Going Beyond Surgery

The Latest Updates in Identification and Medical Management of Cushing Syndrome

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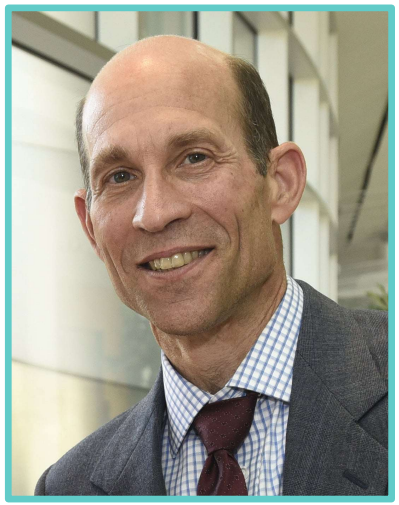
Faculty Information

Iacopo Chiodini, MD
Associate Professor of Endocrinology
University of Milan
Director of the Endocrine Unit
Niguarda Hospital
Milan, Italy

Faculty Information



Richard J. Auchus, MD, PhD, FACE
The James A. Shayman and Andrea S. Kevrick
Professor of Translational Medicine
Division of Metabolism, Endocrinology and Diabetes
Departments of Internal Medicine and Pharmacology
University of Michigan Medical School
Ann Arbor, MI

Disclosures

Faculty Disclosures

- Iacopo Chiodini, MD (Faculty):
  - Advisory Board/Consultant: Corcept Therapeutics; Esteve-HRA; Board Member: Scientific Committee of The Italian Society for Osteoporosis and Metabolic Bone Diseases
- Richard J. Auchus, MD, PhD, FACE (Faculty):
  - Advisory Board/Consultant: Quest Diagnostics, Corcept Therapeutics, Xeris Pharmaceuticals, Crinetics Pharmaceuticals, Novo Nordisk, Neurocrine Biosciences & Neurocrine UK, LTD, Recordati Rare Diseases, H Lundbeck A/S, Sparrow Pharmaceuticals, Astellas Pharmaceuticals, Acerand Therapeutics, OMass Therapeutics, Blue Earth Diagnostics, LTD, Spruce Biosciences, Aspect Biosystems, Merck Sharp & Dohme, LLC, Vertex Pharmaceuticals; Grant/Research Support: Neurocrine Biosciences, Neurocrine UK, LTD, Spruce Biosciences, Corcept Therapeutics, Crinetics Pharmaceuticals, Recordati Rare Diseases, Adrenas Therapeutics, Mineralys Pharmaceuticals, H Lundbeck A/S

Planner/Reviewer Disclosures

- Amy Burmesch, PA-C (Reviewer): Speaker's Bureau: Corcept Therapeutics
- Skand Shekhar, MD, MHSc (Reviewer) has no relevant relationships to disclose.
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Learning Objectives

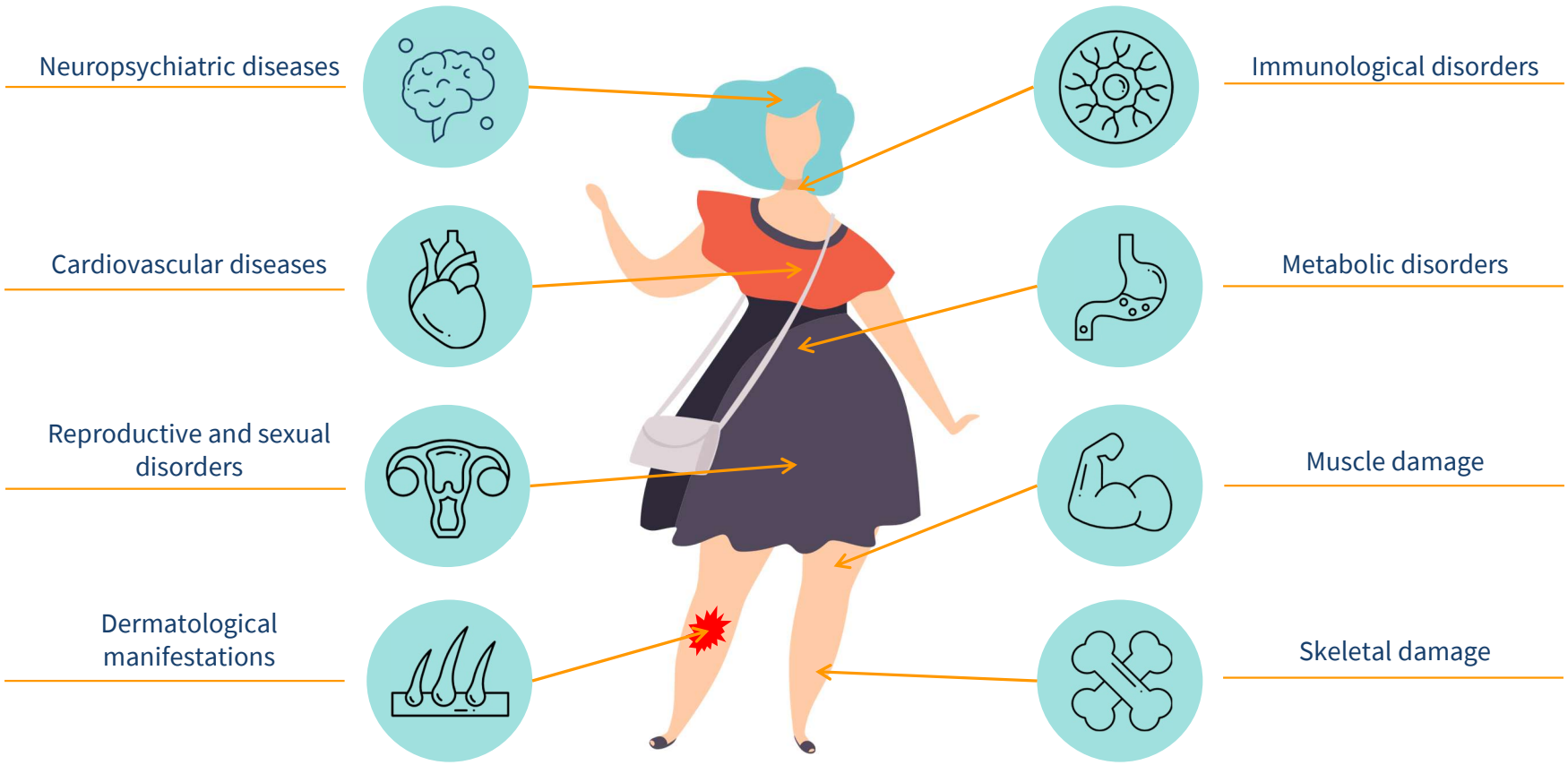
- Evaluate patients to determine if screening for Cushing Syndrome is indicated
- Appraise the roles of surgical vs medical management for the treatment of various forms of Cushing Syndrome.
- Compare medical management options for Cushing Syndrome including mechanism of action, contraindications/safety, and efficacy in treatment.

To claim your credit for this activity, please be sure to complete the posttest and evaluation at the conclusion of the presentation.

Going Beyond Surgery

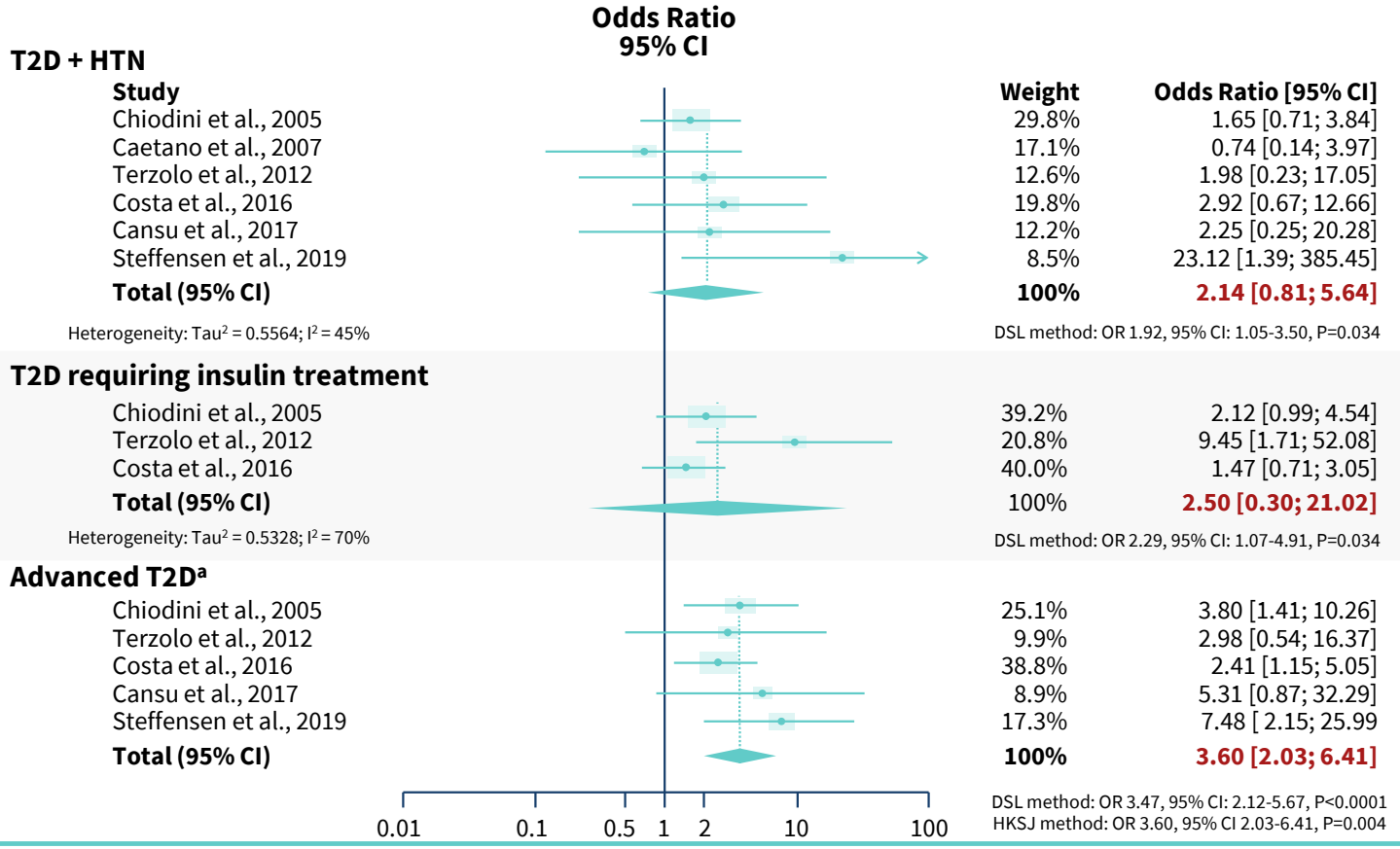
The Latest Updates in Identification and Medical Management of Cushing Syndrome

Hypercortisolism and Comorbidities



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

Patients with Advanced T2D have a High Prevalence of Hypercortisolism

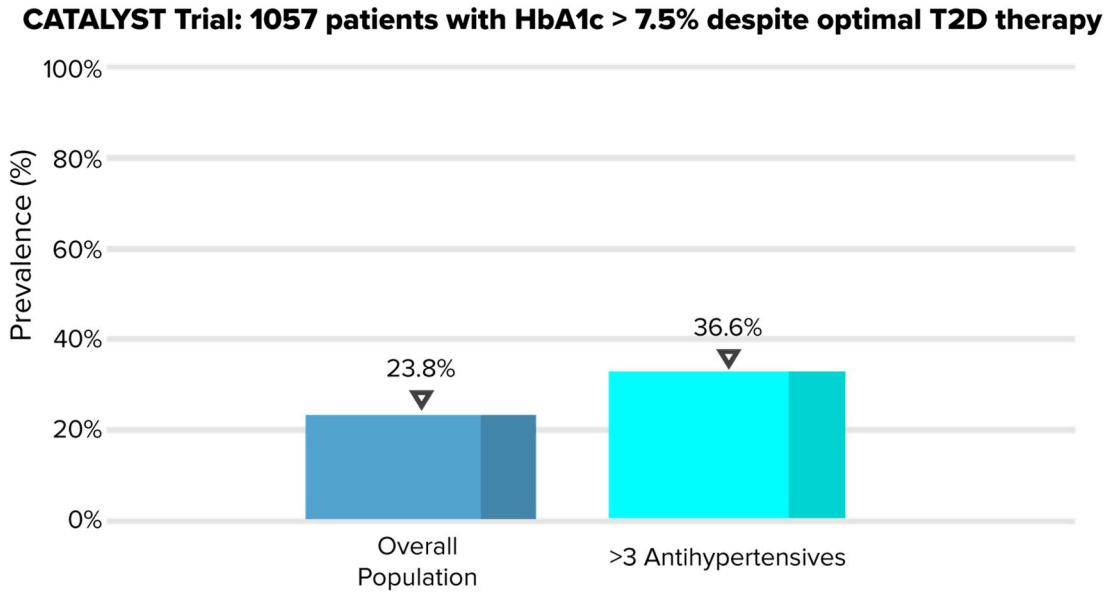


DSL=DerSimonian and Laird method; HKSJ=Hartung-Knapp-Sidik-Jonkman method.

[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.

Updated Prevalence of Hypercortisolism in T2D

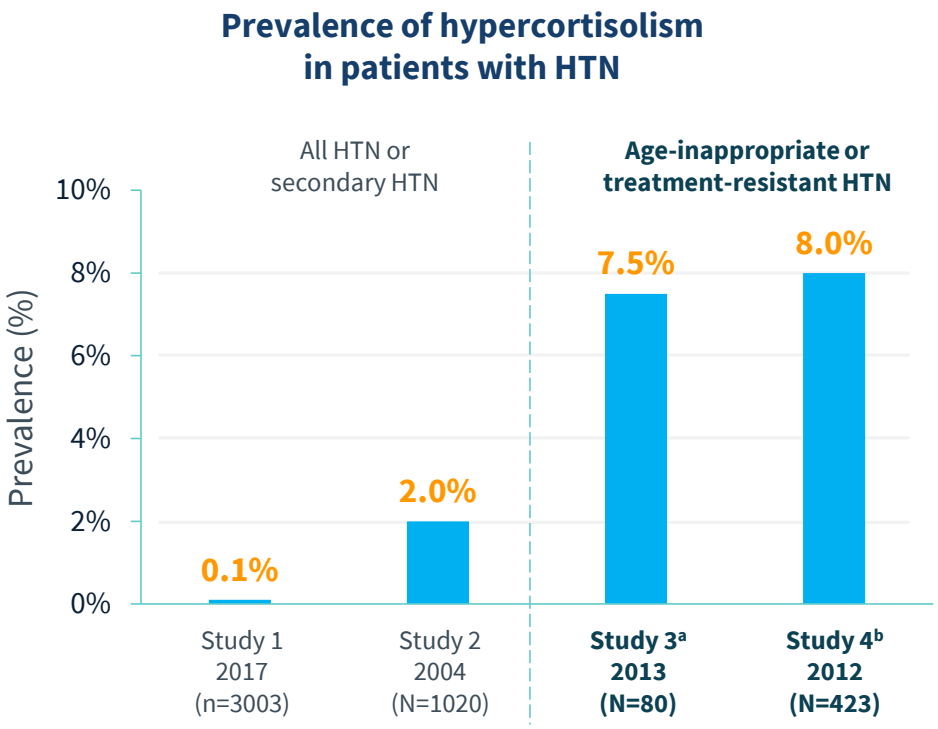


Results:

- 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.

Hypercortisolism in Patients with Hypertension



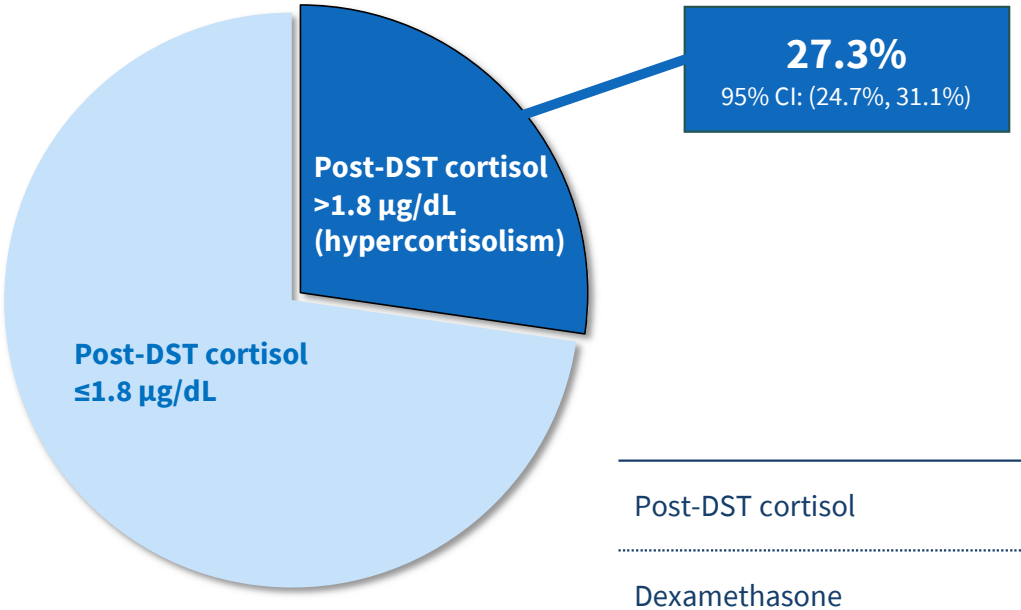
Hypertensive patients with the following characteristics should be screened for CS:

- Age <40 y
- Acute worsening of HTN
- Resistant hypertension
- Nondipping BP profile
- Extensive HTN-mediated organ damage

BP=blood pressure. [a]Patients <40 years of age suspected of endocrine hypertension. [b]Patients with treatment-resistant hypertension (clinic BP ≥140/90 mm Hg and using ≥3 antihypertensive drugs in full dosages, always including a diuretic).

Wang L, et al. *Biomed Res Int*. 2017; Omura M, et al. *Hypertens Res*. 2004; Trifanescu R, et al. *Maedica (Bucur)*. 2013; Martins LC, et al. *J Hypertens*. 2012; Fallo F, et al. *J Hypertens*. 2022.

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 D, et al. *ACC*. 2026.

Few differences in baseline characteristics[1]

	Post-DST cortisol		
	≤1.8 µg/dL (n=789)	>1.8 µg/dL (hypercortisolism) (n=297)	*P*-value
Age, years, mean (SD)	65.0 (10.9)	66.2 (10.2)	NS
Female, %	53.9%	43.8%	0.003
Body mass index, kg/m^2, mean (SD)	33.5 (7.1)	32.0 (6.9)	0.002
Waist circumference, cm, mean (SD)	109.3 (17.0)	106.9 (18.0)	0.048
Race, %			
White	57.0%	57.2%	NS
Black or African American	36.4%	36.7%	
Asian	2.9%	4.0%	
Other	3.7%	2.0%	
Ethnicity, %			
Hispanic/Latino	26.6%	25.3%	NS
Non-Hispanic/Latino	73.4%	74.7%	
SBP, mmHg, mean (SD)	140.2 (17.5)	141.3 (18.3)	NS
DBP, mmHg, mean (SD)	83.9 (12.3)	84.4 (13.1)	NS
HbA1c, %, mean (SD)	6.4 (1.4)	6.6 (1.6)	NS

Patients with hypercortisolism "look no different" than those without, except for *lower* body mass index and waist circumference

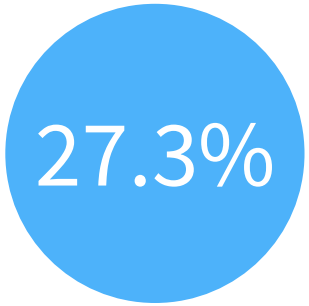
Limitations:

- **US only, few Asians – but similar results in Brazil (26.5%)[2]**
- **Does not prove causality**
- **No follow-up**

DBP, diastolic blood pressure; DST, dexamethasone suppression test; HbA1c, hemoglobin A1c; NS, not significant (*P*>0.05); SBP, systolic blood pressure; SD, standard deviation.

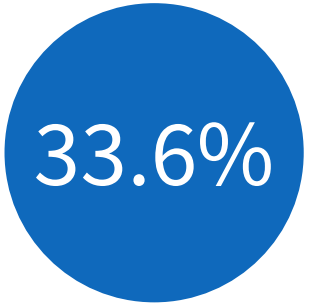
[1]Bhatt D, et al. *ACC*. 2026; [2]Martins LC, et al. *J Hypertens*. 2012.

Cardiac Disorders in Patients with Hypercortisolism in MOMENTUM



Hypercortisolism in Patients with Resistant Hypertension

Atrial Fibrillation

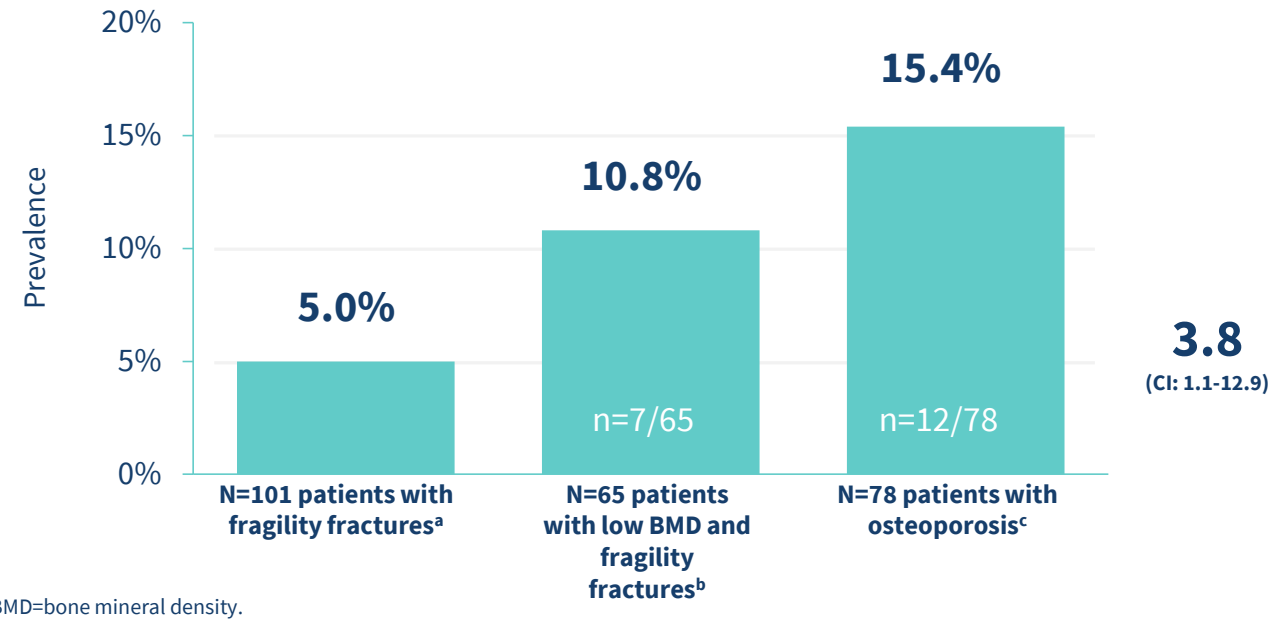


Coronary Artery Disease

Heart Failure with or without reduced ejection fraction

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

Hypercortisolism in Patients with Osteoporosis and/or Fragility Fractures



3.8
(CI: 1.1-12.9)

In a prospective study, screening prompted by osteoporosis increased the probability for CS.

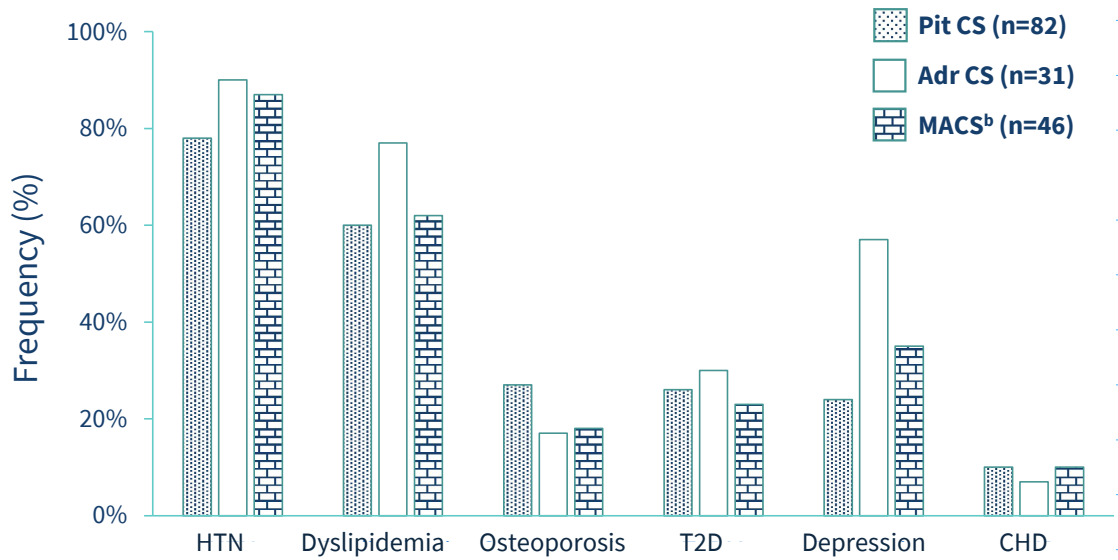
BMD=bone mineral density.

[a]Patients presenting with cause of secondary osteoporosis apart from diabetes mellitus were excluded. [b]Patients with any known secondary cause of osteoporosis or with signs/symptoms of cortisol excess were excluded. [c]Patients treated with glucocorticoids during the last 2 years, with oral contraceptives during the last 12 months, or with anabolic agents, calcitonin, bisphosphonates, or fluoride were excluded from the study. Medication with gonadal steroid hormone replacement therapy was not defined as an exclusion criterion.

Pugliese F, et al. *Endocrine*. 2021; Chiodini I, et al. *Ann Intern Med*. 2007; Kann P, et al. *Clin Rheumatol*. 2001; Braun LT, et al. *J Clin Endocrinol Metab*. 2022.

Patients with MACS have a Similar Prevalence of Comorbidities as Patients with Clinically Overt Hypercortisolism

Frequency of comorbidities

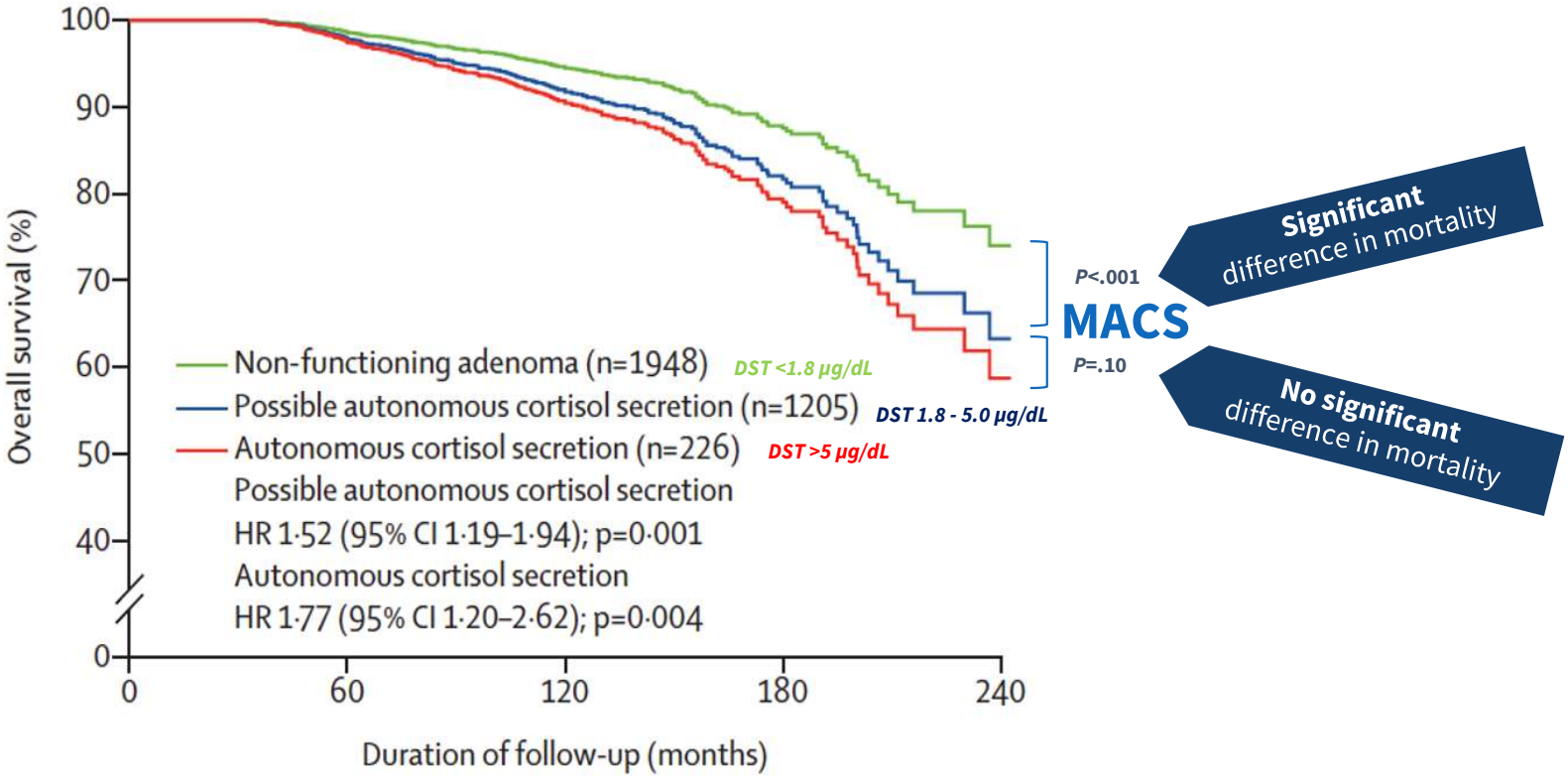


Frequency of clinical signs in patients with CS

Clinical sign	Pit CS (n=82)	Adr CS (n=31)	MACS (n=46)
Weight gain[c]	85%	94%	50%
Facial fullness	80%	75%	15%
Plethora	72%	50%	23%
Dorsocervical fat pad	64%	52%	24%
Hematoma	51%	52%	15%
Hirsutism	46%	31%	2%
Myopathy	40%	39%	23%
Hair loss	38%	19%	13%
Thin skin	35%	19%	19%
Edema	35%	23%	23%
Acne	23%	22%	6%
Striae	22%	19%	0%

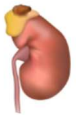
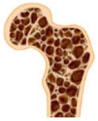
MACS = any weight gain in the past year.
Braun LT, et al. *Eur J Endocrinol*. 2024.

Mortality in MACS



Deutschbein T, et al. *Lancet Diabetes Endocrinol*. 2022.

Hypercortisolism Prevalence in Selected Populations

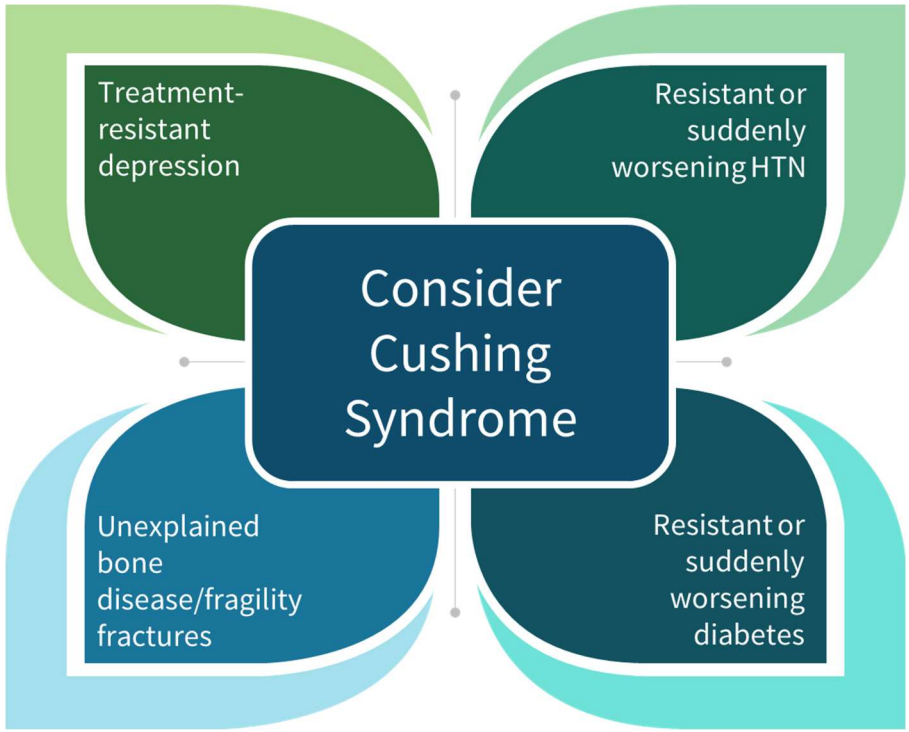
Select Population	Prevalence of Hypercortisolism[a]
 Adrenal incidentaloma[1]	19% to 42.5%
 Bone fragility[2]	1.9% to 17.6%
 Hypertension[3-5]	Up to 8%
 Diabetes mellitus[6]	3.4%
 Obesity[7]	**0.9%** (pooled from 22 studies)

[a]Includes a range of disease severity and etiology.

Paschou SA, et al. *Endocrine*. 2016; Chiodini I, et al. *Eur J Endocrinol*. 2016; Anderson GH Jr, et al. *J Hypertens*. 1994; Omura M, et al. *Hypertens Res*. 2004; Martins LC, et al. *J Hypertens*. 2012;. Steffensen C, et al. *Eur J Endocrinol*. 2016; van Hulsteijn LT, et al. *Eur J Endocrinol*. 2020; Steffensen C, et al. *Horm Metab Res*. 2019.

The Toughest to Recognize: Non-Specific Cushing Syndrome Presentations

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



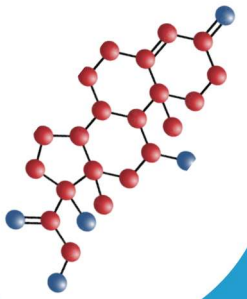
In milder forms of hypercortisolism, metabolic problems dominate over physical findings

Only cortisol-directed therapy can treat all manifestations

Aresta C, et al. *Endocr Pract*. 2021; Neiman LK, et al. *J Clin Endocrinol Metab*. 2008; Giovanelli L, et al. *J Endocrinol Invest*. 2021; Samson S, et al. *Endocr Pract*. 2026.

Treatment Options for Cushing Syndrome

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.

Surgical Management Overview for Cushing Syndrome/Disease

- Surgery is first-line treatment for all forms of Cushing Syndrome
  - Management of macronodular adrenal hyperplasia (bilateral) is challenging
- Surgery for Cushing Disease achieves remission in 65%-90% of cases
  - Nearly 100% biochemical cure after resection of benign adrenal adenoma
- Many patients with Cushing Disease have post-surgical recurrence
  - Studies have shown recurrence in up to 35% of patients within 5 years and up to 69% within 10 years

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

Improvement of Cardiometabolic Risk Factors after Adrenalectomy

Effect of adrenalectomy on cardiometabolic outcomes in patients with adrenal tumors and hypercortisolism (meta-analysis)

Metabolic outcome	No. of studies	Patients, n	Improved
HTN	21	265	**60.5%**
T2D	20	120	**51.5%**
Obesity	16	128	**45%**
Dyslipidemia	13	102	**24%**

This was a systematic review and meta-analysis of 26 studies, which included 25 cohort studies (16 retrospective and 9 prospective studies) and one randomized clinical trial. Studies were from Europe (n=15), Asia (n=9), and USA (n=2). In 24 studies, authors reported on various outcome improvements in patients with hypercortisolism before and after adrenalectomy.
Bancos I, et al. *Eur J Endocrinol*. 2016.

Medical Management is Indicated…

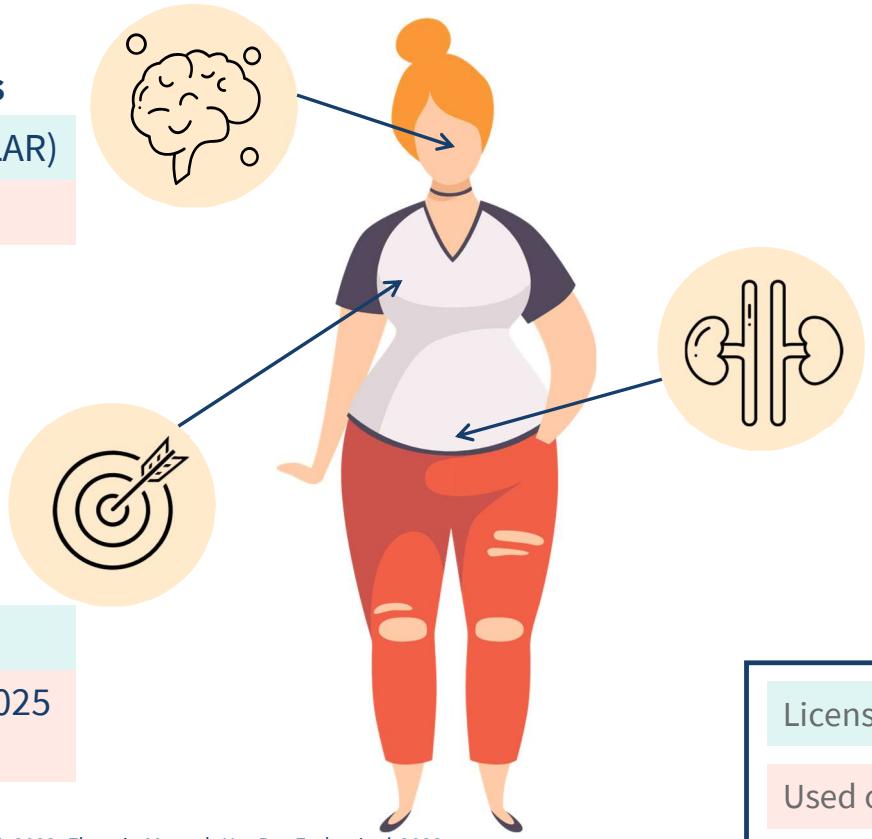
- When surgery is not an option or is refused
- When disease persists after surgery
- When disease recurs after successful surgery
- When severe symptoms mandate emergency treatment
  - Ectopic ACTH syndrome, adrenal carcinoma
- While awaiting surgery or radiation therapy

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 (CRL Dec 2025 - more to come)

Adrenal-Directed Agents: Steroidogenesis Inhibitors

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

Licensed in US for Cushing's indications

Used off-label

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

Mechanism of Action

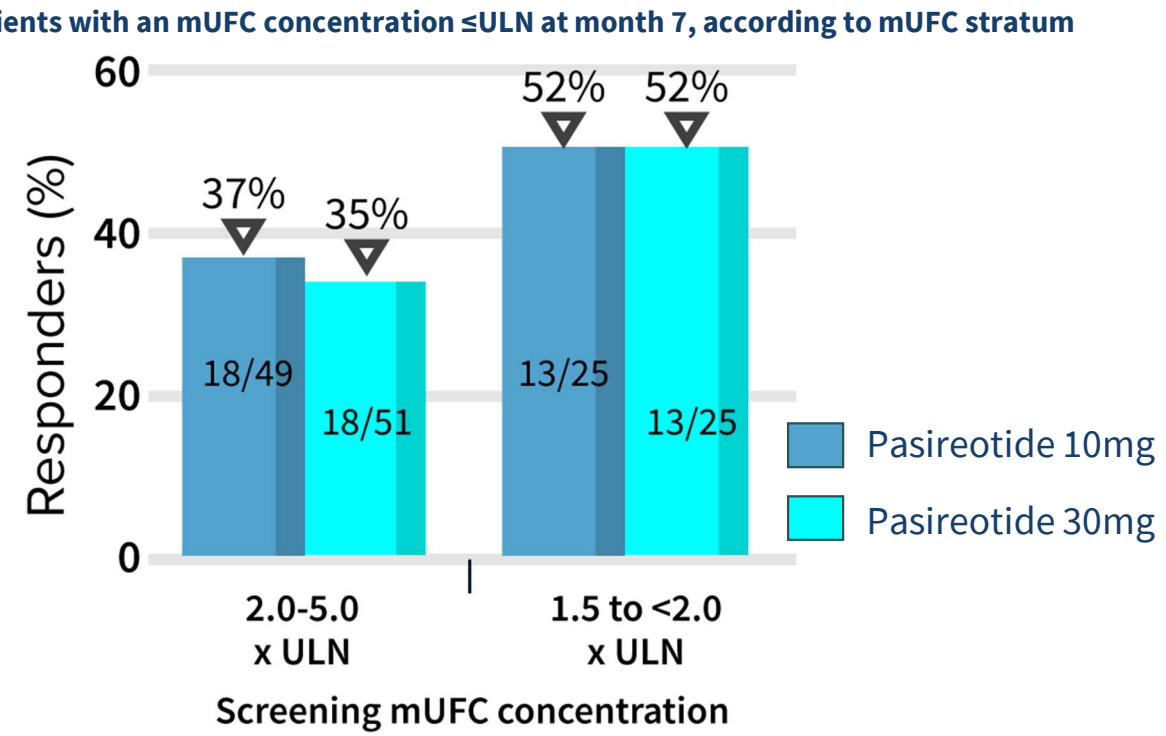
- Pituitary-Directed Agents work by blocking release of ACTH, therefore ONLY work for Cushing's Disease (pituitary cause), not ectopic Cushing or adrenal Cushing's Syndrome
- Pasireotide is a somatostatin analog, which binds to the somatostatin receptor to block the release of ACTH from corticotrophs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

Phase 3 study in Cushing Disease

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

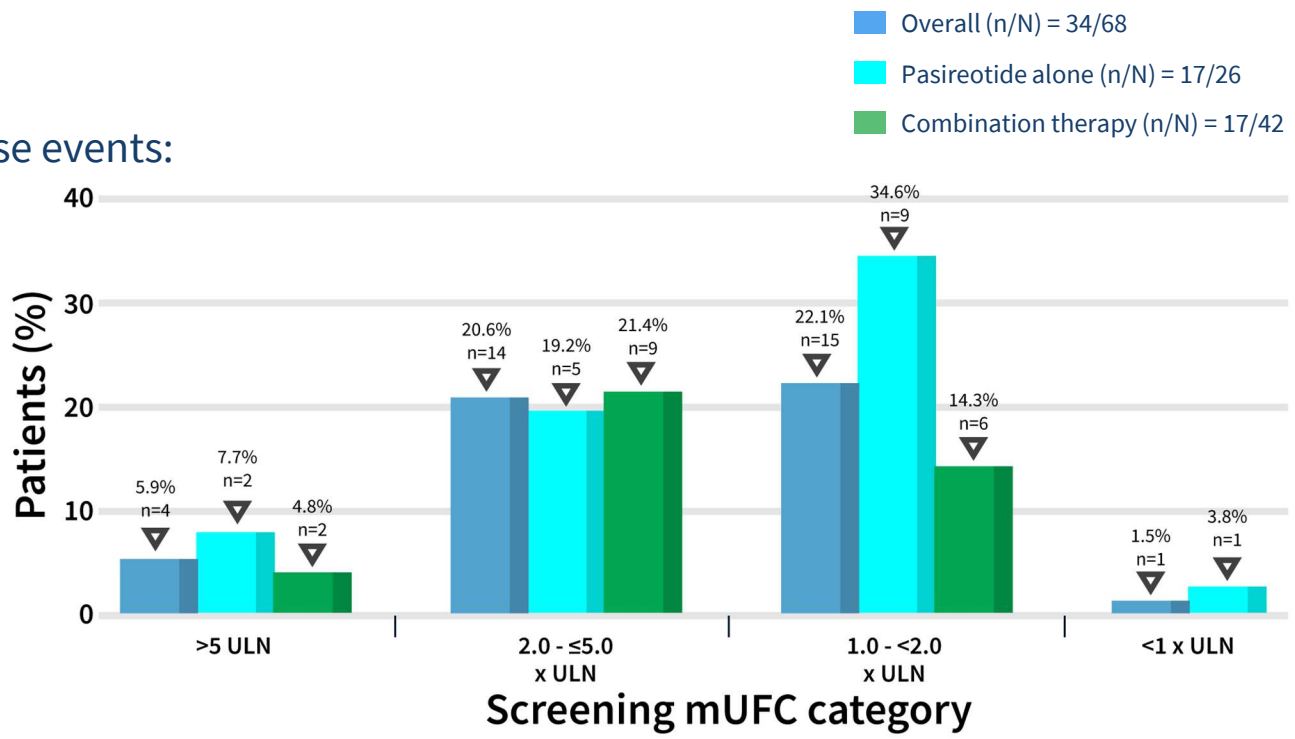
Lacroix A, et al. *Lancet Diabetes Endocrinol*. 2018.

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:

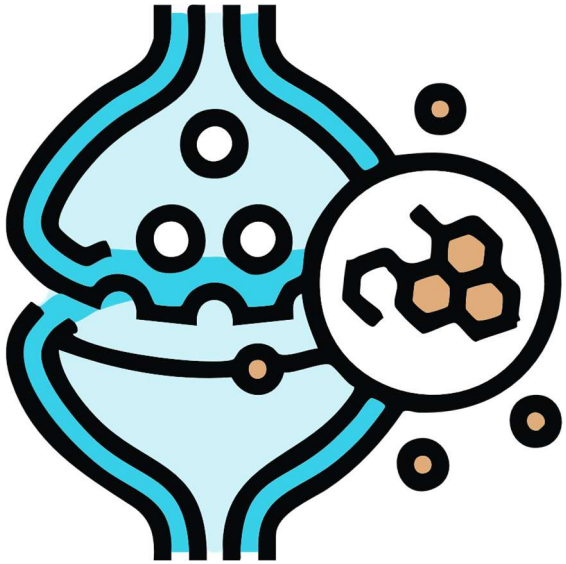
- Hyperglycemia (51.5%)
- Nausea (51.5%)
- Diarrhea (44.1%)
- Cholelithiasis (33.8%)



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

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

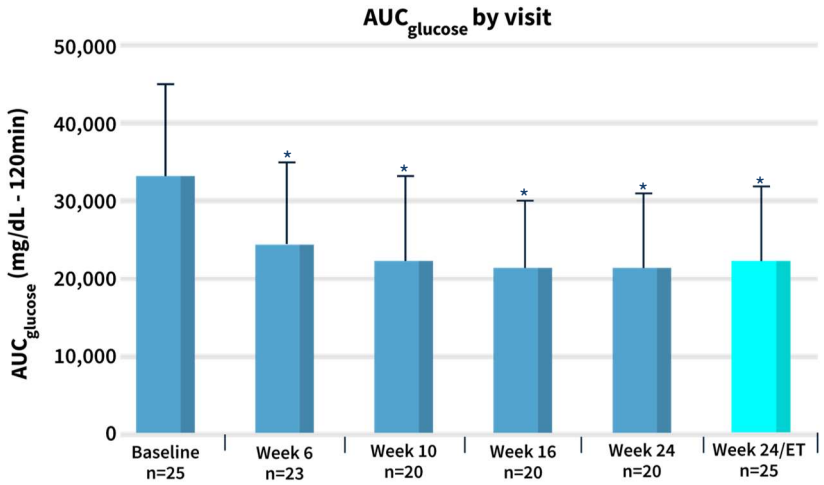


Hinojosa-Amaya JM, et al. *Drugs*. 2019; Pivonello R, et al. *Front Endocrinol*. 2021.

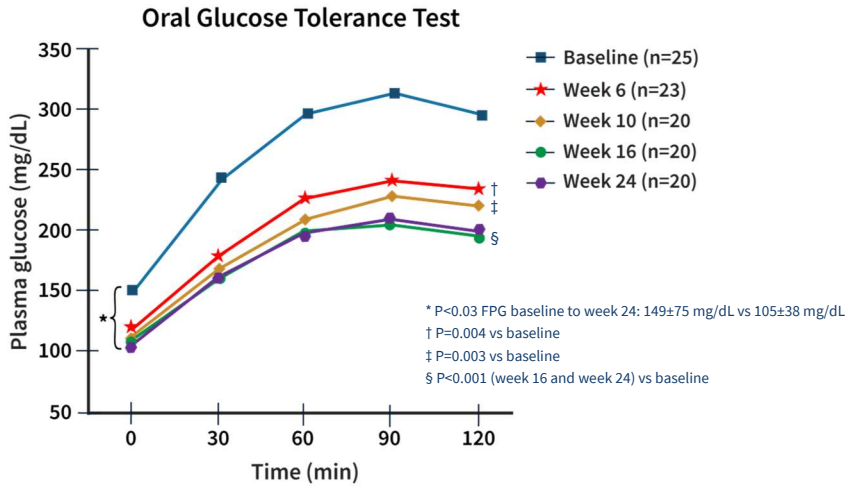
Mifepristone

- 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

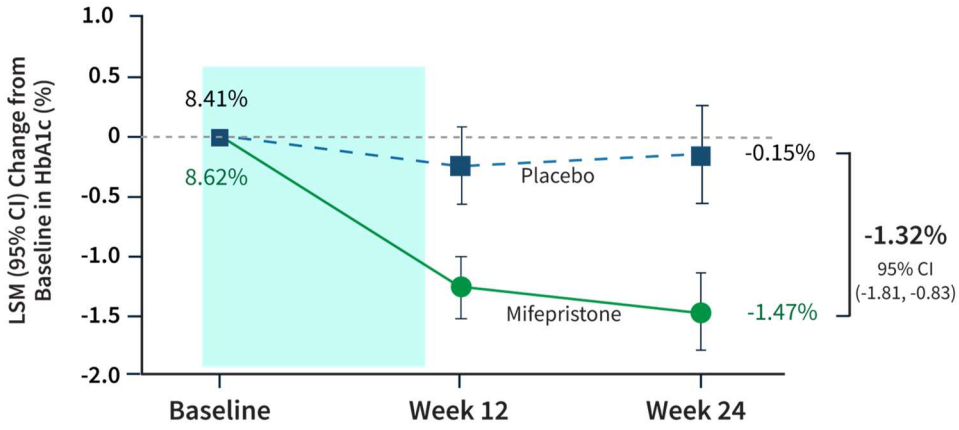
- Common AEs were:
  - Nausea (48%)
  - Fatigue (48%)
  - Headache (44%)
  - Decreased blood K^+ (34%)
  - Arthralgia (30%)
  - Vomiting (26%)
  - Peripheral edema (26%)
  - HTN (24%)
  - Dizziness (22%)
  - Decreased appetite (20%)
  - Endometrial thickening (20%)

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**

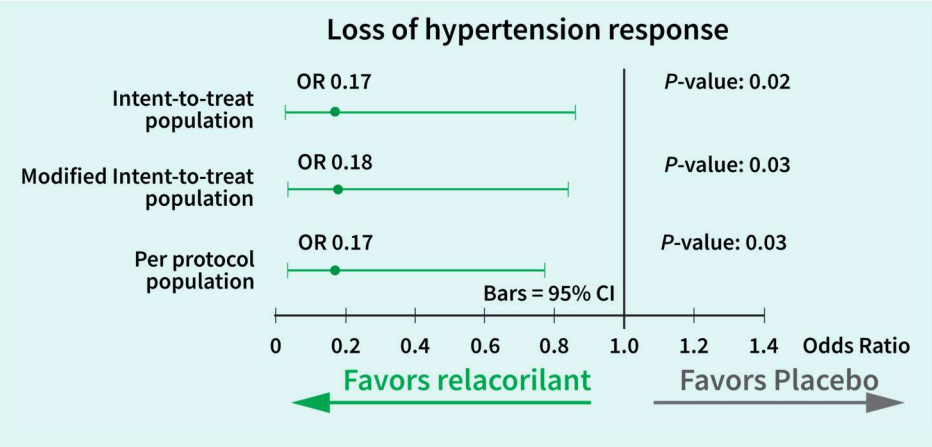
DeFronzo RA, et al. *Diabetes Care*. 2025.

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 relacorilant 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

Relacorilant does not prolong Q-T interval, unlike all other FDA-approved drugs for Cushing syndrome



Common adverse events: Nausea, peripheral edema, pain in extremity, back pain, and fatigue (≥ 20%)

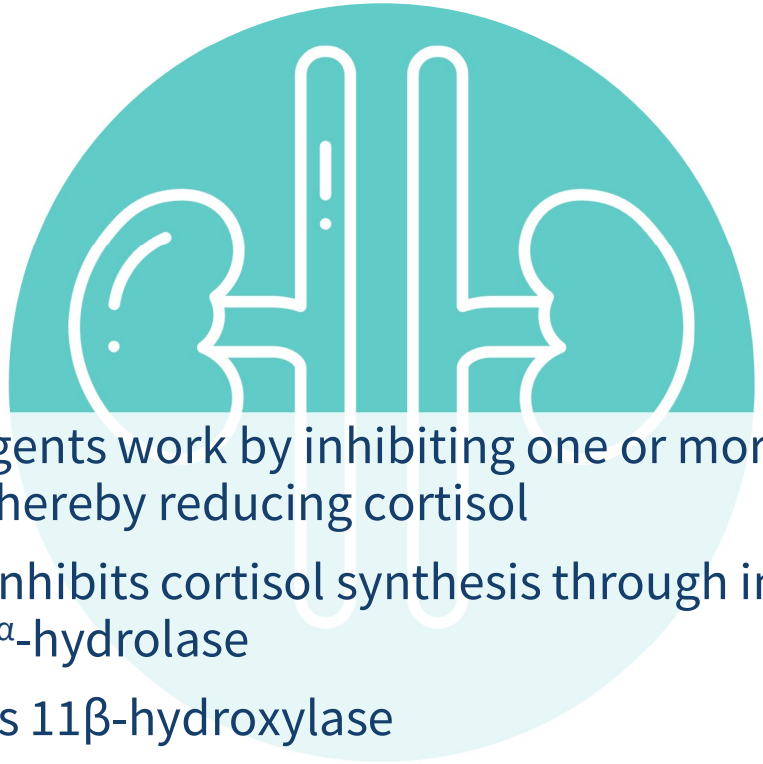
Pivonello R, et al. *J Endocr Soc*. 2024; Pivonello R, et al. *Endocrine Abstracts*. 2025; Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2026.

11β-HSD1 inhibitors

11β-HSD1 inhibitors work by blocking the enzyme that reactivates cortisol from cortisone in peripheral tissues (liver, muscle, adipose tissue), allowing local tissue cortisol levels to be reduced while maintaining systemic cortisol necessary for homeostasis.

- **Clofutriben**, is in Phase 2 development for adrenocortical hyperfunction, RESCUE Trial
  - Metabolic and cardiovascular parameters improved without cortisol deficiency
- **S-707106** An 11β-HSD1 inhibitor evaluated in a Phase I/IIa open-label Japanese trial
- **AZD4017**, a selective 11β-HSD1 inhibitor, was evaluated in the TICSI trial

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

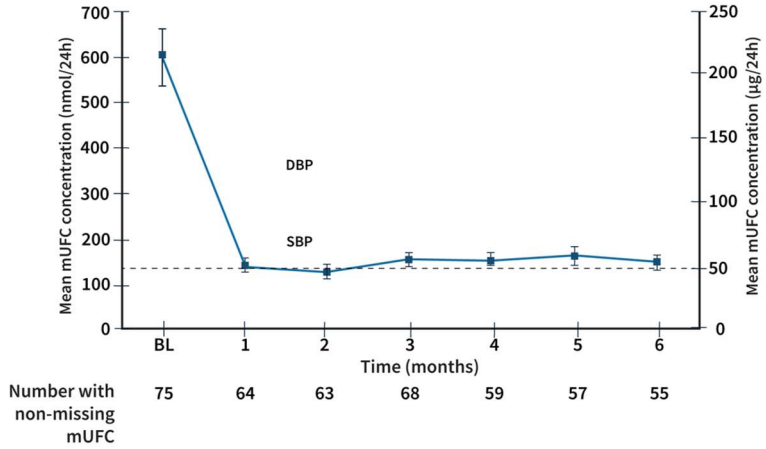
Pivonello R, et al. *Front Endocrinol (Lausanne)*. 2020; Martino M, et al. *Expert Opin Pharmacother*. 2023; Cohan P, et al. *Endocr Pract*. 2014.

Levoketoconazole

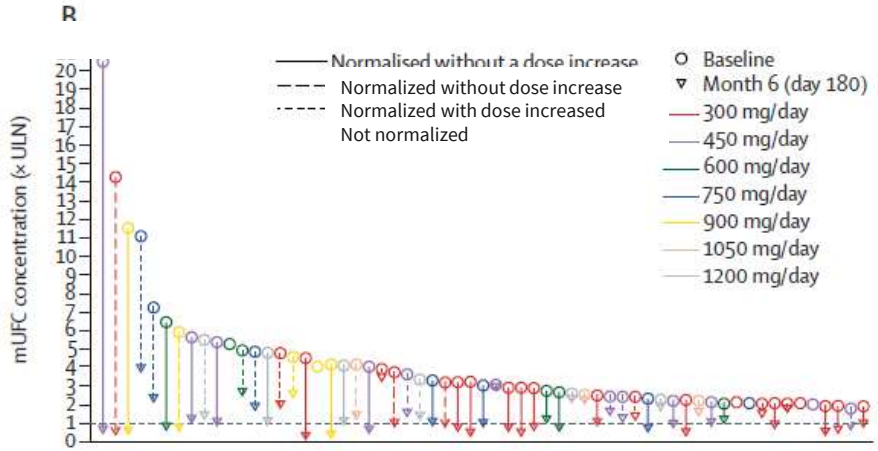
SONICS Study: Efficacy

- 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

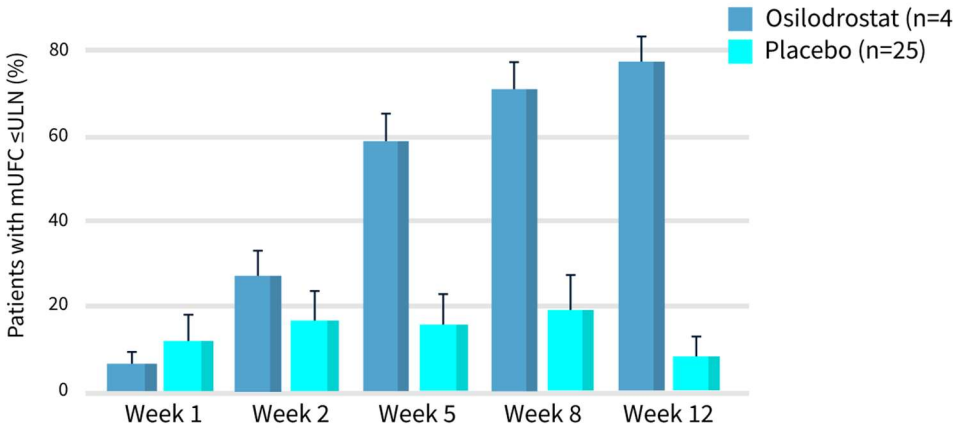
	Patients (n=94)
Any adverse event	92 (98%)
• Serious adverse event	14 (15%)
• Drug-related adverse event	40 (43%)
• Adverse event leading to discontinuation	12 (13%)
Intensity of adverse events	
• Mild	21 (22%)
• Moderate	54 (57%)
• Severe	15 (16%)
• Life threatening	1 (1%)
• Death	1 (1%)
Most common 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.

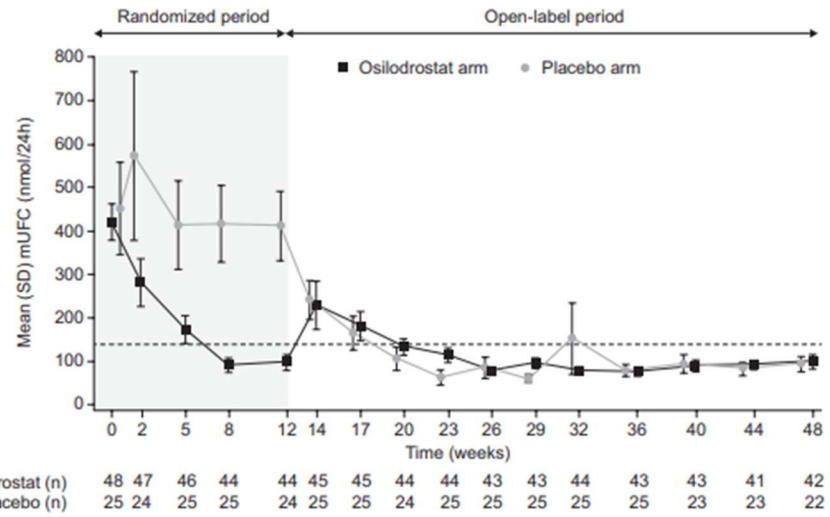
Osilodrostat

LINC-4: Osilodrostat in the Treatment of Cushing Disease

Proportion of randomized patients with mUFC ≤ ULN up to week 12



Mean mUFC at time points up to weeks 12 and 48 by randomized treatment group



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

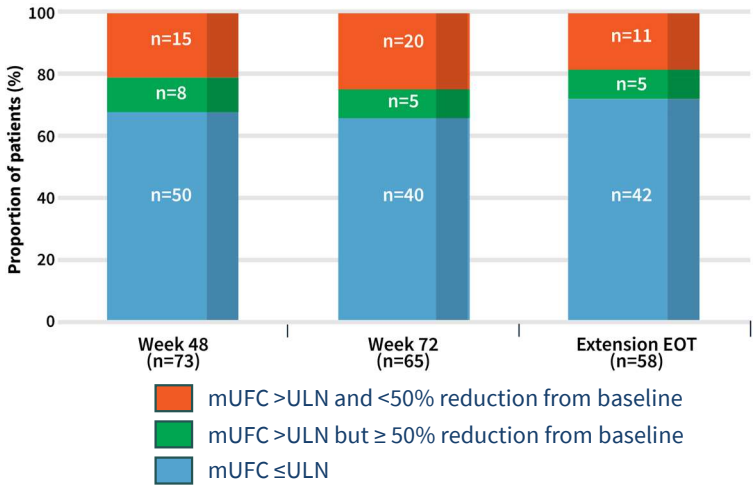
Gadelha M, et al. *J Clin Endocrinol Metab*. 2022

Osilodrostat

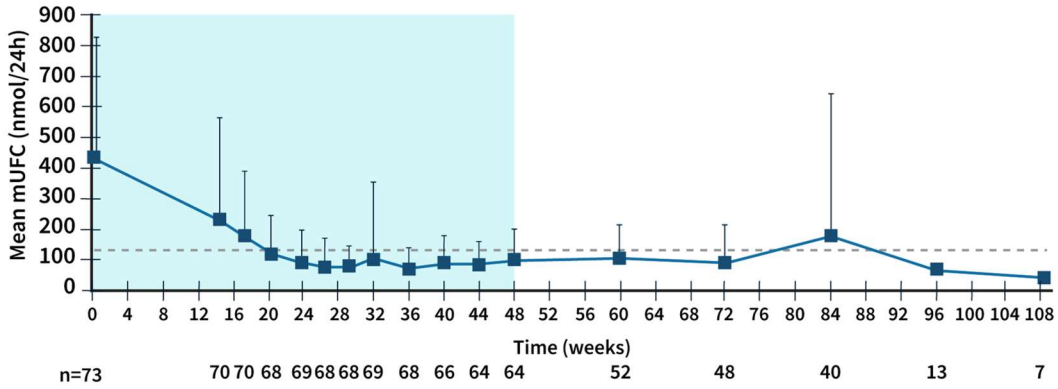
LINC-4 Extension Study:

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



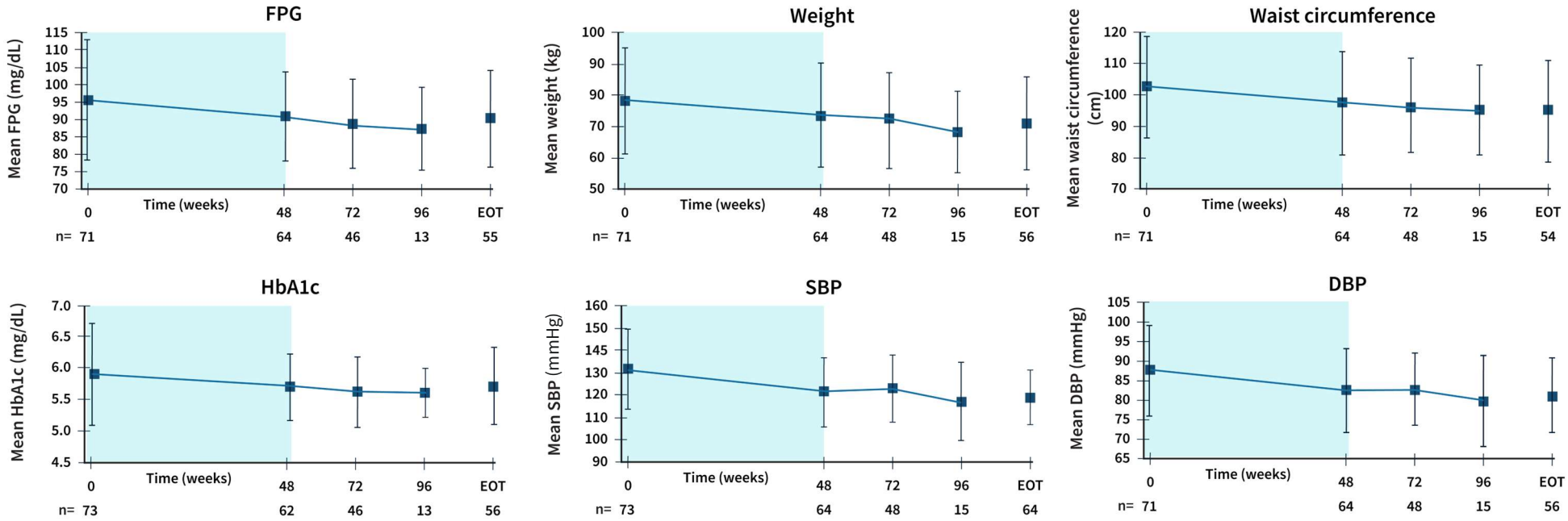
Gadelha M, et al. *Front Endocrinol (Lausanne)*. 2023.

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 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-CD pts reported 29 and 16 SAEs (7 and 4 were considered treatment related), respectively.
  - 5 (3.1%) CD and 2 (4.5%) non-CD 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.

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.

Summary Safety Comparison of Classes

Glucocorticoid Receptor Modulators	Adrenal-Directed Cortisol Synthase-Inhibitors	Pituitary-Directed Therapies
Need to titrate dose slowly to prevent glucocorticoid withdrawal syndrome	Overtreatment: adrenal insufficiency, hypotension, and hypoglycemia	Hyperglycemia common in first 3 months with pasireotide
Can have increases in blood pressure- consider initiating with spironolactone	Monitor carefully for QT prolongation	Works for some pituitary tumors that cause Cushing Disease
	Accumulation of adrenal hormone precursors	

Comprehensive Care for Comorbidities

Diabetes: Often need to REDUCE & down-titrate anti-diabetic drugs during cortisol-directed therapy
- Continue management to prevent and treat diabetic complications

Hypertension: Can improve or worsen with medical therapy
- Also monitor for hyper- or hypokalemia; treat, supplement, modify diuretics

Bone Health: Avoid antiresorptive therapy for about 1 year as bone turnover increases
- For severe disease, anabolic agent followed by antiresorptive agent

Hypopituitarism: Replacement for thyroid & gonadal deficiencies; consider growth hormone
- Will assist in treating bone health, weight management, and quality of life

Myopathy & Cognitive Dysfunction: Often fail to return to baseline after treatment
- Physical therapy and neuropsychological testing to develop treatment plan
- Once patient is through cortisol withdrawal phase and cortisol is well treated

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Going Beyond Surgery

The Latest Updates in Identification and Medical Management of Cushing Syndrome