CLINICAL RESEARCH STUDY

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Quality of Care Among Patients with Diabetes and Cerebrovascular Disease. Insights from The Diabetes Collaborative Registry

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ABSTRACT

BACKGROUND: Although secondary cardiovascular prevention is a focus among patients with type 2 diabetes (T2D) and coronary artery disease (CAD) or peripheral artery disease (PAD), the application of guideline-recommended therapy in T2D patients and isolated cerebrovascular disease (CeVD) remains unknown.

METHODS: In a US outpatient registry, T2D patients with established cardiovascular disease from 2014-2018 were categorized as: isolated CeVD, CeVD plus CAD or PAD, or isolated CAD/PAD. In each group, we determined the proportion with optimal secondary prevention (hemoglobin [Hb]A_{1C} <8%, blood pressure <130/80 mm Hg, use of antithrombotics, use of statins, non-smoking/cessation counseling, and use of glucose-lowering medications with cardioprotective effects (sodium-glucose cotransporter [SGLT]-2 inhibitors, glucagon-like peptide [GLP]-1 receptor agonists, thiazolidinediones [TZDs]). Hierarchical Poisson regression was used to estimate relative rate of achieving each target across groups, adjusted for age and chronic kidney disease (where relevant).

RESULTS: Our study included 727,467 T2D outpatients with cardiovascular disease (isolated CeVD [n = 99,777], CeVD plus CAD/PAD [n = 158,361], isolated CAD/PAD [n = 469,329]). Compared with isolated CAD/PAD patients, isolated CeVD patients more often had an HbA_{1c} <8% (adjusted relative risk [aRR] 1.10; 95% confidence interval [CI], 1.08-1.11) but less often had a blood pressure of ≤130/80 mm Hg (aRR 0.93; 95% CI, 0.92-0.94) or were prescribed antithrombotics (0.84; 95% CI, 0.83-0.85), statins (0.86; 95% CI, 0.85-0.87), GLP-1 agonists (0.75; 95% CI, 0.73-0.78), SGLT2 inhibitors (0.73; 95% CI, 0.71-0.76), and TZDs (aRR 0.76; 95% CI, 0.73-0.78).

CONCLUSION: Among T2D patients, those with isolated CeVD had the lowest rates of secondary cardiovascular prevention goals attainment. More focus is needed on secondary prevention in patients with CeVD.

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KEYWORDS: Cardiovascular disease; Diabetes; Prevention; Stroke

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INTRODUCTION

Not only do patients with type 2 diabetes have increased risks of coronary artery disease and peripheral artery disease, but they also have at least a twofold increased risk of experiencing a stroke. Further, patients with type 2 diabetes who have a stroke have worse outcomes compared with those without type 2 diabetes.[1] While secondary prevention strategies and the quality of care of patients with type 2 diabetes and concomitant coronary artery disease have been well studied,[2] less is known about the management of patients with type 2 diabetes and cerebrovascular disease (eg, stroke, transient ischemic attack, carotid artery disease). Both sodium glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to improve outcomes in patients with established cardiovascular disease,[3,4] with prior stroke being one component of the composite cardiovascular disease for trial eligibility. Among patients specifically after a stroke, pioglitazone lowered the risk of recurrent stroke, although this trial focused on patients with insulin resistance but without overt type 2 diabetes (hemoglobin A_{1C} [HbA_{1C}] <7%).[5] Due in part to a lack of specific trials of glucose-lowering medications in patients with type 2 diabetes and cerebrovascular disease, the current stroke guidelines seldom mention specific management approaches with regards to type 2 diabetes,[6,7] and type 2 diabetes guidelines generally include cerebrovascular disease with other cardiovascular diseases.

CLINICAL SIGNIFICANCE

- The extent of implementation of guideline-recommended therapy in type 2 diabetes patients and isolated cerebrovascular disease is unknown.
- In a large US outpatient registry of type 2 diabetes patients, those with isolated cerebrovascular disease had lowest rates of secondary cardiovascular prevention goals attainment as compared with patients with cerebrovascular disease plus coronary artery disease or peripheral artery disease, or those with isolated coronary artery disease/peripheral artery disease.

Beyond the limitations in the current guidelines, little is known about the patterns of secondary prevention among patients with type 2 diabetes and cerebrovascular disease and, more specifically, as compared with other forms of cardiovascular disease, such as coronary artery disease or peripheral artery disease—conditions for which there are extensive and clear recommendations. As such, we used a nationwide diabetes registry to better quantify the quality of care of patients with type 2 diabetes and cerebrovascular disease, so as to inform a more integrated management of these 2 conditions.

METHODS

Study Population

The Diabetes Collaborative Registry is a US-based prospective, outpatient, quality-improvement registry of patients with diabetes that includes primary care, endocrinology, and cardiology practices.[8] Patient data were extracted from electronic health records from 2014-2018, with the most recent visit used for analysis. As participation in the registry requires no data collection beyond that of the routine clinical care, a waiver of written informed consent was granted by Chesapeake Research Review Incorporated.

Our study sample was restricted to patients with type 2 diabetes and a diagnosis of cerebrovascular disease (history of stroke, transient ischemic attack, carotid artery intervention), coronary artery disease, or peripheral artery disease. All diagnoses were made at the discretion of the treating health care provider with no adjudication of comorbidities or outcomes. Secondary prevention measures examined included: blood pressure (BP) control <130/80 mm Hg (or BP <140/90 mmHg as a secondary measure, due to changing guidelines on BP targets for individuals with diabetes[9]), HbA_{1c} <8%,[10] non-smoking/cessation counseling (either non-smoking status or provision of cessation counseling), use of antiplatelet (aspirin, clopidogrel, ticagrelor, prasugrel) or anticoagulant (warfarin, any direct oral anticoagulant), use of statin, and use of glucose-lowering medications with cardiovascular risk reduction (SGLT2 inhibitors, GLP-1 receptor agonists, thiazolidinediones [TZDs]).

Statistical Analysis

Patients were categorized into 3 groups: isolated cerebrovascular disease, cerebrovascular disease plus coronary artery disease/peripheral artery disease, and isolated coronary artery disease/peripheral artery disease; with patient characteristics compared using χ^2 tests for categorical variables and one-way analysis of variance for continuous variables. Because attainment of secondary prevention goals was not rare, relative rates for each goal were estimated directly using Poisson regression to avoid overestimation of effect sizes, as would be seen with odds ratios calculated with logistic regression. Isolated coronary artery disease/peripheral artery disease was considered the reference group. Robust variance estimates were used in the models to account for the patient clustering within sites. Models were adjusted only for patient factors that would be expected to appropriately impact treatment choices, as per guideline recommendations. As such, all models were adjusted for age; models for glucose-lowering medications included chronic kidney disease (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 or history of chronic kidney disease, if glomerular filtration rate data unavailable); and the model for TZD also included history of heart failure. Statistical inference testing was 2-sided, with results considered statistically significant at $P < .05$.

Table 1 Characteristics of Study Participants

Characteristics	Isolated Cerebrovascular Disease (n = 99,777)	Cerebrovascular Disease Plus CAD/PAD (n = 158,361)	Isolated CAD/PAD (n = 469,329)	*P* Value
Age (years)	65.5 ± 13.5	71.7 ± 11.0	69.0 ± 11.8	< .001
Female	58,590 (58.7%)	68,818 (43.5%)	197,153 (42.0%)	< .001
Race				< .001
White	63,243 (63.4%)	107,429 (67.8%)	303,379 (64.6%)	
Black	9952 (10.0%)	12,258 (7.7%)	40,705 (8.7%)	
Other	435 (0.4%)	818 (0.5%)	2586 (0.6%)	
Hispanic or Latino ethnicity	7219 (7.2%)	10,148/ (6.4%)	30,541 (6.5%)	
Current tobacco use	26,029 (26.1%)	50,780 (32.1%)	141,473 (30.1%)	< .001
HbA_{1c} (%)	6.8 ± 1.6	7.0 ± 1.6	7.2 ± 1.7	< .001
Body mass index (kg/m^2)	31.2 ± 6.5	30.7 ± 6.2	31.6 ± 6.4	< .001
Systolic blood pressure (mm Hg)	129.9 ± 16.9	129.7 ± 18.1	129.8 ± 17.7	.068
Diastolic blood pressure (mm Hg)	75.8 ± 10.3	72.4 ± 10.6	73.2 ± 10.6	< .001
Estimated GFR (mL/min/1.73 m^2)	71.6 ± 23.6	60.9 ± 23.1	64.0 ± 24.5	< .001
Chronic kidney disease	15,666 (15.7%)	45,040 (28.4%)	100,139 (21.3%)	< .001
Dyslipidemia	74,904 (75.1%)	140,722 (88.9%)	378,747 (80.7%)	< .001
Hypertension	81,424 (81.6%)	148,105 (93.5%)	420,590 (89.6%)	< .001
Heart failure	8083 (8.1%)	43,365 (27.4%)	96,283 (20.5%)	< .001
Atrial fibrillation/flutter	14,072 (14.1%)	42,483 (26.8%)	87,980 (18.7%)	< .001
Specialty of providers				< .001
Cardiology	39,633 (39.7%)	98,500 (62.2%)	247,174 (52.7%)	
Endocrinology	12,324 (12.4%)	8685 (5.5%)	32,543 (6.9%)	
Primary Care	47,820 (47.9%)	51,176 (32.3%)	189,612 (40.4%)	

Data are mean ± standard deviation or n (%).
CAD = coronary artery disease; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; PAD = peripheral arterial disease.

Analyses were performed using the SAS statistical package version 9.4 (SAS Institute, Cary, NC).

RESULTS

Characteristics of Study Sample

Among 1,809,286 patients with type 2 diabetes in the Diabetes Collaborative Registry, 727,647 patients (40.2%) had some form of established cardiovascular disease: 99,777 (5.5%) with isolated cerebrovascular disease, 158,361 (8.8%) with cerebrovascular disease plus coronary artery disease/peripheral artery disease, and 469,329 (25.9%) with isolated coronary artery disease/peripheral artery disease (Table 1). The cases of cerebrovascular disease were mainly ischemic (62.6% [n = 147,637] ischemic vs 37.4% [n = 88,327] hemorrhagic stroke). Mean age of the analytic cohort was 69.1 ± 12.1 years, 44.6% were women, and 65.1% were white. Patients with isolated cerebrovascular disease were more likely to be younger, non-white race, and to have fewer cardiac and non-cardiac comorbidities.

Secondary Cardiovascular Prevention

The proportion of patients meeting the secondary cardiovascular prevention targets are shown in Figure 1. In the Poisson models (reference group: patients with isolated coronary artery disease/peripheral artery disease), patients with isolated cerebrovascular disease were more likely to have an HbA_{1c} <8% (adjusted relative risk [aRR] 1.10; 95% confidence interval [CI], 1.08-1.11) but less likely to have controlled BP ≤130/80 mm Hg (aRR 0.93; 95% CI, 0.92-0.94), to be on an antiplatelet or anticoagulant (aRR 0.84; 95% CI, 0.83-0.84), and to be on a statin (aRR 0.86; 95% CI, 0.85-0.87; Table 2). Furthermore, those with isolated cerebrovascular disease were less likely be prescribed SGLT2 inhibitors (aRR 0.73; 95% CI, 0.71-0.76), GLP-1 receptor agonists (aRR 0.75; 95% CI, 0.73-0.78), and TZDs (aRR 0.76; 95% CI, 0.73-0.78). Patients with both cerebrovascular disease and coronary artery disease or peripheral artery disease were more likely to be on an antiplatelet or anticoagulant (aRR 1.11; 95% CI, 1.10-1.12) and to be on a statin (aRR 1.07; 95% CI, 1.07-1.08), as compared with patients with isolated coronary artery disease/peripheral artery disease, while other measures were similar between the 2 groups (Figure 2 and Table 2). Among patients with isolated cerebrovascular disease, the cardiovascular prevention targets tended to be better among patients under the care of a cardiologist as compared with other specialties such as endocrinology and primary care (Table 3).

DISCUSSION

In a large contemporary cohort of US patients with type 2 diabetes and cardiovascular disease, we found that patients with isolated cerebrovascular disease (vs those with coronary artery disease or peripheral artery disease) were less likely to have controlled BP and were less likely to be on an antiplatelet or anticoagulant, statins, and glucose-lowering medications with cardiovascular risk reduction. The underuse of guideline-recommended secondary preventive therapies was not observed when patients with cerebrovascular disease had concomitant coronary artery disease or peripheral artery disease. Our findings suggest that greater focus is needed to apply appropriate secondary prevention strategies to patients with isolated cerebrovascular disease. To support this effort, we believe there is a pressing need for guideline and position statements to emphasize (and specify) aggressive secondary prevention strategies for

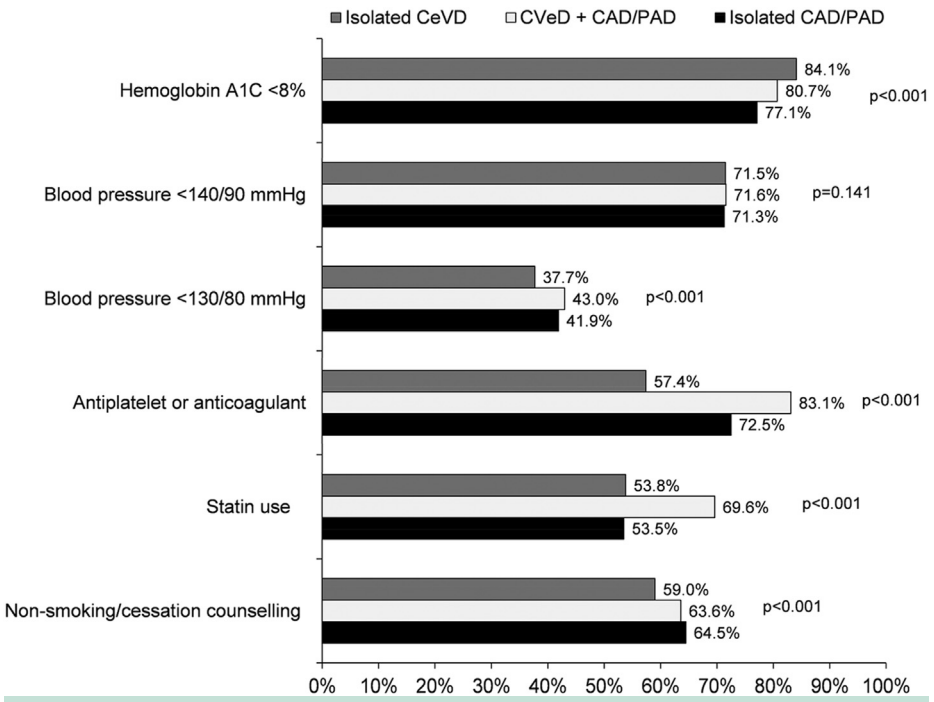

Figure 1 Proportion of patients meeting secondary cardiovascular prevention targets. CAD = coronary artery disease; CeVD = cerebrovascular disease; PAD = peripheral arterial disease.

Table 2 Quality of Cardiovascular Preventive Care Among Patients with Diabetes and Cardiovascular Disease, Compared with Patients with Isolated CAD or PAD

Outcomes	Isolated CeVD Relative Risk (95% CI)	*P* Value	CeVD + CAD or PAD Relative Risk (95% CI)	*P* Value
Secondary general cardiovascular prevention				
Hemoglobin A_{1C} <8%	1.10 (1.08-1.11)	< .001	1.01 (1.00-1.02)	.146
Blood pressure <140/90 mm Hg	0.99 (0.98-1.00)	.005	1.01 (0.99-1.01)	.125
Blood pressure <130/80 mm Hg	0.93 (0.92-0.94)	< .001	1.02 (1.01-1.03)	< .001
Antiplatelet or anticoagulant use	0.84 (0.84-0.85)	< .001	1.10 (1.09-1.10)	< .001
Statin use	0.86 (0.85-0.87)	< .001	1.07 (1.07-1.08)	< .001
Non-smoking/smoking cessation counseling	0.99 (0.98-1.01)	.449	1.04 (1.03-1.05)	< .001
Glucose-lowering medications				
SGLT2 inhibitor	0.73 (0.71-0.76)	< .001	0.98 (0.95-1.00)	.089
GLP-1 receptor agonist	0.75 (0.73-0.78)	< .001	1.01 (0.99-1.04)	.392
Thiazolidinedione	0.76 (0.73-0.78)	< .001	1.04 (1.01-1.06)	.008

CAD = coronary artery disease; CeVD = cerebrovascular disease (stroke, transient ischemic attack, or carotid disease); CI = confidence interval; GLP-1 = glucagon-like peptide-1; PAD = peripheral arterial disease; SGLT2 = sodium-glucose cotransporter-2.

All models adjusted for age. Glucose-lowering medication models also included chronic kidney disease. Thiazolidinedione model also included heart failure.

patients with cerebrovascular disease that mirror those for other types of cardiovascular disease.

Comparison with Prior Studies

While diabetes is known to be a strong risk factor for cerebrovascular disease,[1] studies have seldom examined the quality of preventive care specifically among those with coexisting diabetes and cerebrovascular disease.[11-13] A few studies examined the persistent use of secondary stroke prevention treatments (eg, warfarin, antiplatelet, antihypertensive, lipid-lowering medications) and found that use decreased over the first 2 years after a stroke, particularly for statins and warfarin.[11-13] None of these studies examined use of specific glucose-lowering medications with cardiovascular risk reduction or compared results to other cardiovascular disease states (for which there are more robust and established guidelines for secondary cardiovascular prevention). Our analysis thus provides important complementary information on preventive cardiovascular care in this subpopulation of patients with cerebrovascular disease and concomitant type 2 diabetes.

Clinical Implications

Given the evident morbidity and mortality with type 2 diabetes and concomitant cardiovascular disease, integrated management of these 2 conditions has been increasingly

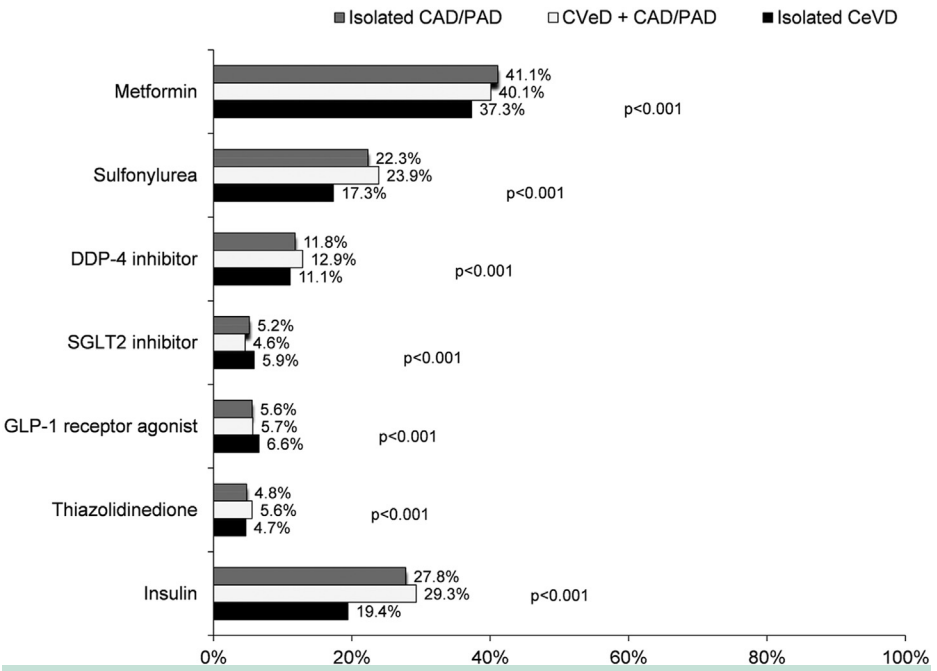

Figure 2 Use of glucose-lowering medications. CAD = coronary artery disease; CeVD = cerebrovascular disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; PAD = peripheral arterial disease; SGLT2 = sodium-glucose cotransporter-2.

Table 3 Cardiovascular Preventive Care Among Patients with Diabetes and Isolated Cerebrovascular Diseases by Specialty of Health Providers

Outcomes	Cardiology (n = 39,633)	Endocrinology (n = 12,324)	Primary Care (n = 47,820)	*P* Value
Secondary general cardiovascular prevention				
Hemoglobin A_{1C} <8%	85.4%	75.0%	87.3%	< .001
Blood pressure <140/90 mm Hg	68.2%	76.8%	72.9%	< .001
Blood pressure <130/80 mm Hg	36.5%	41.6%	37.6%	< .001
Antiplatelet use	15.7%	46.3%	47.4%	< .001
Statin use	57.1%	54.8%	50.8%	< .001
Smoking cessation	49.1%	54.5%	64.2%	< .001
Glucose-lowering medications				
Metformin	39.1%	50.1%	32.6%	< .001
Sulfonylureas	17.7%	26.1%	14.7%	< .001
Thiazolidinediones	4.0%	11.7%	3.4%	< .001
DDP-4 inhibitors	10.7%	21.2%	8.9%	< .001
GLP-1 receptor agonists	4.8%	23.2%	3.8%	< .001
SGLT2 inhibitors	4.4%	18.9%	3.8%	< .001
Insulin use	17.8%	44.8%	14.1%	< .001
Thiazolidinediones	4.0%	11.7%	3.4%	< .001

DDP-4 = dipeptyl peptidase-4; GLP-1 = glucagon-like peptide-1; PAD = peripheral arterial disease; SGLT2 = sodium-glucose cotransporter-2.

emphasized.[2,14] However, these recommendations and guidance have focused primarily on coronary artery disease (and to a lesser extent peripheral artery disease), but stroke guidelines do not specifically address management approaches in the context of type 2 diabetes.[6,7] While cardiovascular outcomes trials showed no significant reduction in the rates of nonfatal or fatal strokes with SGLT2 inhibitors,[15] there does appear to be a reduction in the risk of stroke with GLP-1 receptor agonists.[16] In a recent network meta-analysis, there was a 16% decreased odds of stroke with GLP-1 receptor agonists, most prominently with semaglutide and dulaglutide. However, even more importantly, patients with isolated cerebrovascular disease who were included in all of the recent cardiovascular outcomes trials had similar overall cardiovascular risk reduction compared with other forms of cardiovascular disease.[17] This question may be optimally answered with additional meta-analyses of the extant trial data. Furthermore, in a clinical trial specifically among patients with stroke, pioglitazone reduced the risk of a composite of recurrent stroke and myocardial

infarction.[5] Patients with cerebrovascular disease are at high risk for recurrent stroke as well as other ischemic/vascular events, and so aggressive secondary prevention efforts are imperative after cerebrovascular events. As ~30% of stroke patients have diabetes,[18] there is tremendous opportunity for cross-specialty collaboration between neurologists and endocrinologists, who have not traditionally co-managed patients.[19]

Limitations

Several potential limitations to our study warrant further discussion. First, although the Diabetes Collaborative Registry is the largest diabetes registry in the United States and includes nearly 2 million unique patients, participation is voluntary and thus, our results may not be generalizable to the overall US population of patients with type 2 diabetes. Second, our analysis included data until 2018, which partly explains the low use of SGLT2 inhibitors and GLP-1 receptor agonists. While these medications were clinically available and had clear evidence of cardiovascular benefit, they were not yet as strongly recommended by guidelines and position statements.[20-23] As the uptake of these medications increases in contemporary clinical practice, it will be important to understand whether these discrepancies in use persist. Finally, while adjusting for additional patient factors could potentially explain some of the underlying reasons for discrepancies in use of secondary prevention measures, we only included factors that should impact application of these measures according to guidelines. For example, women may be less likely to be on statins, but they should not be, according to guidelines, and thus we did not adjust for patient sex in the models.

CONCLUSIONS

In a large cohort of US patients with type 2 diabetes and cardiovascular disease, we found that those with isolated cerebrovascular disease were more likely to have suboptimal secondary cardiovascular prevention care, as compared with patients with coronary artery disease or peripheral artery disease. These findings highlight the need to improve care for patients with type 2 diabetes and cardiovascular disease—regardless of the vascular bed affected.

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