Unraveling the cortisol connection: Hard-to-control hypertension and hyperglycemia

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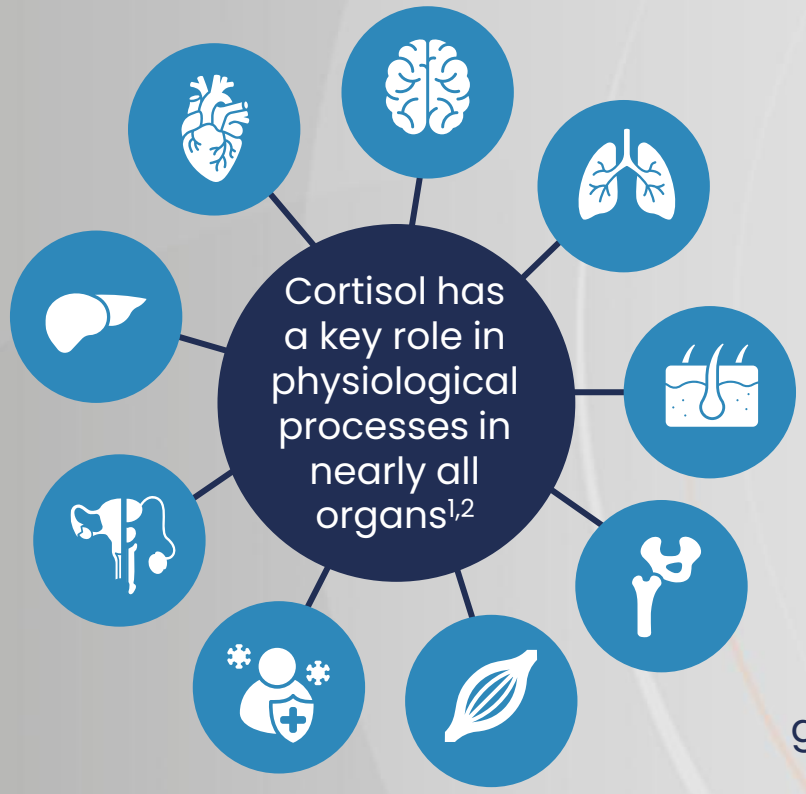
Identifying hidden hypercortisolism in at-risk populations

Agenda

1. Defining hypercortisolism and its link to multiple comorbidities
2. Spectrum of hypercortisolism and clinical presentations
3. Prevalence of hypercortisolism in at-risk populations
4. Reasons and consequences of delayed diagnosis

Cortisol is essential to homeostasis

Hypercortisolism describes cortisol excess



Hypercortisolism:
Pathophysiology derived from exposure to excess cortisol[3]

Cushing's syndrome:
Characteristic physical manifestations of hypercortisolism[3,4]

Can result from **exogenous** glucocorticoid medication or **endogenous** cortisol overproduction[3–5]

- **Iatrogenic**
- **Neoplastic**
- **Non-neoplastic**

1. Zefferino R, et al. *Brain Behav.* 2020;11:e01960; 2. Sulaiman RS, et al. *Steroids.* 2018;133:60–6; 3. Hamidi O, et al. *J Clin Endocrinol Metab.* 2026;111:1513–27; 4. Nieman LK, et al. *J Clin Endocrinol Metab.* 2008;93:1526–40; 5. Findling JW, Raff H. *J Endocr Soc.* 2023;7:bvad087.

Hypercortisolism is associated with many comorbidities

Nervous system

15–83%	Cognitive impairment[1]
50–81%	Major depression[2]
36–80%	Lethargy, depression, labile mood[2]
60%	Sleeping disorder, fatigue[2]

Liver and adipose

38–71%	Dyslipidemia[2]
21–64%	Abnormal glucose tolerance[2]
20–47%	Diabetes mellitus[2]

Cardiovascular

58–85%	Hypertension[2]
54%	Hypercoagulopathy[2]
27–31%	Atherosclerotic changes[2]
3–18%	Thromboembolism[3,4]

Skeletal

60–80%	Osteopenia[2]
≤80%	Osteoporosis fragility fractures[2]

Reproductive

70–80%	Menstrual changes[2]
78% (men) 38% (women)	Sexual dysfunction[5]
24–80%	Decreased libido[2]

Immune system

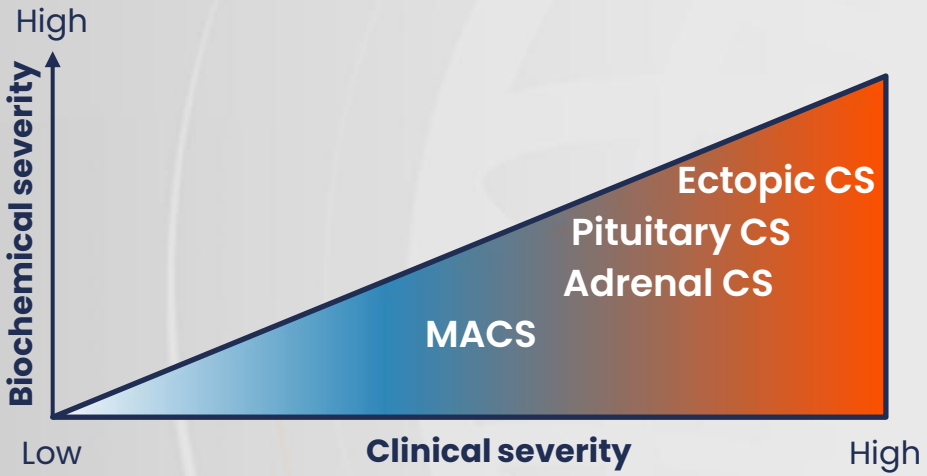
20–50%	Infections[6]

Hypercortisolism is often **unrecognized in clinical practice** due to its broad spectrum of clinical features that **overlap with common conditions**[7]

1. De Alcubierre D, et al. *J Endocrinol Invest.* 2023;46: 1961–82; 2. Braun LT, et al. *Front Endocrinol (Lausanne).* 2019;10:766; 3. Wagner J, et al. *Front Endocrinol (Lausanne).* 2019;9:805; 4. Suarez MG, et al. *J Endocr Soc.* 2019;4:bvz033; 5. Huan C, et al. *Biomed Mater Eng.* 2014;24:3439–46; 6. Barbot M, et al. *J Endocrinol Invest.* 2024;48(Suppl. 1):35–43; 7. Kushner P, et al. *Fed Pract.* 2024;41(Suppl. 6):S23–8.

Hypercortisolism exists as a continuum with a heterogeneous presentation[1]

Biochemical severity correlates with clinical severity across Cushing's syndrome subtypes[2]



Scoring of severity included the following assessments[2]

Biochemical severity

- 1-mg DST
- 24h urinary free cortisol
- Late night salivary cortisol
- ACTH dependence
- Sex- and age-adjusted DHEA-S

Clinical severity

Metabolic abnormalities

- Hypertension
- Pre-diabetes or T2D
- Decreased bone density*
- VTE†
- Weight gain

Physical findings

- Central obesity
- Supraclavicular +/- dorsocervical fat pads
- Rounding of face‡
- Skin changes§
- Proximal muscle weakness

*Includes osteopenia, osteoporosis by bone mineral density or fragility fracture in the past 12 months. †Includes deep vein thrombosis or pulmonary embolism in the past 12 months. ‡With or without plethora; §Violaceous striae, thinning and/or bruising of the skin.

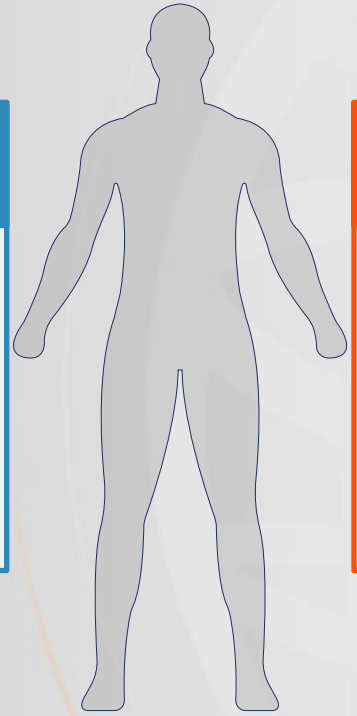
ACTH, adrenocorticotropic hormone; CS, Cushing's syndrome; DHEA-S, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; MACS, mild autonomous cortisol secretion; T2D, diabetes; VTE, venous thromboembolism.

1. Kushner P, et al. *Fed Pract.* 2024;41(Suppl. 6):S23–8; 2. Li D, et al. *Eur J Endocrinol.* 2023;188:603–12.

Typical clinical features of overt Cushing's syndrome

Selected 'classical' features[1–3]

- Weight gain
- Dorsocervical fat pad
- Thin skin
- Easy bruising
- Violaceous striae
- Decreased bone density



Features with best discriminatory value[2]

- Easy bruising
- Facial plethora
- Proximal myopathy or muscle weakness
- Striae (reddish-purple and >1 cm wide, non-blanching)

Use of excessive exogenous glucocorticoid medication should be excluded[2]

1. Aresta C, et al. *Endocr Pract.* 2021;27:1216–24; 2. Nieman LK, et al. *J Clin Endocrinol Metab.* 2008;93:1526–40; 3. Nieman LK. *Endocrinol Metab (Seoul).* 2018;33:139–46.

Evolving understanding of Cushing's syndrome:

Disease presentation beyond overt CS

Most patients with hypercortisolism do not look like they have classically described Cushing's syndrome **= hidden hypercortisolism**[1,2]

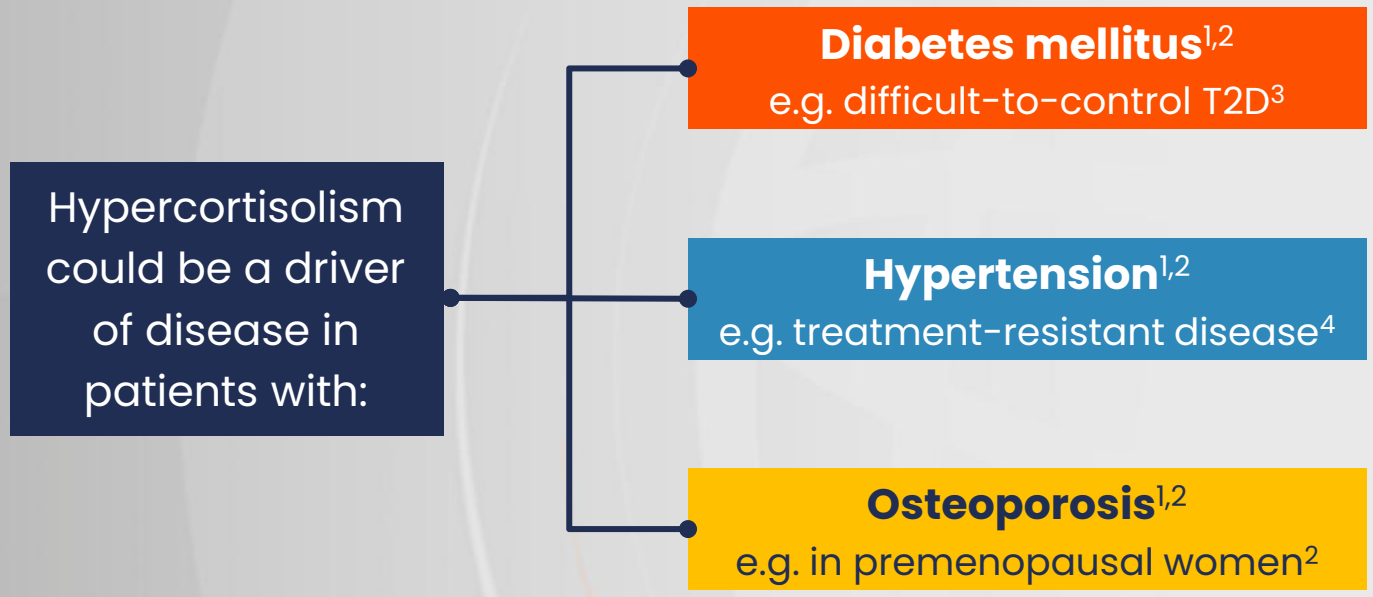
- Patients may have **subtle physical features**[1,2]
- Patients may have **multiple comorbidities**[2]
- Patients often have **autonomous adrenal tumors**[3]

Hypercortisolism occurs in 0.2–2% of general population and is **more common in at-risk populations**[1,4]

CS, Cushing's syndrome.

1. Aresta C, et al. *Endocr Pract.* 2021;27:1216–24; 2. Araujo-Castro M, et al. *Ann Endocrinol (Paris).* 2023;84:272–84; 3. Reimondo G, et al. *Minerva Endocrinol.* 2019;44:33–42; 4. Kushner P, et al. *Fed Pract.* 2024;41(Suppl. 6):S23–8.

Which patients are at risk of hidden hypercortisolism?



Hypercortisolism may be suspected in patients with **unusual features for their age**, e.g. hypertension, T2D or fragility fractures in young people[2]

T2D, diabetes.

1. Aresta C, et al. *Endocr Pract.* 2021;27:1216–24; 2. Kushner P, et al. *Fed Pract.* 2024;41(Suppl. 6):S23–8; 3. Buse JB, et al. *Diabetes Care.* 2025;48:2012–20; 4. Bhatt DL, et al. Presented at: ACC.26 Scientific Sessions, New Orleans, LO, USA. March 28–30, 2026. Available at: https://bit.ly/4sZf5Co.

CATALYST study: Part 1

Prevalence of hypercortisolism in patients with difficult-to-treat diabetes

Study population

N=1,057

Adults in the US with difficult-to-control T2D defined as HbA1c 7.5–11.5% (58–102 mmol/mol) despite multiple SoC therapies*

Primary endpoint

Prevalence of hypercortisolism, diagnosed as post–1 mg DST cortisol >1.8 µg/dL with dexamethasone ≥140 ng/dL

Results

24% of patients had hypercortisolism

27% of those with hypercortisolism had **adrenal nodules detected** with imaging

37% of patients with difficult-to-control T2D **and** resistant hypertension† had hypercortisolism

*Taking ≥3 glucose-lowering medications; or taking insulin and any other glucose-lowering medication(s); or taking ≥2 glucose-lowering medications and having ≥1 microvascular or macrovascular complications; and/or taking ≥2 glucose-lowering and ≥2 blood pressure–lowering medications. †Taking ≥3 blood pressure-lowering medications.
DST, dexamethasone suppression test; HbA1c, glycated hemoglobin; SoC, standard of care; T2D, diabetes.
Buse JB, et al. *Diabetes Care.* 2025;48:2012–20.

MOMENTUM study

Prevalence of hypercortisolism in patients with treatment-resistant hypertension

Study population

N=1,086

Adults in the USA with resistant hypertension based on 2017 AHA criteria:

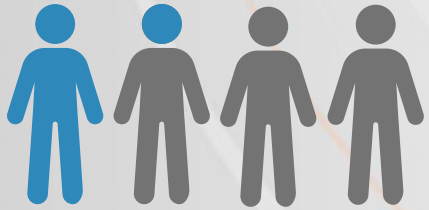
- SBP ≥130 mmHg despite use of ≥3 BP medications from different classes at maximally tolerated doses, including a diuretic
- SBP at any level with use of ≥4 BP medications from different classes

Primary endpoint

Prevalence of hypercortisolism, diagnosed as post–1 mg DST cortisol >1.8 μg/dL with dexamethasone ≥140 ng/dL

Results

27% of patients had hypercortisolism



24% of those with hypercortisolism had **adrenal nodules detected** with imaging

AHA, American Heart Association; BP, blood pressure; DST, dexamethasone suppression test; SBP, systolic blood pressure.

Bhatt DL, et al. Presented at: ACC.26 Scientific Sessions, New Orleans, LO, USA. March 28–30, 2026. Available at: https://bit.ly/4sZf5Co.

Hypercortisolism diagnosis is often delayed

Delayed diagnosis and intervention have significant consequences

- As hypercortisolism has a broad range of overlapping clinical features and is not routinely screened for, **diagnosis may be delayed by up to 10 years**[1–3]
- A meta-analysis of >5,300 patients with Cushing's syndrome showed a **mean diagnostic delay of 34 months**[4]

Delayed diagnosis means delayed intervention

Why does delay matter?

- Hypercortisolism **duration is the most relevant determinant** for morbidity/mortality[4]
- **Prolonged exposure** to elevated cortisol leads to **increased risk** of cardiometabolic abnormalities, osteoporosis, and psychiatric disorders[1]
- For patients who undergo surgery to reduce cortisol levels, restitution of symptoms and body changes, as well as psychiatric recovery, **depend on disease duration**[4]

1. Kushner P, et al. *Fed Pract.* 2024;41(Suppl. 6):S23–8; 2. Valassi E, et al. *Endocr Connect*. 2022;11:e220027; 3. Page-Wilson G, et al. *Pituitary*. 2023;26:364–74; 4. Rubinstein G, et al. *J Clin Endocrinol Metab*. 2020;105:dgz136.

Summary

Hypercortisolism is a **spectrum of disease** that causes a range of comorbidities and impacts on quality of life, regardless of presentation

Hypercortisolism is present in around **1 in 4** individuals with **difficult-to-control diabetes** or **treatment-resistant hypertension**

Due to the constellation of symptoms that overlap with other common conditions, **diagnosis is often delayed**, leading to increased morbidity and mortality

Heightened awareness, proactive screening in at-risk populations, and timely intervention is needed to reduce risk

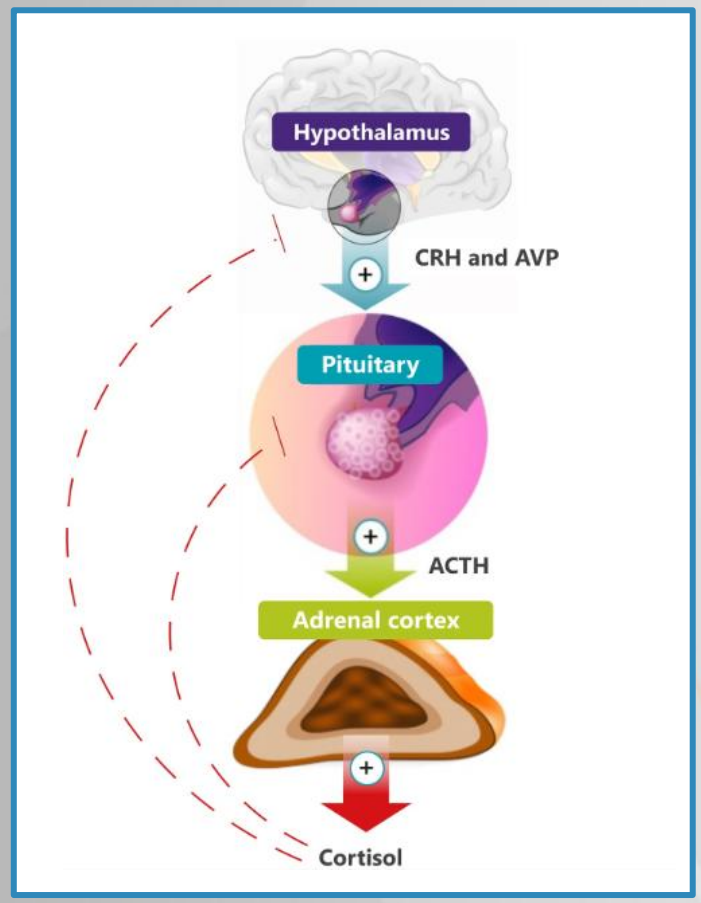
Exploring the mechanistic role of cortisol excess in hyperglycemia and hypertension

Agenda

1. Normal cortisol physiology
2. How hypercortisolism leads to dysregulation of glucose metabolism
3. Mechanistic links between hypercortisolism and hypertension
4. Cardiometabolic consequences of hypercortisolism and impact of cortisol reduction

Normal cortisol physiology

HPA axis



HPA axis regulates cortisol secretion by coordinating release of cortisol secretagogues

ACTH and cortisol release is **coordinated in a circadian rhythm** and is essential for many physiological functions, including regulation of energy metabolism, immune function, and stress response

Patients with endogenous CS have **disruption of the circadian and ultradian rhythms** of cortisol secretion, leading to excessive exposure

Figure reproduced from Hamidi O, et al under Creative Commons Attribution 4.0 International license.
ACTH, adrenocorticotropic hormone; AVP, vasopressin; CRP, corticotropin-releasing hormone; CS, Cushing's syndrome; HPA, hypothalamic–pituitary–adrenal.
Hamidi O, et al. *J Clin Endocrinol Metab.* 2026;111:1513–27.

Disruption of normal cortisol secretion has a variety of causes

Factors leading to endogenous CS

Neoplastic causes of endogenous CS[1]

ACTH-dependent CS

Pituitary adenoma: Cushing's disease
Ectopic syndrome: Pancreatic or pulmonary NET, SCLC, etc.

ACTH-independent CS

Adrenal tumors
Benign: adenoma, multinodular
Malignant: adrenocortical carcinoma

Non-neoplastic causes of endogenous hypercortisolism

OB/GYN[2]

- Pregnancy
- Hypothalamic amenorrhea

Metabolic[2]

- Severe obesity
- Extreme exercise
- Anorexia nervosa and malnutrition
- Severely uncontrolled diabetes

Psychosocial[2]

- Alcohol abuse
- Psychiatric illness

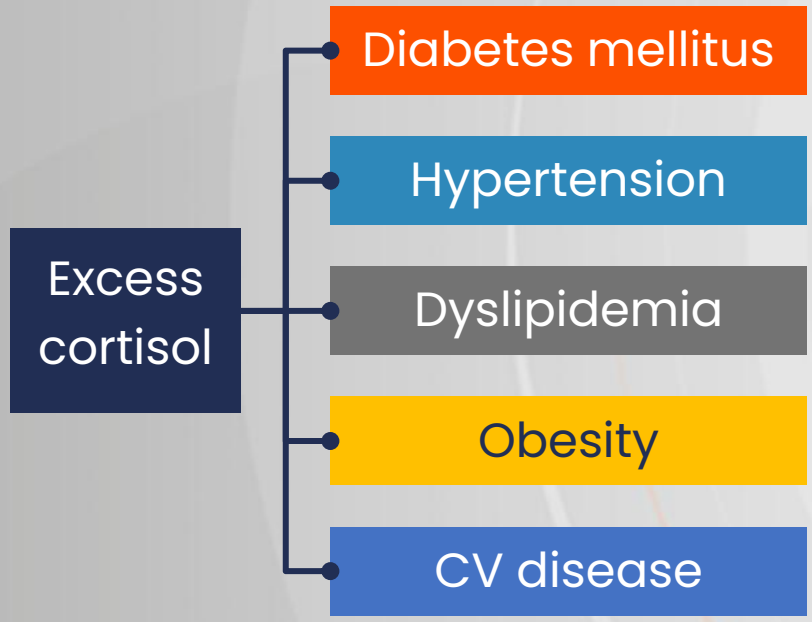
Other[2]

- Severe medical or surgical stress
- Chronic severe pain
- Genetic CBG excess

ACTH, adrenocorticotropic hormone; CBG, corticosteroid-binding globulin; CS, Cushing's syndrome; NET, neuroendocrine tumor; OB/GYN, obstetric/gynecological; SCLC, small cell lung cancer.

1. Hamidi O, et al. *J Clin Endocrinol Metab.* 2026;111:1513–27; 2. Nieman LK, et al. *J Clin Endocrinol Metab.* 2008;93:1526–40.

Excess cortisol increases cardiometabolic risk



Multiple pathophysiological mechanisms contribute to increased cardiometabolic risk in patients with hypercortisolism

CV, cardiovascular disease.
Araujo-Castro M, et al. *Ann Endocrinol (Paris)*. 2023;84:272–84.

Link between hypercortisolism, glucose metabolism and diabetes

Abnormal glucose metabolism has been reported in 14–74% of patients with hypercortisolism; **21–47% are reported to have diabetes**[1]

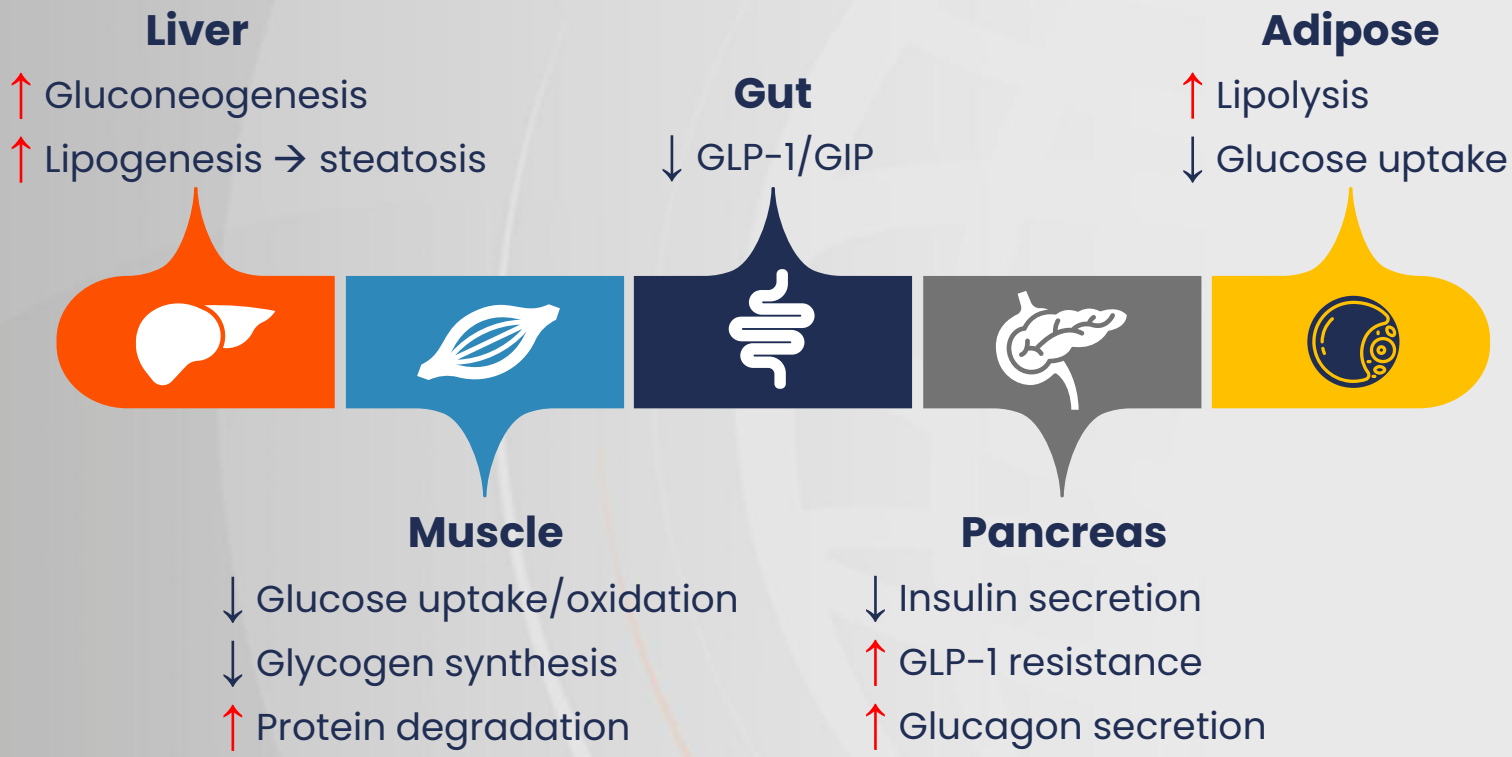
Glucose homeostasis is regulated in a circadian rhythm; dysregulation of the HPA axis by excess cortisol can exacerbate insulin resistance and glucose intolerance[2]

Excess cortisol **impacts a number of systems** that control glucose homeostasis[2]

HPA, hypothalamic–pituitary–adrenal.

1. Li D, et al. *Gland Surg.* 2020;9:43–58; 2. DeFronzo RA, Auchus RJ. *Diabetes.* 2025;74:2168–78.

How does hypercortisolism disrupt glucose homeostasis?



GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1.
DeFronzo RA, Auchus RJ. *Diabetes.* 2025;74:2168–78.

Link between hypercortisolism and hypertension

Hypertension is one of the most reported features in patients with hypercortisolism, prevalent in up to 90% of patients with overt CS[1]

HPA axis contributes to circadian BP regulation; HPA axis dysregulation by excess cortisol can contribute to hypertension[2]

Excess cortisol **impacts a number of systems** that regulate BP[2,3]

BP, blood pressure; CS, Cushing's syndrome; HPA, hypothalamic–pituitary–adrenal.

1. Araujo-Castro M, et al. *Ann Endocrinol (Paris).* 2023;84:272–84; 2. Isidori AM, et al. *J Hypertens*. 2015;33:44–60; 3. Bhatt DL, et al. Presented at: ACC.26 Scientific Sessions, New Orleans, LO, USA. March 28–30, 2026. Available at: https://bit.ly/4sZf5Co.

How does hypercortisolism lead to hypertension?[1,2]

Angiotensinogen synthesis in liver
Renin (kidney) → Angiotensin I ← ACE (lung)
Angiotensin II receptor expression

- Vaso-constriction
- Aldosterone co-secretion by adrenal mass (in kidney)
- H_2O and Na^+ reabsorption (in kidney)

Vasoconstriction (due to increases in ET-1 and erythropoietin)

Vasodilation (due to impairment of NO pathway and kallikrein-kinin system)

RAAS activity | **MR activation** | **Vasoregulatory factors** | **Sympathetic nervous system**

Cortisol (active) → 11βHSD2 → Cortisone (inactive)

Excess cortisol overwhelms 11βHSD2, increasing MR activation

Cortisol → MR → MR activation → H_2O and Na^+ reabsorption and K^+ excretion

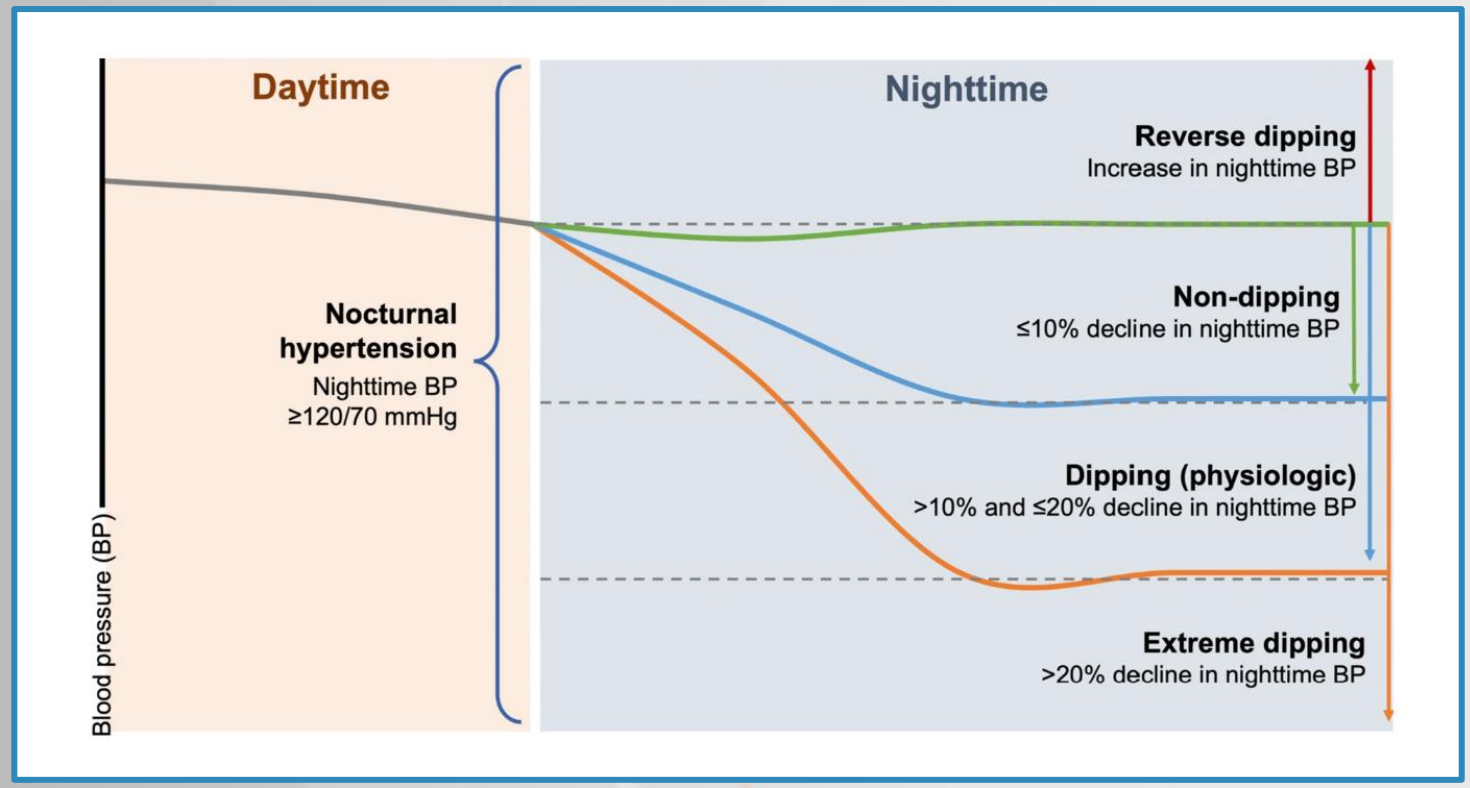
Pressor sensitivity to noradrenaline and β-adrenergic agonists

11βHSD2, 11β-hydroxysteroid dehydrogenase; ACE, angiotensin-converting enzyme; ET-1, endothelin-1; MR, mineralocorticoid receptor; NO, nitric oxide.

1. Isidori AM, et al. *J Hypertens*. 2015;33:44–60; 2. Bhatt DL, et al. Presented at: ACC.26 Scientific Sessions, New Orleans, LO, USA. March 28–30, 2026. Available at: https://bit.ly/4sZf5Co.

Non-dipping nighttime BP profile can be indicative of hypercortisolism[1]

Nighttime BP dipping patterns[2]



BP, blood pressure.
1. Fallo F, et al. *J Hypertens.* 2022;40:2085–101; 2. Tang A, et al. *Curr Hypertens Rep.* 2024;26:21–30.

Impact of hypercortisolism on cardiovascular morbidity

Patients with **active CS** have:

- **2.1x** risk of **acute MI**[1]*
- **4.5x** risk of **stroke**[1]*
- **6x** risk of **heart failure**[1]*

Diabetes

Patients in **CATALYST** with hypercortisolism had **significantly more cardiac disorders**† than those without ($p<0.0001$)[2]

Hypertension

In **MOMENTUM**, **cardiac disorders**‡ **were numerically more common** in patients with hypercortisolism, compared with those without[3]

*Compared with matched controls. †'Cardiac disorders overall' as defined in MedDRA, version 26.0. ‡Including atrial fibrillation, coronary artery disease and heart failure.
CS, Cushing's syndrome; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction.
1. Isidori AM, et al. *J Hypertens*. 2015;33:44–60; 2. Buse JB, et al. *Diabetes Care.* 2025;48:2012–20; 3. Bhatt DL, et al. Presented at: ACC.26 Scientific Sessions, New Orleans, LO, USA. March 28–30, 2026. Available at: https://bit.ly/4sZf5Co.

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Impact of cortisol reduction on glucose dysregulation, hypertension and cardiovascular risk

Diabetes

- Reversal of hypercortisolism leads to **improvement in glucose metabolism**[1]
- Prevalence of diabetes in patients with CS decreases from 20–47% before treatment to **10–33% after treatment**[1]
- Pharmacotherapy for hypercortisolism can **improve glycemic control**[1]

Hypertension

- Resolution of hypercortisolism **improves BP control** in 30–70% of patients[1]
- However, **CS-related hypertension can persist** several years after clinical/hormonal disease remission[2]
- Patients may have persistent hypertension due to **irreversible** structural changes[1]

Remission from CS leads to a **decrease in CV risk factors and events**[1]

Risk of CV events and mortality **remain elevated despite remission**[1]

Emphasizes the importance of early diagnosis and intervention

BP, blood pressure; CS, Cushing's syndrome; CV, cardiovascular.

1. Li D, et al. *Gland Surg.* 2020;9:43–58; 2. Isidori AM, et al. *J Hypertens*. 2015;33:44–60.

Summary

Diabetes mellitus is common in CS; **a variety of mechanisms contribute to dysregulation of glucose metabolism**

Hypercortisolism has a complex and multifactorial impact on BP, leading to frequent hypertension in patients with CS

Disrupted glucose metabolism and hypertension, as well as other pathophysiological processes, **increase CV risk in patients with CS**

Resolution of hypercortisolism can reduce CV risk; however, increased morbidity and mortality can persist after cortisol correction, **underscoring the need for early diagnosis and intervention**

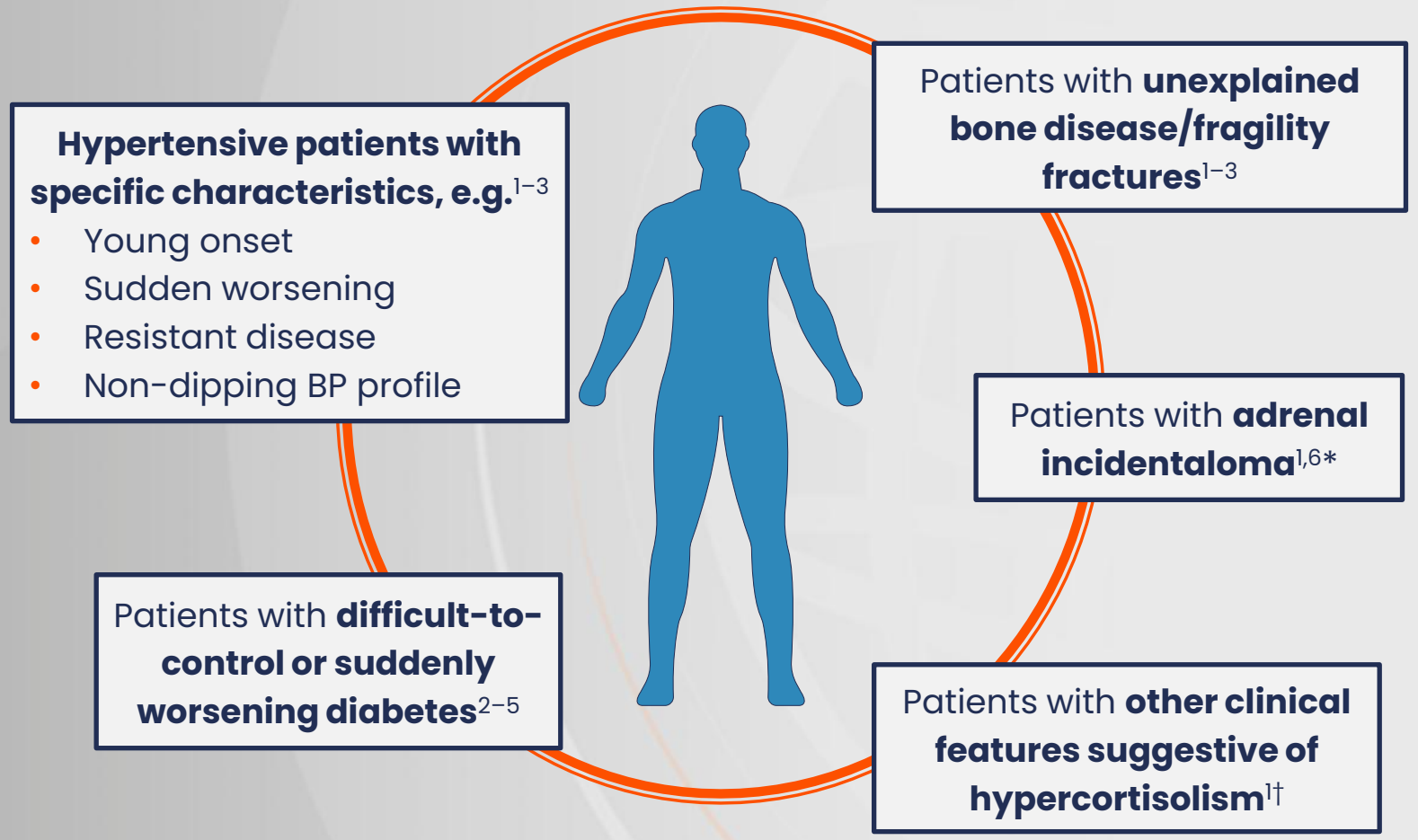
BP, blood pressure; CS, Cushing's syndrome; CV, cardiovascular.

Screening and management of cortisol-driven disease in at-risk populations

Agenda

1. Which patients to screen for hypercortisolism
2. Screening tools in at-risk populations
3. Management strategies
4. Best practices for monitoring and holistic care

Who should be screened for hypercortisolism?



*Adrenal mass detected on imaging not performed for suspected adrenal disease. †Including easy bruising, facial plethora, striae, proximal myopathy, proximal muscle weakness, unusual features for age, or multiple and progressive features.
BP, blood pressure.

1. Fallo F, et al. *J Hypertens.* 2022;40:2085–101; 2. Giovanelli L, et al. *J Endocrinol Invest.* 2021;44:1581–96; 3. Kushner P, et al. *Fed Pract.* 2024;41(Suppl. 6):S23–8; 4. Samson SL. *Endocr Pract.* 2026;32:473–518; 5. Buse JB, et al. *Diabetes Care.* 2025;48:2012–20; 6. Fassnacht M, et al. *Eur J Endocrinol.* 2023;189:G1–42.

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Initial screening tools for hypercortisolism

Overnight 1-mg DST

Test specifics:
1-mg dexamethasone given orally at bedtime, serum cortisol measured next morning[1]

What it measures:
Dexamethasone should suppress endogenous cortisol production; non-suppression is indicative of CS[2]

Recommended cut-off:
1.8 μg/dL[2,3]

24-hour urinary free cortisol

Test specifics:
24-hour urine collection; at least 2–3 collections advised due to intra-patient variability[2]

What it measures:
Total bioavailable cortisol excreted in 24 hours; high levels are indicative of CS[2]

Recommended cut-off:
Assay-specific reference range[2]

Late night salivary cortisol

Test specifics:
Saliva collected between 11:00 p.m. and 12:00 a.m.; at least 2–3 tests advised[2,4]

What it measures:
Patients with CS lose the normal circadian nadir of cortisol secretion; high late-night levels are indicative of CS[2]

Recommended cut-off:
Assay-specific reference range[2]

Overnight 1-mg DST is recommended as first-line screening method; offers **best combination of sensitivity and specificity** across hypercortisolism subtypes.[2,3,5,6] **Further testing is needed** to confirm CS and determine the cause;[2,3] common causes of **false positives* need to be excluded**.[7,8]

*Including systemic glucocorticoid exposure; use of oral contraceptives; pregnancy or lactation; excessive alcohol consumption; severe untreated sleep apnea; severe psychiatric, medical, or surgical illness; night shift work; or hemodialysis/end-stage renal disease. CS, Cushing's syndrome; DST, dexamethasone suppression test.

1. Dogra P, Vijayashankar NP. Dexamethasone Suppression Test. 2024. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026. PMID: 31194457; 2. Fleseriu M, et al. *Lancet Diabetes Endocrinol.* 2021;9:847–75; 3. Fallo F, et al. *J Hypertens.* 2022;40:2085–101; 4. Mohamed RS, et al. *Endocr Connect.* 2022;11:e220050; 5. Sherlock M, et al. *Endocr Rev.* 2020;41:775–820; 6. Fassnacht M, et al. *Eur J Endocrinol.* 2023;189:G1–42; 7. Buse JB, et al. *Diabetes Care.* 2025;48:2012–20; 8. Bhatt DL, et al. Presented at: ACC.26 Scientific Sessions, New Orleans, LO, USA. March 28-30, 2026. Available at: https://bit.ly/4sZf5Co.

Management approaches

Whatever the underlying etiology, hypercortisolism has detrimental cardiometabolic effects and requires management

- **Surgical resection** of the tumor responsible for excess cortisol production is the **first-line treatment option** for most patients with hypercortisolism[1–3]
- Surgery has also shown benefit for patients with mild autonomous cortisol secretion[4]

- **Pharmacological therapy** also has an important role:[3,5]
  - Preoperatively
  - For patients who are not surgical candidates/decline surgery
  - For patients with residual/recurrent disease after surgery
  - Where the source of cortisol is unknown

~75% of patients in the **CATALYST** and **MOMENTUM** studies did not have detectable adrenal nodules;[6,7] **patients with an abnormal overnight DST may benefit from cortisol-directed pharmacotherapy**[5]*

*Assuming common causes of false positives have been excluded.

1. Fleseriu M, et al. *Lancet Diabetes Endocrinol.* 2021;9:847–75; 2. Fallo F, et al. *J Hypertens.* 2022;40:2085–101; 3. Dillon BR, et al. *Drugs.* 2025;85:1207–30; 4. Ren X, et al. *Front Endocrinol (Lausanne).* 2024:15:1399311; 5. DeFronzo RA, et al. *Diabetes Care.* 2025;48:2036–44; 6. Buse JB, et al. *Diabetes Care.* 2025;48:2012–20; 7. Bhatt DL, et al. Presented at: ACC.26 Scientific Sessions, New Orleans, LO, USA. March 28–30, 2026. Available at: https://bit.ly/4sZf5Co.

Pharmacological options to manage hypercortisolism

Glucocorticoid receptor modulators	Steroidogenesis inhibitors	Pituitary-targeting therapies
MoA: Blunt the effects of cortisol rather than blocking secretion; potentially useful regardless of hypercortisolism etiology[1]	**MoA:** Block one or more enzymes responsible for adrenal steroidogenesis; the most widely used cortisol-lowering drugs for CS treatment[1]	**MoA:** Target corticotroph adenoma; activate somatostatin or dopamine receptors, cause alkylating damage, or activate immune system[1]
Examples:[1] • Mifepristone (also binds progesterone receptor)[1,2] • Relacorilant[3] (investigational)	**Examples:**[1] • Osilodrostat[4] • Levoketoconazole[5] • Ketoconazole (O/L) • Metyrapone (O/L) • Etomidate (O/L) • Mitotane (O/L)	**Examples:**[1] • Pasireotide[6] • Cabergoline (O/L) • Temozolomide (O/L) • Immunotherapy (O/L)

Novel agents including **atumelnant** (a selective ACTH receptor antagonist) and **clofutriben** (an HSD-1 inhibitor) are under active investigation[7–10]

ACTH, adrenocorticotropic hormone; CS, Cushing's syndrome; HSD-1, 11β-hydroxysteroid dehydrogenase type 1; MoA, mode of action; O/L, off-label.

1. Dillon BR, et al. *Drugs.* 2025;85:1207–30; 2. FDA. Mifepristone PI. Available at https://bit.ly/4wfoOHv (accessed May 6, 2026); 3. Pivonello R, et al. *Lancet Diabetes Endocrinol.* 2026;14:291–304; 4. FDA. Osilodrostat PI. Available at: https://bit.ly/4f7mIn1 (accessed May 6, 2026); 5. FDA. Levoketoconazole PI. Available at: https://bit.ly/4usaNoe (accessed May 6, 2026); 6. FDA. Pasireotide PI. Available at: https://bit.ly/4tjS3WY (accessed May 6, 2026); 7. Elenius H, et al. *J Endocr Soc.* 2024;8(Suppl. 1):bvae163.114; 8. Fleseriu M, et al. *J Endocr Soc.* 2025;9(Suppl. 1):bvaf149.1471; 9. Clinical trials.gov. NCT05804669. Available at: https://bit.ly/4ujguFy (accessed May 6, 2026); 10. Clinical trials.gov. NCT07296484. Available at: https://bit.ly/4wldHY7 (accessed May 6, 2026).

touch™ ENDOCRINOLOGY

Management of hyperglycemia secondary to hypercortisolism

Mifepristone indication

Only agent approved for hyperglycemia secondary to endogenous hypercortisolism in adult patients with **endogenous CS and T2D/glucose intolerance** for whom surgery failed or who are not candidates for surgery[1,2]

Based on findings from the open-label **SEISMIC** study of mifepristone, which recruited patients with **overt, endogenous CS** and either T2D, impaired glucose tolerance, or hypertension[1–3]

Could mifepristone be useful in a broader population of patients with hypercortisolism?[2]

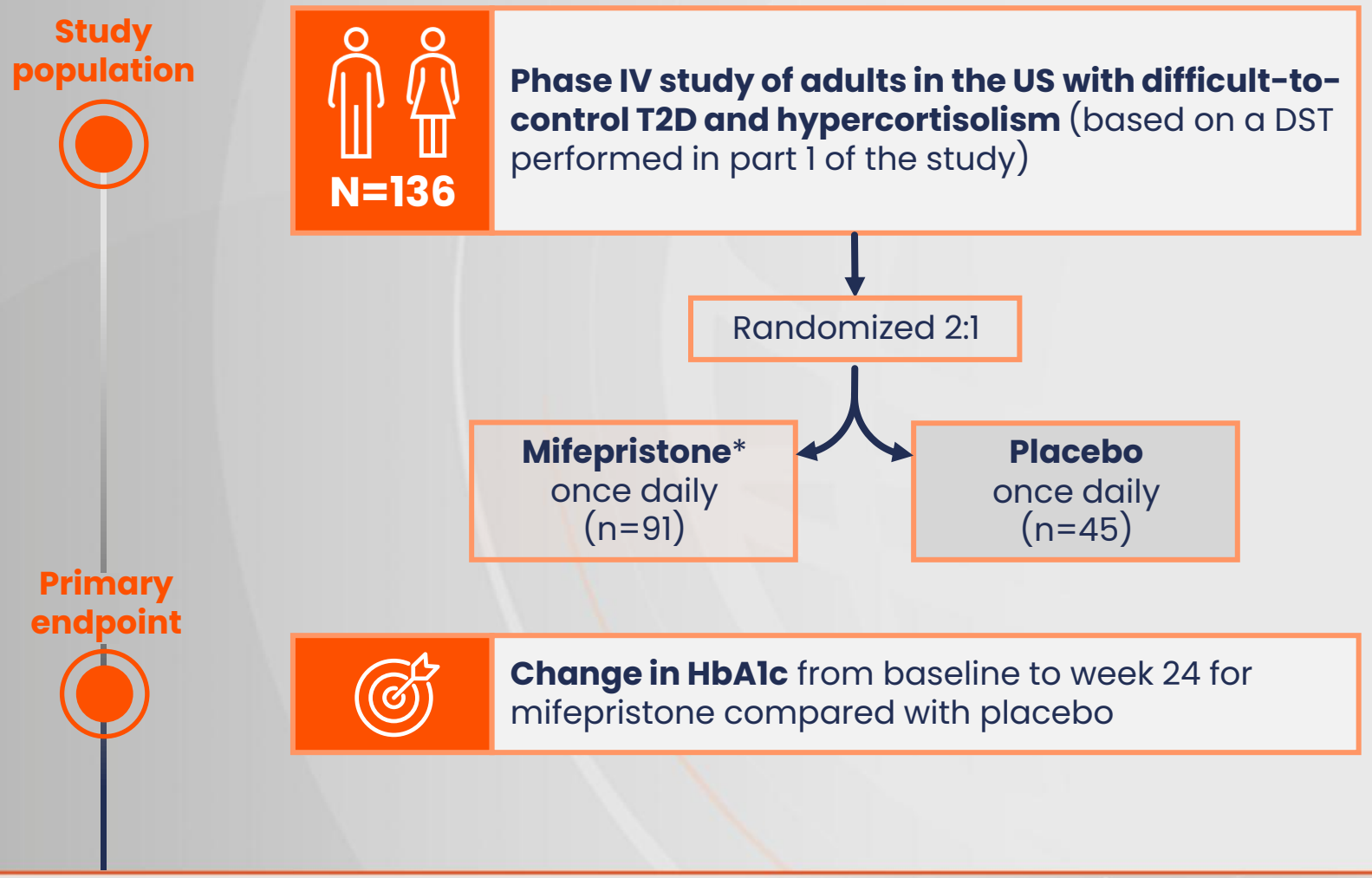
CATALYST study: part 2

A double-blind, placebo-controlled trial that investigated mifepristone treatment for patients with **previously undiagnosed hypercortisolism** and difficult-to-control T2D[2]

CS, Cushing's syndrome; T2D, diabetes.

1. FDA. Mifepristone PI. Available at: https://bit.ly/4wfoOHv (accessed May 6, 2026); 2. DeFronzo RA, et al. *Diabetes Care.* 2025;48:2036–44; 3. Fleseriu M, et al. *J Clin Endocrinol Metab.* 2012;97:2039–49.

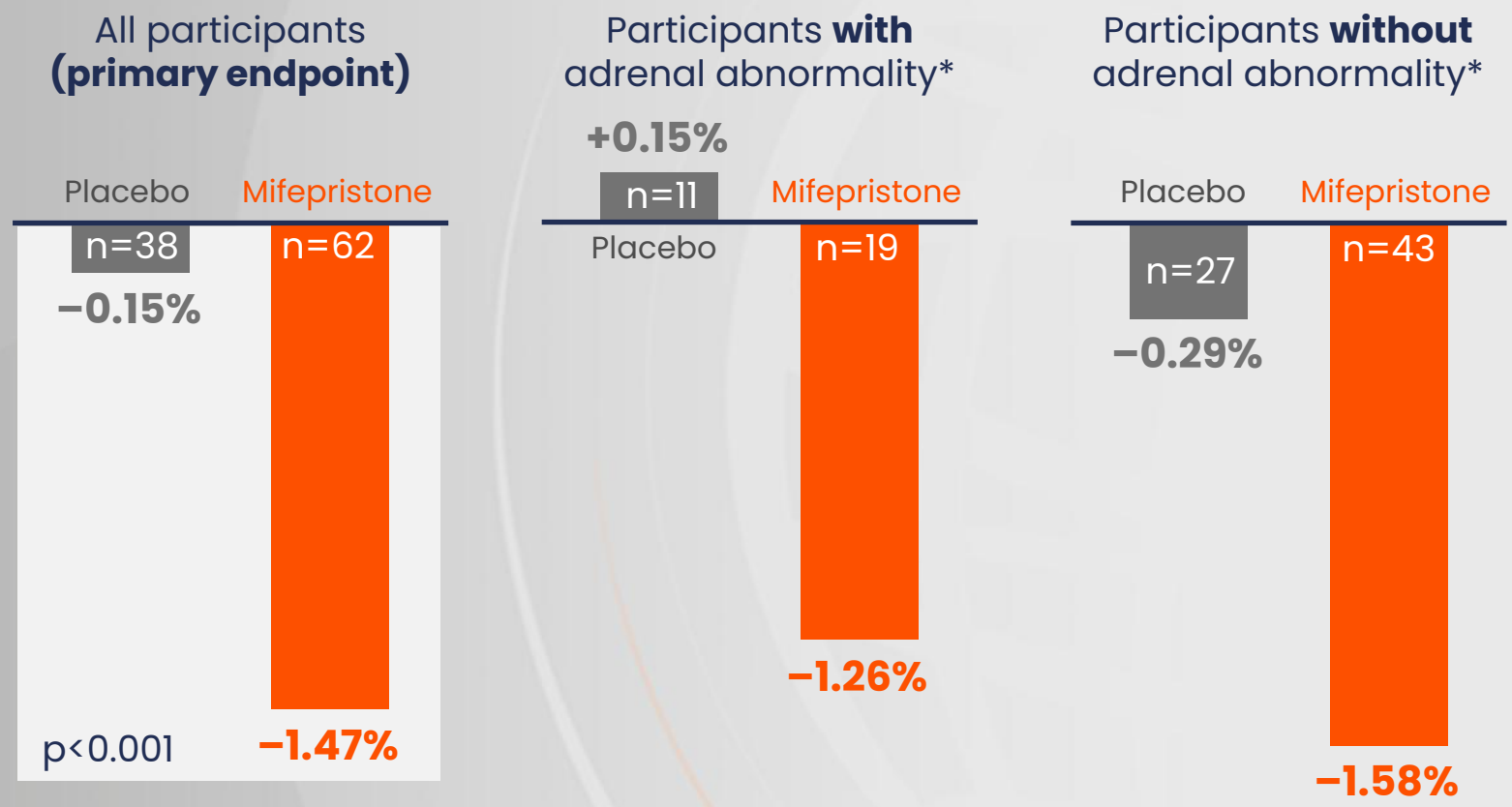
CATALYST study: Part 2



*Initially 300 mg daily, rising to 600 mg daily after 4 weeks, depending on tolerance, with an option to increase to 900 mg daily at week 8 or 12.
DST, dexamethasone suppression test; HbA1c, glycated hemoglobin.
DeFronzo RA, et al. *Diabetes Care.* 2025;48:2036–44.

CATALYST study: Part 2

LSM change from baseline in HbA1c at week 24



Mifepristone treatment led to reductions in HbA1c, regardless of whether patients had an adrenal abnormality*

*Detected on computed tomography scan.
HbA1c, glycated hemoglobin; LSM, least squares mean.
DeFronzo RA, et al. *Diabetes Care.* 2025;48:2036–44.

CATALYST study: Part 2

Selected secondary endpoints at week 24

	LSM difference between mifepristone and placebo
Body weight	−5.12 kg
BMI	−1.75 kg/m^2
Waist circumference	−5.1 cm
Fasting plasma glucose	−20.0 mg/dL
Total cholesterol	−17.2 mg/dL

There were also more discontinuations/dose reductions of **glucose-lowering medications** in the mifepristone group (n=54) compared to placebo (n=8) by week 12

BMI, body mass index; LSM, least squares mean.

DeFronzo RA, et al. *Diabetes Care.* 2025;48:2036–44.

CATALYST study: Part 2

Effects on blood pressure and TEAEs

- Variable effects of mifepristone on BP have been reported
- In CATALYST, mean BP **remained at or near recommended target** of <130/80 mmHg throughout the study
- At week 24, there was a **10.1 mmHg increase in BP with mifepristone** (placebo-adjusted LSM), leading to increased use of BP-lowering medications
- No BP increase was observed for patients with baseline BP ≥130 mmHg

Most common TEAEs (>11%)	Mifepristone (n=91)	Placebo (n=43)
Hypokalemia	30%	0%
Fatigue	21%	16%
Nausea	21%	12%
Vomiting	15%	7%
Headache	12%	12%
Peripheral edema	15%	2%

BP, blood pressure; LSM, least squares mean; TEAE, treatment-emergent adverse events

DeFronzo RA, et al. *Diabetes Care.* 2025;48:2036–44.

GRACE study

Study population

N=152

Phase III study of adults globally with endogenous hypercortisolism with hypertension and/or hyperglycemia

- Hypercortisolism diagnosis based on two positive tests among: 24-hour UFC, LNSC, DST
- Hypertension: mean SBP 135–170 mmHg or mean DBP 85–110 mmHg
- Hyperglycemia: T2D or impaired glucose tolerance

Study design

Relacorilant* once daily (n=95 completed; 62 met response criteria)

Met response criteria → randomized 1:1

Relacorilant* once daily (n=30)

Placebo once daily (n=32)

Open-label phase (22 weeks)

Randomized-withdrawal phase (12 weeks)

Primary endpoint

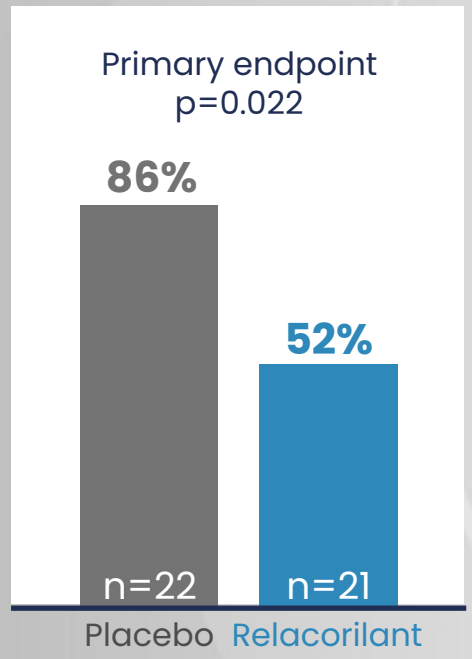
Loss of hypertension control† during the randomized-withdrawal phase, among patients who had a hypertension response‡ in the open-label phase

*Starting dose in open-label phase: 100 mg orally once daily for 2 weeks. From open-label weeks 2–10, dose was escalated every 4 weeks by 100 mg, to target dose of 400 mg. In randomized-withdrawal phase, patients received 400 mg once daily or highest tolerated dose. †Loss of response defined as: (1) in patients who met only SBP response criterion, an increase in SBP of ≥5 mmHg 24h ABPM; (2) in patients who met only DBP response criterion, an increase in DBP of ≥5 mmHg by 24h ABPM; (3) in patients who met both SBP and DBP response criteria, an increase in either SBP or DBP of ≥5 mmHg by 24h ABPM; (4) an increase or modification in antihypertensive medication due to worsening hypertension; or (5) treatment discontinuation in the randomized-withdrawal phase. ‡Defined as ≥5 mmHg decrease in mean SBP or DBP from baseline to week 22, without worsening of either. ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; SBP, systolic blood pressure; T2D, diabetes; UFC, urinary free cortisol. Pivonello R, et al. *Lancet Diabetes Endocrinol.* 2026;14:291–304.

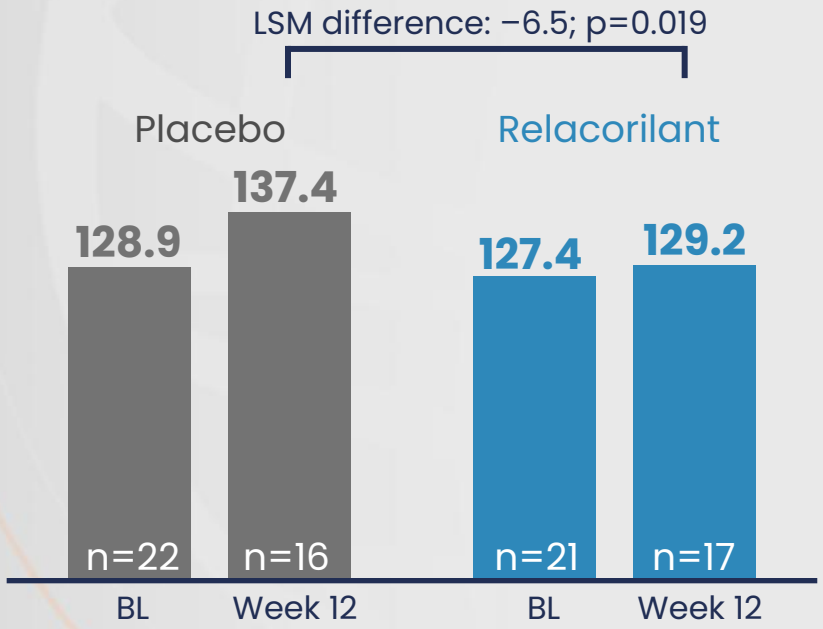
GRACE study

Loss of hypertension response

Proportion of patients* with loss of hypertension response at randomized-withdrawal phase week 12



Mean 24h SBP (mmHg) at baseline and week 12 of randomized-withdrawal phase



*Among patients in the ITT population with hypertension who had a hypertension response in the open-label phase and were randomized.
BL, baseline; ITT, intent to treat; LSM, least squares mean; SBP, systolic blood pressure.
Pivonello R, et al. *Lancet Diabetes Endocrinol.* 2026;14:291–304.

GRACE study

TEAEs

Most common TEAEs (≥10%)	Relacorilant (n=30)	Placebo (n=32)
Back pain	17%	19%
Acne	10%	0
Arthralgia	10%	9%
Bursitis	10%	0
Headache	10%	13%
Insomnia	0	13%

TEAE, treatment-emergent adverse event.

Pivonello R, et al. *Lancet Diabetes Endocrinol.* 2026;14:291–304.

Summary: Impact of cortisol-directed treatments on hyperglycemia and hypertension

Therapy	Impact on hyperglycemia	Impact on hypertension
Osilodrostat	Improves[1]	Can worsen, improve, or no change[1]
Levoketoconazole	Improves[2]	Can worsen or no change[3–5]
Pasireotide	Often worsens, requires careful monitoring[6]	Improves[7]
Mifepristone	Improves[8,9]	Can worsen, improve or no change[8,9]
Relacorilant*	Improves or no change[10]	Improves[10]

*Investigational.

1. Fleseriu M, et al. *Pituitary.* 2025;28:22; 2. Pivonello R, et al. *Front Endocrinol (Lausanne).* 2021:12:595894; 3. Pivonello R, et al. *Pituitary.* 2022;25:911–26; 4. Fleseriu M, et al. *Eur J Endocrinol.* 2022;187:859–71.4; 5. Fleseriu M, et al. *Lancet Diabetes Endocrinol.* 2019;7:855–65. 6. FDA. Pasireotide PI. Available at: https://bit.ly/4tjS3WY (accessed May 6, 2026); 7. Pivonello R, et al. *Clin Endocrinol (Oxf).* 2014;81:408–17; 8. DeFronzo RA, et al. *Diabetes Care.* 2025;48:2036–44; 9. Fleseriu M, et al. *J Clin Endocrinol Metab.* 2012;97:2039–49; 10. Pivonello R, et al. *Lancet Diabetes Endocrinol.* 2026;14:291–304.

Ongoing assessment and management of diabetes, hypertension and cardiovascular risk

- It is important to carefully manage the comorbidity (diabetes/hypertension) **as well as** treating underlying hypercortisolism[1]
- Diabetes may not resolve after hypercortisolism treatment; if glucose levels remain uncontrolled, **ongoing diabetes assessment and management** is required[1,2]
- Similarly, as hypertension may persist after treatment of hypercortisolism, **ongoing blood pressure assessment and management** is required[1–3]
- Cardiovascular status should be assessed **during active disease and postoperative follow-up**, as cardiovascular risk can persist for a long time[3]

1. Araujo-Castro M, et al. *Biomedicines.* 2023;11:3115; 2. Li D, et al. *Gland Surg.* 2020;9:43–58; 3. Fallo F, et al. *J Hypertens.* 2022;40:2085–101.

Summary

At-risk populations, including certain patients with difficult-to control-diabetes or hypertension, **should be screened** for hypercortisolism

The preferred first-line screening test for hypercortisolism is the **1-mg overnight DST**

Hypercortisolism requires prompt management; surgery is the first-line treatment option to correct cortisol excess

Pharmacological treatment also has a role in management; **patients with an abnormal DST may benefit from cortisol-directed therapy**

As diabetes and hypertension may persist following treatment to correct hypercortisolism, ongoing assessment and management is required

DST, dexamethasone suppression test.