowly to prevent glucocorticoid withdrawal syndrome
- Can have increases in blood pressure- consider initiating with spironolactone

**Adrenal-Directed Agents: Steroidogenesis Inhibitors**

- Overtreating causes adrenal insufficiency, hypotension, and hypoglycemia
- Monitor carefully for QT prolongation
- Accumulation of adrenal hormone precursors