CATALYST
Study of Hypercortisolism in Patients with Difficult-to-Control Type 2 Diabetes

Prevalence of Hypercortisolism in Patients With Difficult-to-Control Type 2 Diabetes and Cardiovascular Disease: Results From CATALYST

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Summary & Conclusions

- Despite advancements in medical treatment, difficult-to-control type 2 diabetes (T2D) remains common in clinical practice and can lead to diabetes-related complications
- Hypercortisolism is a known contributing cause of hyperglycemia and is independently linked to higher mortality
- In the CATALYST study (NCT05772169), the largest prospective study to date examining the prevalence and characteristics of hypercortisolism in individuals with difficult-to-control T2D, hypercortisolism was found in 24% of participants
- Our findings show that the subgroup with cardiovascular disease (CVD) had a higher prevalence of hypercortisolism compared with the group without CVD (33.3% vs 20.9%, *P*<0.0001)
- Given the high prevalence of hypercortisolism, screening may be warranted in individuals with difficult-to-control T2D and CVD
- The ongoing CATALYST treatment phase will provide data on therapeutic intervention in individuals with hypercortisolism

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Background

- Despite recent advancements in diabetes treatments, approximately 25% of individuals with T2D continue to have inadequately controlled glucose levels, with HbA1c >8%[1-5]
- Excess cortisol activity, known as hypercortisolism, may contribute to the poor glycemic control observed in some patients with T2D, despite adherence to typically effective treatments[6]
- Hypercortisolism can negatively impact glycemic regulation through various mechanisms, such as inducing insulin resistance, impairing beta-cell function, and increasing hepatic glucose output, and is independently associated with cardiovascular disease and the increased mortality seen in individuals with T2D[7,8]
- Prior research has reported the prevalence of hypercortisolism in individuals with inadequately controlled T2D to range from 5% to 33%, but these studies had limitations[9-11]
- CATALYST (NCT05772169), the largest prospective study to date assessing the prevalence and characteristics of individuals with hypercortisolism among those with inadequately controlled T2D, found a hypercortisolism prevalence of 24% in this population[12,13]
    - Preliminary results from CATALYST were previously reported[13]; final results are being presented at this congress

Aim

- To describe the characteristics of the CATALYST subgroup of individuals with both T2D and reported CVD, and to ascertain the prevalence of hypercortisolism within this subgroup

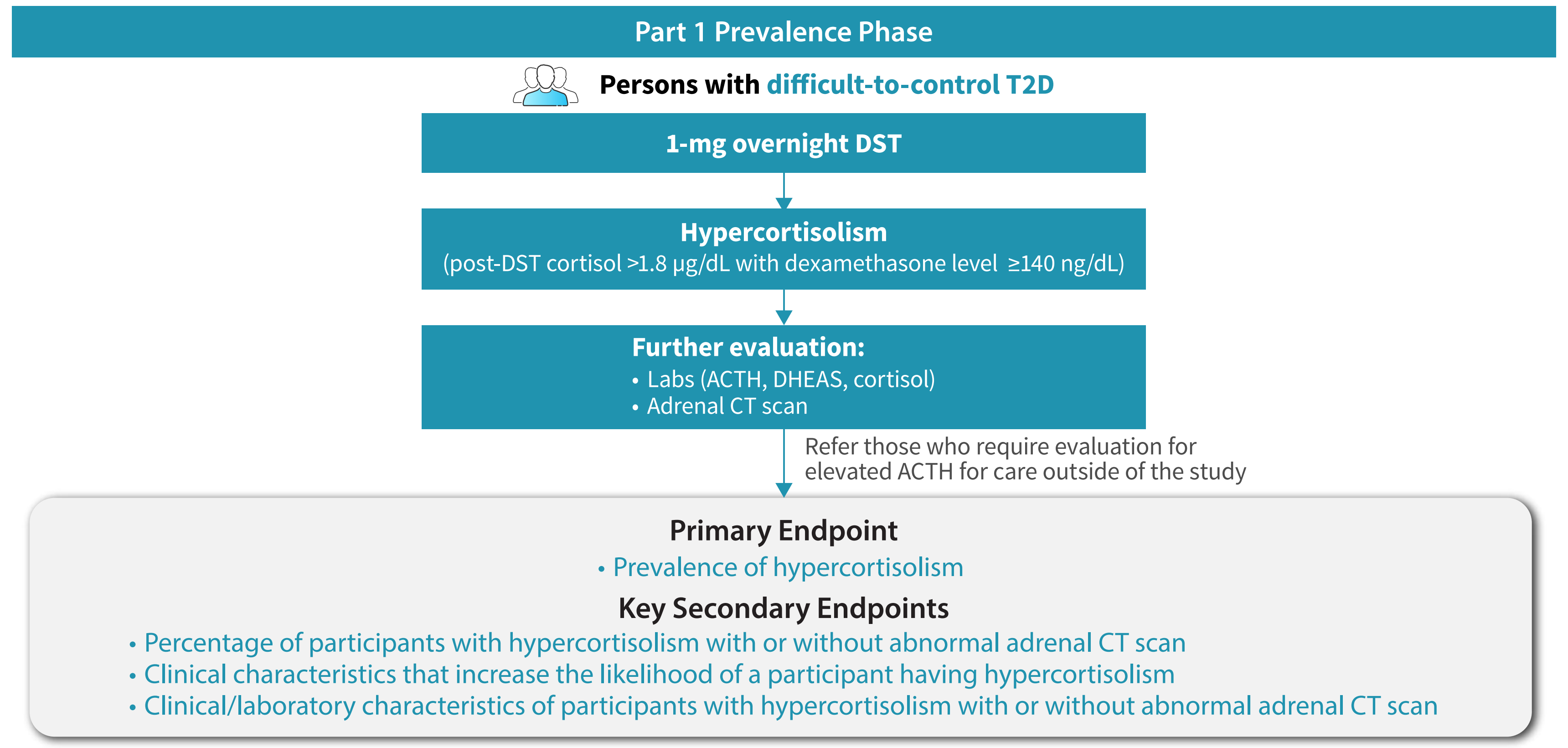
CVD, cardiovascular disease; T2D, type 2 diabetes.

Methods

Study Design

- **CATALYST is a prospective, 2-part, multicenter study conducted at 36 sites across the United States in diverse clinical settings**
- Part 1 of the CATALYST study (**Figure 1**) was a noninterventional phase conducted between March 2023 and April 2024
- Detailed study design and methods have been previously reported[13]
    - The study enrolled adults aged 18 to 80 years with difficult-to-control T2D and HbA1c 7.5% to 11.5% despite taking multiple glucose-lowering medications with or without micro-/macrovascular complications or taking multiple blood pressure-lowering medications
    - Participants were screened for hypercortisolism, defined as post-1-mg dexamethasone suppression test (DST) cortisol >1.8 μg/dL (50 nmol/L), with adequate dexamethasone levels ≥140 ng/dL
    - Participants with common causes of false-positive DST test results (eg, use of oral contraceptive pills; excessive alcohol consumption; severe untreated sleep apnea; severe psychiatric, medical, or surgical illness; night-shift work; or hemodialysis/end-stage renal disease) were excluded

Figure 1. CATAYLST Study Design



Part 1 Prevalence Phase

Persons with difficult-to-control T2D

1-mg overnight DST

Hypercortisolism
(post-DST cortisol >1.8 μg/dL with dexamethasone level ≥140 ng/dL)

Further evaluation:
- Labs (ACTH, DHEAS, cortisol)
- Adrenal CT scan

Refer those who require evaluation for elevated ACTH for care outside of the study

Primary Endpoint
- Prevalence of hypercortisolism

Key Secondary Endpoints
- Percentage of participants with hypercortisolism with or without abnormal adrenal CT scan
- Clinical characteristics that increase the likelihood of a participant having hypercortisolism
- Clinical/laboratory characteristics of participants with hypercortisolism with or without abnormal adrenal CT scan

Assessments

- CVD history was collected by self-report or review of electronic medical records

Statistical Analysis

- Parameters potentially associated with hypercortisolism were assessed using univariate analysis
    - A simple logistic regression model was performed for each outcome and variable separately, with the Wald chi-square *P*-value, odds ratio (OR), and the corresponding 95% CI reported
- Multiple logistic regression was performed to identify baseline characteristics independently associated with hypercortisolism
    - A stepwise selection method (backward and forward, with *P*<0.1 for inclusion and *P*<0.05 for retention) was used to determine the final models, which were presented with *P*-value, OR, and the 95% CI for the OR

ACTH, adrenocorticotropic hormone; CI, confidence interval; CT, computed tomography; CVD, cardiovascular disease; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; OR, odds ratio; T2D, type 2 diabetes.

1 Results: Demographics and Characteristics

Patient population

- A total of 1,057 participants completed the overnight 1-mg DST with a dexamethasone level ≥140 ng/dL
- The characteristics of the overall CATALYST population and the CVD subgroup are shown in **Table 1**
- 23.8% (252/1,057) of CATALYST participants had CVD
- Hypercortisolism prevalence was 33.3% (84/252) in the CVD subgroup, which was higher than in the overall study population

Table 1. Demographics and Baseline Characteristics in Participants With and Without Hypercortisolism in the CATALYST Subgroup With CVD

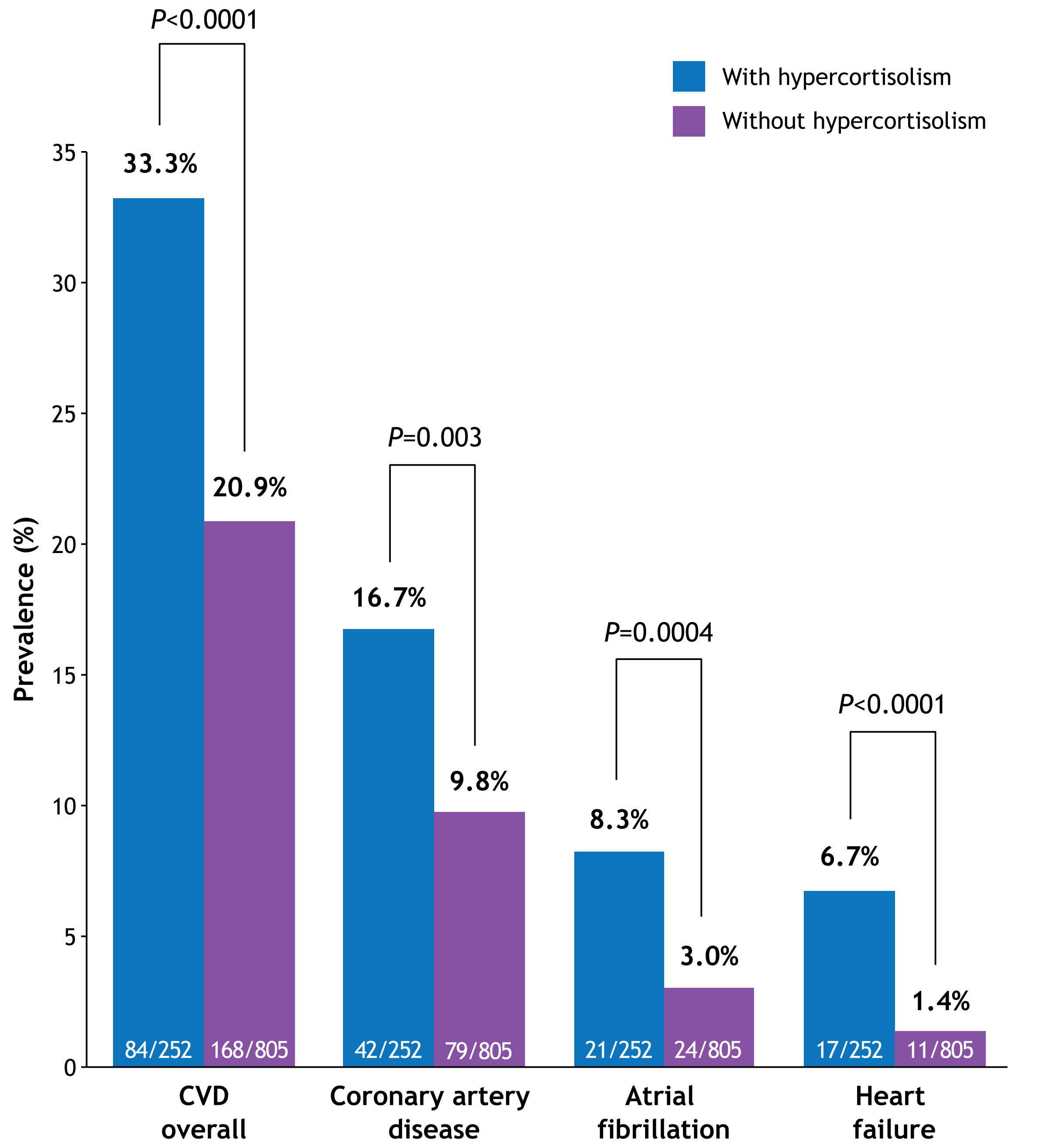
	Overall CATALYST population (N=1,057)	CATALYST subgroup with CVD[a] (N=252)		Univariate analysis for hypercortisolism vs no hypercortisolism in the CATALYST subgroup with CVD[d]	
		Hypercortisolism[b] (n=84)	No hypercortisolism (n=168)	Odds ratio	95% CI
Age, years, mean (SD)	60.7 (10.4)	66.9 (9.5)	64.6 (8.9)	–	–
Female, n (%)	479 (45.3)	38 (45.2)	64 (38.1)	–	–
BMI, kg/m², mean (SD)	33.5 (7.2)	33.0 (8.1)	33.2 (6.7)	–	–
Waist circumference, inches, mean (SD)	44.4 (6.7)	44.8 (7.2)	44.6 (6.4)	–	–
Ethnicity: Not Hispanic/Latino[c], n (%)	802 (75.8)	83 (99.0)	133 (79.2)	21.84	2.94, 162.44
HbA1c, %, mean (SD)	8.8 (1.0)	8.6 (1.0)	8.6 (1.0)	–	–
SBP, mm Hg, mean (SD)	127.6 (16.1)	126.3 (18.4)	126.4 (15.5)	–	–
DBP, mm Hg, mean (SD)	75.3 (9.8)	72.4 (8.9)	74.2 (9.5)	–	–
BP-lowering medications, n (%)					
≥3 BP-lowering medications	235 (27.1)	38 (48.1)	52 (33.5)	–	–
RAS agents	734 (69.4)	61 (72.6)	122 (72.6)		
Beta blockers	334 (31.6)	60 (71.4)	106 (63.1)	–	–
Diuretics	331 (31.3)	47 (56.0)	61 (36.3)	2.23	1.31, 3.80
Calcium channel blockers	261 (24.7)	25 (29.8)	39 (23.2)	–	–
Other cardiovascular medications, n (%)	90 (8.5)	29 (34.5)	43 (25.6)	–	–
Lipid modifying agents, n (%)	880 (83.3)	77 (91.7)	148 (88.1)	–	–
Analgesics, n (%)	321 (30.4)	32 (38.1)	62 (36.9)	–	–
Psychiatric medications, n (%)	312 (29.5)	39 (46.4)	46 (27.4)	2.30	1.33, 3.97

[a]CVD subgroup excludes participants with hypertension. [b]Hypercortisolism defined as post-DST cortisol >1.8 μg/dL with adequate dexamethasone level in this population. [c]Ethnicity group 'Not Hispanic/Latino' includes 'missing.' [d]"–" indicates nonsignificant results in the univariate analysis (95% CI crosses 1).

BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DST, dexamethasone suppression test; RAS, renin-angiotension-system; SBP, systolic blood pressure; SD, standard deviation.

- In the total study population, participants with hypercortisolism had higher rates of CVD, including coronary artery disease, atrial fibrillation, and heart failure compared to those without (**Figure 2**)

Figure 2. Characteristics of Participants With and Without Hypercortisolism

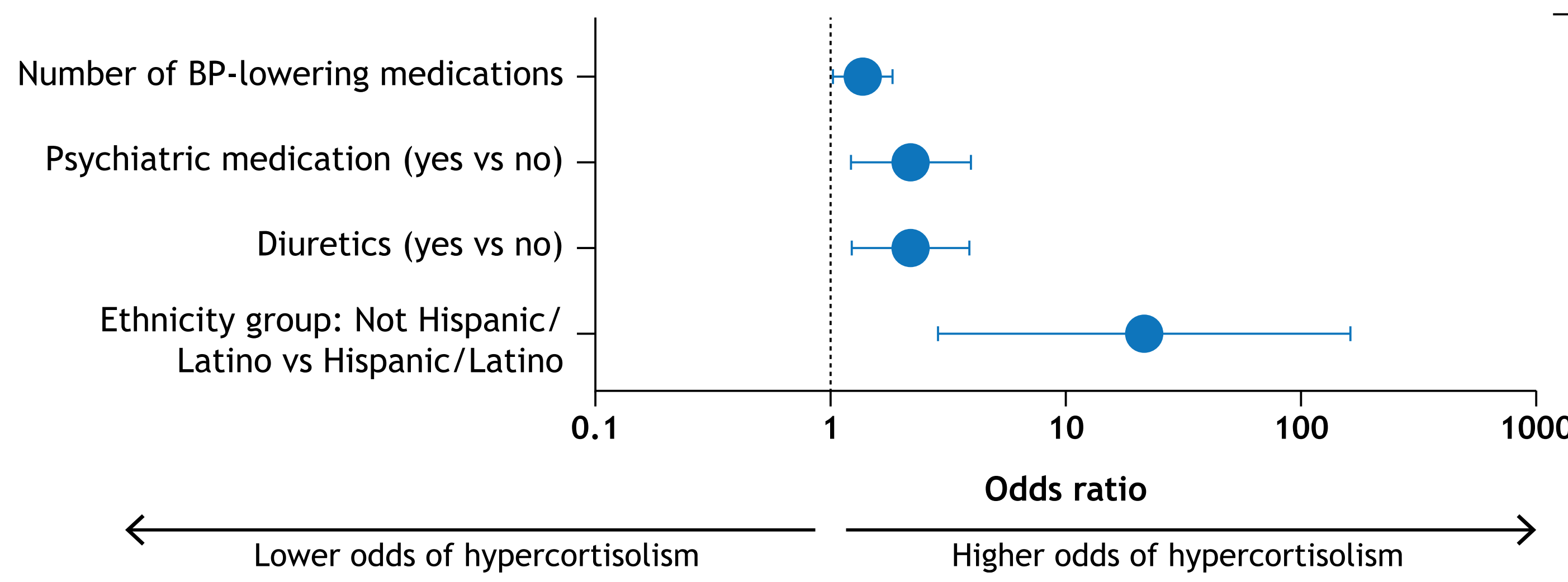


2 Results: Characteristics of Individuals With Hypercortisolism

- A univariate logistic regression model was performed to identify characteristics potentially associated with the presence of hypercortisolism in the CATALYST subgroup with CVD (**Table 1**)
- Factors independently associated with hypercortisolism in the CVD subgroup (based on multivariate analysis) are shown in **Figure 3** and include greater number of BP-lowering medications, use of diuretics, use of psychiatric medications, and not Hispanic/Latino ethnicity
- While participants of Hispanic/Latino ethnicity appeared to have a lower risk of hypercortisolism, the study was not designed to assess the underlying reason why ethnicity might be associated with hypercortisolism. This finding may be impacted by differences in demographic, physical, genetic, or medication characteristics and access to medical care

BP, blood pressure; CVD, cardiovascular disease.

Figure 3. Multiple Logistic Regression Model for Hypercortisolism vs No Hypercortisolism in the CVD Subgroup



	Odds ratio	95% CI	*P*-value
Number of BP-lowering medications	1.372	1.025, 1.836	0.0335
Psychiatric medication (yes vs no)	2.202	1.224, 3.963	0.0085
Diuretics (yes vs no)	2.196	1.236, 3.903	0.0073
Ethnicity group: Not Hispanic/Latino vs Hispanic/Latino	21.585	2.864, 162.680	0.0029

References

(1) CDC. National Diabetes Statistics Report. Accessed November 21, 2024. https://www.cdc.gov/diabetes/php/data-research/index.html. (2) Fang M, et al. *N Engl J Med*. 2021;384(23):2219–2228. (3) Khunti K, et al. *Diabetes Res Clin Pract*. 2018;137:137–148. (4) Avramidis I, et al. *Clin Diabetes*. 2020;38(3):248–255. (5) Caballero AE, et al. *J Diabetes Complications*. 2021;35(11):108011. (6) Aresta C, et al. *Endocr Pract*. 2021;27(12):1216–1224. (7) Li D, et al. *Gland Surg*. 2020 Feb;9(1):43–58. (8) Petramala L, et al. *Endocrine*. 2020;70(1):150–163. (9) Chiodini I, et al. *Eur J Endocrinol*. 2005;153(6):837–844. (10) Catargi B, et al. *J Clin Endocrinol Metab*. 2003;88(12):5808–5813. (11) Jusufović S, et al. *Clinical Diabetology*. 2024. DOI:10.5603/cd.101189. (12) DeFronzo RA, et al. *BMJ Open*. 2024;14(7):e081121. (13) Fonseca V. Results of the CATALYST Trial Part 1. Prevalence of hypercortisolism in difficult-to-control type 2 diabetes [symposium]. Presented at the 84th American Diabetes Association Scientific Sessions; June 21–24, 2024; Orlando, FL.

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