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 High Blood Pressure: Results From CATALYST

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Summary & Conclusions

- Despite advances in medical management, difficult-to-control type 2 diabetes (T2D) remains relatively common in clinical practice, and poor control of hyperglycemia can lead to complications of diabetes
- Hypercortisolism is a known contributing cause of hyperglycemia and is independently associated with increased mortality
- In the CATALYST study (NCT05772169), the largest prospective study to date assessing the prevalence and characteristics of individuals with hypercortisolism among those with difficult-to-control T2D, the prevalence of hypercortisolism was 24%
- Our results show a 40% prevalence of hypercortisolism among the subgroup of CATALYST participants with difficult-to-control T2D and difficult-to-control hypertension as evidenced by systolic blood pressure ≥135 mm Hg despite taking ≥3 blood pressure medications
- Given the high prevalence of hypercortisolism, screening may be warranted in individuals with difficult-to-control T2D and hypertension
- The ongoing CATALYST treatment phase will provide data on therapeutic intervention in individuals with hypercortisolism

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Background

- Despite recent advances in diabetes treatments, approximately 25% of individuals with T2D in the United States have inadequately controlled glycemia (HbA1c >8%)[1-5]
- Excess cortisol activity (hypercortisolism) can contribute to hyperglycemia and may lead to poor control of T2D, even with adherence to typically effective treatments[6]
- Hypercortisolism can negatively impact glycemic control through various mechanisms (eg, insulin resistance, impaired beta-cell function, and increased hepatic glucose output) and is independently associated with hypertension 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 prevalence and characteristics of the subgroups of CATALYST participants with poorly controlled blood pressure, defined as SBP ≥135 mm Hg, and those with poorly controlled blood pressure despite taking ≥3 medications

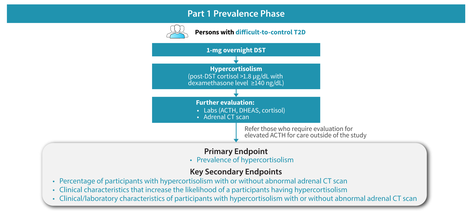
SBP, systolic blood pressure; T2D, type 2 diabetes.

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 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



Assessments

- Hypertension and medication history was collected by self-report or electronic medical record review
- Office blood pressure testing was performed

Statistical Analysis

- Parameters potentially associated with hypercortisolism were assessed using univariate analysis
  - A simple logistic regression model was performed separately for each outcome and variable. The Wald chi-square *P*-value, odds ratio (OR), and the corresponding 95% CI for the OR were reported for each variable
- 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 and presented with *P*-value, OR, and the 95% CI for the OR

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

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.

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 subgroup with SBP ≥135 mm Hg are shown in **Table 1**
- 31.0% (328/1,057) of CATALYST participants had SBP ≥135 mm Hg and 8.5% (90/1,057) were taking ≥3 BP medications

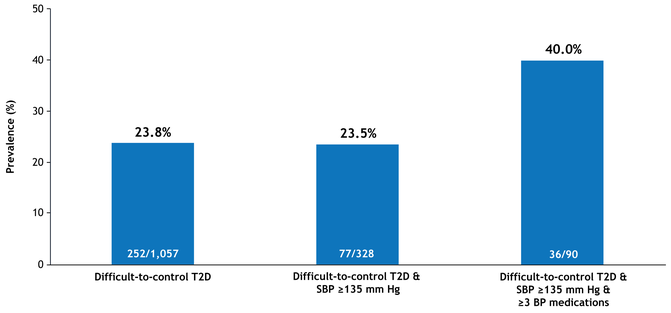
Table 1. Demographics and Characteristics of CATALYST Population and the SBP ≥135 mm Hg Subgroup

	Overall CATALYST population (N=1,057)	CATALYST subgroup with SBP ≥135 mm Hg (N=328)		Univariate analysis for hypercortisolism vs no hypercortisolism in the CATALYST subgroup with SBP ≥135 mm Hg	
		Hypercortisolism[a] (n=77)	No hypercortisolism (n=251)	Odds ratio	95% CI[c]
Age, years, mean (SD)	60.7 (10.4)	64.2 (9.5)	60.8 (10.3)	1.036	1.008, 1.064
Female, n (%)	479 (45.3)	34 (44.2)	111 (44.2)	—	—
BMI, kg/m^2, mean (SD)	33.5 (7.2)	33.6 (7.8)	34.7 (7.6)	—	—
Waist circumference, inches, mean (SD)	44.3 (6.7)	45.0 (7.9)	45.4 (7.1)		
Ethnicity: Not Hispanic/Latino, n (%)[b]	802 (75.8)	69 (89.6)	190 (75.7)	2.769	1.261, 6.081
HbA1c, %, mean (SD)	8.8 (1.0)	8.8 (1.1)	8.8 (1.0)	—	—
SBP, mm Hg, mean (SD)	127.6 (16.1)	147.1 (9.4)	146.4 (10.1)	—	—
DBP, mm Hg, mean (SD)	75.3 (9.8)	80.4 (9.5)	81.8 (9.6)	—	—
BP-lowering medications, n (%)					
≥3 BP-lowering medications	235 (27.1)	36 (50.7)	54 (25.5)	3.203	1.868, 5.494
RAS agents	734 (69.4)	57 (74.0)	186 (74.1)	—	—
Beta blockers	334 (31.6)	35 (45.5)	60 (23.9)	2.653	1.555, 4.526
Diuretics	331 (31.3)	42 (54.5)	80 (31.9)	2.565	1.523, 4.320
Calcium channel blockers	261 (24.7)	34 (44.2)	83 (33.1)	—	—
Other cardiovascular medications, n (%)	90 (8.5)	8 (10.4)	18 (7.2)	—	—
Lipid modifying agents, n (%)	880 (83.3)	66 (85.7)	204 (81.3)	—	—
Analgesics, n (%)	321 (30.4)	33 (42.9)	73 (29.1)	1.829	1.080, 3.099
Psychiatric medications, n (%)	312 (29.5)	26 (33.8)	66 (26.3)	—	—

[a]Hypercortisolism defined as post-DST cortisol >1.8 µg/dL with adequate dexamethasone level in this population. [b]Ethnicity group 'Not Hispanic/Latino' includes 'missing.' '—' indicates nonsignificant results in the univariate analysis (95% CI crosses 1).
BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; DST, dexamethasone suppression test; RAS, renin-angiotension-system; SBP, systolic blood pressure; SD, standard deviation.

- The prevalence of hypercortisolism was similar among those with SBP ≥135 mm Hg and among the overall study population but was higher among participants with SBP ≥135 mm Hg taking ≥3 BP medications (**Figure 2**)

Figure 2. The Prevalence of Hypercortisolism in the CATALYST Population



2 Results: Demographics and Characteristics of the Subgroup With Poorly Controlled Blood Pressure

- The characteristics of those with and without SBP ≥135 mm Hg are shown in **Table 2**
- Participants with SBP ≥135 mm Hg, compared with those with SBP <135 mm Hg, were slightly older and had a higher BMI and waist circumference
- Participants with an SBP ≥135 mm Hg had higher DBP and a greater prevalence of vascular disorders and hypertension
- No difference was observed in HbA1c between the SBP groups
- More participants with SBP ≥135 mm Hg had received sulfonylureas and fewer received GLP-1s and SGLT2s, compared with those with SBP <135 mm Hg
- As expected, use of BP medication was higher in participants with SBP ≥135 mm Hg

Table 2. Baseline Characteristics and Select Medications in the SBP Subgroups

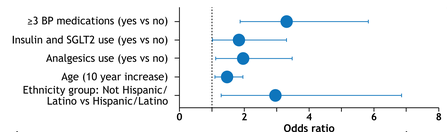
Characteristics	SBP <135 mm Hg (n=728)	SBP ≥135 mm Hg (n=328)	*P*-value[a]
Baseline characteristics,[b] mean (SD)			
Age, yrs	60.3 (10.5)	61.6 (10.2)	NS
BMI, kg/m^2[c]	33.1 (7.0)	34.4 (7.6)	0.0064
Waist circumference, inches	44.0 (6.4)	45.3 (7.3)	0.0031
DBP, mm Hg	72.6 (8.6)	81.5 (9.6)	<.0001
HbA1c, %	8.8 (1.1)	8.8 (1.0)	NS
Prevalence of hypercortisolism, n (%)[d]	175 (24.0)	77 (23.5)	NS
Common cardiovascular comorbidities, n (%)[d]			
Cardiac disorders	184 (25.3)	67 (20.4)	NS
Coronary artery disease	85 (11.7)	36 (11.0)	NS
Atrial fibrillation	36 (4.9)	9 (2.7)	NS
Cardiac failure congestive	17 (2.3)	11 (3.4)	NS
Vascular disorders	587 (80.6)	289 (88.1)	0.0028
BP medications, n (%)			
Any BP medications	582 (79.9)	283 (86.3)	0.0133
Diuretics	208 (28.6)	122 (37.2)	0.0051
Beta blockers	239 (32.8)	95 (29.0)	NS
Calcium channel blockers	143 (19.6)	117 (35.7)	<.0001
RAS agents	491 (67.4)	243 (74.1)	0.0301
Medications for T2D, n (%)			
Fast-acting insulin	282 (38.7)	128 (39.0)	NS
Long- or intermediate-acting insulin	482 (66.2)	213 (64.9)	NS
Metformin	543 (74.6)	240 (73.2)	NS
Sulfonylureas	192 (26.4)	109 (33.2)	0.0223
Pioglitazone	80 (11.0)	40 (12.2)	NS
DPP-4 inhibitors	61 (8.4)	39 (11.9)	NS
GLP-1 analogs	367 (50.4)	142 (43.3)	0.0322
SGLT2 inhibitors	410 (56.3)	140 (42.7)	<.0001
Tirzepatide	80 (11.0)	30 (9.1)	NS

[a]NS = *P* value > 0.05; [b]*P*-value was based on 2-sample t-test assuming equal variance; [c]BMI = weight(kg)/[height (cm)/100]^2; [d]*P*-value was based on chi-square test.
BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; DDP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NS, not significant; RAS, renin-angiotension-system; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

3 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 SBP ≥135 mm Hg (**Table 1**)
- Factors independently associated with hypercortisolism in the SBP ≥135 mm Hg subgroup (based on multivariate analysis) are shown in **Figure 3** and include: Taking ≥3 BP medications, older age, not Hispanic/Latino ethnicity, use of analgesic medications, use of insulin and SGLT2 inhibitor medications
- 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

Figure 3. Multiple Logistic Regression Model for Hypercortisolism vs No Hypercortisolism in the SBP ≥135 mm Hg Subgroup



	Odds ratio	95% CI	*P*-value
≥3 BP medications (yes vs no)	3.307	1.872, 5.840	<0.0001
Insulin and SGLT2 use (yes vs no)	1.839	1.022, 3.310	0.0421
Analgesics use (yes vs no)	1.972	1.115, 3.486	0.0195
Age (10 year increase)	1.469	1.099, 1.963	0.0094
Ethnicity group: Not Hispanic/Latino vs Hispanic/Latino	2.966	1.283, 6.855	0.0110

BP, blood pressure; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2.

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