GLYCEMIC CONTROL PREDICTS DIABETIC EXTRARENAL MICROVASCULAR COMPLICATIONS BUT NOT RENAL SURVIVAL IN PATIENTS WITH MODERATE TO SEVERE CHRONIC KIDNEY DISEASE

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Background: Control of blood pressure (BP) and blood glucose can slow the development of diabetic nephropathy (DN). However, BP control may be of relatively more importance than glycemic control on the progression of DN.

Objective: To determine the effects of glycemic control on renal survival in a predominately African American diabetic population with moderate-to-severe renal disease.

Design: This was a retrospective chart review of all diabetic patients seen in an academic nephrology clinic in 2001 and 2002 for renal survival and its predictors and micro/macrovascular disease. The weighted mean glycosylated hemoglobin (GHb) over followup was determined. Mean GHb ≤9 was defined as low, and GHb >9 was high. The effect of glycemic control on endpoints was determined by Cox proportional hazards and logistic regression.

Results: One hundred fifty-five diabetic patients (87.7% African American, mean creatinine =2.2 mg/dL) had sufficient GHb measurements. Compared to the high group (n=81), the low group (n=74) was significantly younger, had a shorter duration of diabetes, and worse renal function. No significant association of glycemic control with renal survival (ESRD) was seen. Glycemic control and the presence of DN were significantly related to extrarenal microvascular complications, independent of other factors.

Conclusion: Glycosylated hemoglobin (GHb) is not a significant predictor of renal survival in patients with diabetes and moderate renal disease. However, glycemic control does predict extrarenal microvascular complications in this population. Therefore, good metabolic control remains important in patients with diabetes and renal disease. (*Ethn Dis*. 2006;16:865–871)

Key Words: African American, Chronic Kidney Disease, Diabetes Mellitus, Diabetic Nephropathy, Diabetic Retinopathy, Glycemic Control

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INTRODUCTION

Microvascular complications of diabetes, such as nephropathy, neuropathy, and retinopathy, are common and are the cause of significant morbidity and mortality in patients with diabetes. The relationship between chronic hyperglycemia and the development of these microvascular complications is well established.[1–3] Interventional trials have demonstrated generalized reductions in incident nephropathy, retinopathy, and neuropathy in both type 1 and 2 diabetes.[1,2] In addition, a growing body of evidence now supports an association between chronic hyperglycemia and the macrovascular complications of diabetes.[4,5]

Diabetic nephropathy (DN) is the number one cause of end-stage renal disease (ESRD) in the United States.[6,7] In persons with DN and, at least, moderate reductions in renal function, the benefits of glycemic control on renal survival have not been substantiated.[7,8] In this population, blood pressure (BP) control is a relatively more important determinant of renal survival than glycemic control.[3,7,8] Moreover, the relationship of chronic glycemic control to the progression of DN may not be as strong as the relationship of neuropathy and retinopathy to chronic glycemic control.[9–11] Unfortunately, most studies investigating the relationship between glycemic control and renal disease have not included many ethnic minorities.

In this study we examined the association of glycemic control with renal survival in a predominantly African American cohort of patients with diabetes and renal disease.

Minorities, particularly African Americans, are at high risk for diabetic complications, and these complications are often evident at the time of diagnosis.[12,13] The relationship between glycemic control and renal survival in ethnic minorities remains unclear.[14]

In this study we examined the association of glycemic control with renal survival in a predominantly African American cohort of patients with diabetes and renal disease. We hypothesized that patients with better chronic glycemic control would have superior renal survival. In addition, we examined the relationship of glycemic control to the presence of proliferative diabetic retinopathy and diabetic neuropathy.

METHODS

The study was approved by the Human Investigations Committee at Wayne State University School of Medicine (WSUSOM). We identified pre-ESRD patients who had been seen in the nephrology clinic at WSUSOM over the two-year period from January 1, 2001, to December 31, 2002. Race (by self-identification and/or designa-

tion by treating nephrologist), sex, diabetes status, and primary renal diagnosis (if available) were identified. From this group, the charts of patients with diabetes were reviewed. Patients were designated as having diabetes if a history of the diagnosis was recorded in the chart or if they were on glucose-lowering medications. Patients were designated as type 1 diabetes if they had such designation in their charts and clinical evidence supported this designation: age of onset before age 30 years, dependence on insulin from onset, history of ketoacidosis, and never off insulin for a prolonged period. All others were designated as type 2 diabetes. Data on demographics, BP, renal function, antihypertensive agents, cardiovascular disease, lipids, diabetic medication use, diabetic complications, and glycemic control at the initial visit and over followup were abstracted from clinic and hospital records. Given the predominance of African Americans, we grouped all patients into African American (including all Black races) or non-African American ethnic groups.

Measurements for lipids and glycemic control were not uniformly available, with respect to who had them and when they were measured. All lipid, glycosylated hemoglobin (GHb), and hemoglobin A1C (HbA1C) measurements that were available on patients from six months before first visit throughout followup were recorded. To be included in this analysis, patients needed to have had at least two measurements of GHb that were at least three months apart. Baseline lipid, Ghb, or HbA1C values are the mean of such values performed within 6 months of the first visit. To smooth the effect of clustered measurements, values from more than six months after initial visit were grouped into two-year time periods; the first period was >6 months to two years of follow-up. Averages of values within these time periods were determined, and a weighted mean follow-up value was calculated from among means of the time intervals. In general GHb (reference: 4%–8.1%, determined by HPLC) was the primary measurement performed and reported in our clinical laboratory throughout the period of interest (April 1991–March 2004). Although HbA1C has become the preferred method of expressing chronic glycemic control, it was not always reported over this time period. When reported, it was calculated by the formula: HbA1C=total GHb × (.588) + 1.706 (HbA1C reference 4%–6.5 %). In many cases, HbA1C measurements were available from other laboratories, but HbA1C values vary from laboratory to laboratory. Therefore, GHb was used in analysis. We split the cohort into two groups based on weighted mean GHb: 1) high GHb where GHb >9%, and 2) low GHb where GHb ≤9 %.

In general, providers measured BP with a standard mercury sphygmomanometer, with the patient in the seated position. If BP was checked more than once on any visit, we used the lowest documented measurement for that visit. Blood pressure (BP) over followup is the mean of the single lowest BP taken at each follow-up nephrology clinic visit. Use of renin angiotensin system (RAS) inhibitors at presentation, before presentation, or over follow-up was noted. More than 90% of all patients had macroalbuminuria by standard definitions; therefore, we designated high urine protein excretion as (in order of preference) a 24-hour urine protein of >2000 mg, a urine protein-to-creatinine ratio >2, or a value of 3+ or 4+ protein on urine dipstick. We used the primary renal diagnosis as determined by the treating nephrologist. When no primary renal diagnosis was given, DN was assigned if retinopathy or micro- or macroalbuminuria was present, diabetes had been diagnosed ≥5 years ago, and no other obvious cause of renal disease was seen. Extrarenal microvascular complications are defined as the documented presence of proliferative diabetic retinopathy or diabetic neuropathy. Patients who had amputations of lower extremities because of diabetes were classified as having diabetic neuropathy if that diagnosis had not been given.

We used the abbreviated Modification of Diet in Renal Disease equation to estimate glomerular filtration rate.[15,16] Initiation of renal replacement therapy (ESRD) was the primary endpoint for renal survival. Cardiovascular outcomes included coronary artery disease (unstable angina, myocardial infarction, and asymptomatic occlusive coronary disease), congestive heart failure, and stroke (including transient ischemic attacks).

Statistical Analysis

Data was entered into STATVIEW (SAS, Cary, NC) and analyzed. For renal survival analysis, we used ESRD as the primary endpoint. In subsequent analysis, we used the combined endpoint of ESRD or doubling of serum creatinine as an endpoint. To determine the association of GHb with renal survival, we initially performed Kaplan-Meier analysis. Cox proportional hazards was used to determine the interaction of other variables known to affect renal survival in diabetes with glycemic control. Results are expressed as hazard ratio and 95% confidence interval (CI). In renal survival analysis, data on those not reaching the endpoint were censored at the time of the last clinic visit (duration of follow-\up). The relationship of glycemic control to extrarenal microvascular complications and to cardiovascular events (prevalent and incident) was by logistic regression. Comparison between continuous variables was by unpaired *t* test and between descriptive variables was by chi-square tests. *P* values <.05 were considered statistically significant.

RESULTS

We identified 1127 unique pre-ESRD patients that were seen in the

Table 1. Baseline characteristics of patients by glycosylated hemoglobin (GHb) status

	Mean (standard deviation) or *n*/*N* (%)*		
	Low GHb (*n*=74)	**High GHb (*n*=81)**	***P***
Baseline GHb (%)	7.4 (1.2)	12.0 (3.5)	<.0001
Age (years)	57.7 (1.4)	62.3 (1.5)	.03
Age at diagnosis of diabetes (years)	48.2 (16.8)	40.9 (14.3)	.005
Sex (female)	50 (67.6%)	60 (74.1%)	.38
Ethnicity (African American)	64 (86.5 %)	71 (87.7%)	.99
Duration of diabetes (years)	13.1 (11.4)	16.5 (10.3)	.06
DN as primary renal diagnosis	45 (60.8%)	53 (65.4%)	.62
BMI (kg/m^2)	31.7 (7.9)	33.2 (7.9)	.24
Estimated GFR (mL/min/1.73 m^2)	36.3 (21.0)	47.8 (31.4)	.009
Systolic blood pressure (mm Hg)	154.6 (26.7)	148.6 (25.4)	.16
Diastolic blood pressure (mm Hg)	81.0 (10.8)	79.9 (13.0)	.59
High urine protein	33/67 (49.3%)	29/70 (41.4%)	.39
Number of blood pressure medications	2.64 (1.4)	2.46 (1.7)	.48
Number on RAS inhibitors	32/49 (65.3%)	39/65 (60%)	.70
Number on insulin	29 (40.8%)	48 (59.3%)	.03
Dyslipidemia	30/65 (46.2%)	51/79 (64.6%)	.03
Cardiovascular disease	38/73 (52.1%)	38/81 (46.9%)	.63
Extrarenal microvascular complications	21/74 (28.4%)	40/81 (49.4%)	.009
Any retinopathy	36/74 (48.6%)	50/81 (61.7%)	.11
Proliferative retinopathy	18/74 (24.3%)	26/81 (32.1%)	.29
Peripheral neuropathy	9/61 (14.8%)	28/72 (38.9%)	.002
Diabetes-related amputations	4/70 (5.7%)	6/81 (7.4%)	.75

* In some cases the *n* for a variable is not equal to the total *N*.

DN=diabetic nephropathy; BMI=body mass index; GFR=glomerular filtration rate; RAS=renin-angiotensin system.

two-year period, and 395 (35.1%) had diabetes. Race was determined on 1063 patients of which 83.1% were African American. Diabetes was more common among females (38.8 % vs 29.9 % in males, P=.002) and tended to be more common among African Americans. A total of 387 charts were available for review from the patients with diabetes, and 155 met inclusion criteria for this analysis. The baseline characteristics for the patients in this study are shown in Table 1 according to GHb group. Patients in the high group (n=81) were older and tended to have had diabetes longer. In addition, the high group was more likely to be on insulin and to have dyslipidemia and extrarenal microvascular complications. Baseline renal function was better in the high group, but no differences were seen in baseline levels of BP, lipids (not shown), or use of specific BP-lowering or glucose-lowering medications other than insulin.

Eighteen patients from the low group and 11 patients from the high group reached ESRD. A total of 28 and 21 patients from the low and high group, respectively, reached the combined endpoint of ESRD or doubling of serum creatinine (P not significant). No significant difference in renal survival was seen with either endpoint. Cumulative renal survival (with ESRD as endpoint) was virtually identical by Kaplan-Meier analysis at 40 months of followup (high: 78.2 % vs low: 76.4%, P=.65). Likewise, when adjusted for initial renal function, no significant association was seen between glycemic control and renal survival on Cox proportional hazards analysis (hazard ratio for ESRD [high vs low group] .70, CI .32–1.6, P=.4). Moreover, the continuous variable of weighted mean GHb was not significantly associated with renal survival in univariate or adjusted Cox proportional hazards analysis.

During followup, no significant change in GHb was seen in either group. No significant differences were seen in BP, incident cardiovascular events, or incident extrarenal microvascular complications between groups over followup (Table 2). No significant difference was seen in total prevalence of cardiovascular disease at the end of followup; however, the total prevalence of extrarenal microvascular complications at the end of followup was significantly increased in the high-GHb group. Factors that were significant predictors of having extrarenal microvascular complications by the end of the follow-up period in a univariate logistic regression analysis are shown in Table 3. Patients who had DN as their primary renal diagnosis, a higher GHb (as nominal or continuous variable), a longer duration of diabetes, a higher systolic BP over followup, and a greater decrement in estimated GFR over followup were more likely to have extrarenal microvascular complications. The use of insulin and sulfonylureas was associated with extrarenal microvascular complications, but these relationships were no longer significant when duration of diabetes and/or GHb was considered. The relationship between GHb and the prevalence of extrarenal microvascular complications remained significant after adjustment for several factors (Table 3). The presence of DN as a primary renal diagnosis was the strongest predictor of extrarenal microvascular complications and remained independently associated with this outcome in all multivariate models (Table 3). No significant association of GHb to cardiovascular disease was seen by logistic regression (not shown). Baseline GHb was significantly associated with the presence of DN as a primary renal diagnosis (hazards ratio 1.15 [per 1% GHb], CI 1.01–1.32, P=.034). However, when adjusted for age, sex, and/or ethnicity, this relationship was no longer significant.

Table 2. Incident and total prevalence of cardiovascular and extrarenal microvascular complications

	Mean (SD) or *n* (%)		
	Low GHb (*n*=74)	High GHb (*n*=81)	*P*
Weighted mean GHb	7.4 (1.1)	12.0 (3.1)	<.0001
Systolic BP over followup	151.5 (18.9)	146.9 (19.9)	.15
Diastolic BP over followup	78.1 (8.6)	79.8 (10.0)	.25
No. of patients with new cardiovascular events*	14 (18.9%)	23 (28.4%)	.19
No. of patients with new ERMC events†	6 (8.1%)	13 (16.0%)	.15
Total prevalence of CVD at end of followup	40 (54.1%)	44 (54.3%)	.19
Total prevalence of ERMC at end of followup	26 (35.1%)	44 (54.3%)	.0234
Follow-up time (months)	25.3 (23.9)	27.7 (25.5)	.53

* Actual number of new CVD events: low group: CAD=7, CHF=8, CVA=2; high group: CAD=15, CHF=13, CVA=5 (differences between groups not significant).

† Actual number of new ERMCs events: low group: neuropathy =3, proliferative retinopathy =1, diabetic related amputation =2; high group: neuropathy =6; proliferative retinopathy =4; diabetic related amputation =4 (differences between groups not significant).

GHb=glycosylated hemoglobin; SD=standard deviation; BP=blood pressure; ERMC=extrarenal microvascular complications; CVD=cardiovascular disease; CAD=coronary artery disease; CHF=congestive heart failure; CVA=cardiovascular accident.

Table 3. Association of factors with ERMCs*

Characteristic	Odds Ratio (CI)	*P*
Unadjusted logistic regression for likelihood of having ERMC at end of study		
GHb <9 % (low GHb)	.46 (.24 – .87)	.017
Weighted mean GHb (per 1%)	1.11 (1.11 – 1.23)	.047
Duration of diabetes (per year)	1.06 (1.03 – 1.08)	<.0001
Absence of diabetic nephropathy as primary renal diagnosis	.15 (.05 – .45)	<.0001
Low urine protein excretion (<2 g/24 hour)	.55 (.35 – .88)	.012
Absence of history of hypertension on presentation	.30 (.12 – .77)	.012
Absence of cardiovascular disease at end of study	.68 (.44 – 1.05)	.08
Average systolic BP over followup	1.01 (1.00 – 1.02)	.007
Change in eGFR over followup†	.98 (.97 – 1.00)	.038
Absence of doubling of creatinine	.52 (.32 – .86)	.011
Never used insulin	.38 (.25 – .60)	<.0001
Never used RAS Inhibitors	.62 (.36 – 1.06)	.079
Model 1: adjusted for age, sex, ethnicity, eGFR		
GHb <9 (low GHb)	.43 (.22 – .85)	.015
Weighted mean GHb	1.12 (1.00 – 1.26)	.042
Absence of DN as primary renal diagnosis	.30 (.18 – .49)	<0.0001
Model 2: entered age, sex, ethnicity, duration of diabetes, systolic BP over followup, GHb category, and DN as renal diagnosis		
GHb <9 (low GHb)	.47 (.22 – .99)	.047
Absence of DN as primary renal diagnosis	.41 (.18 – .93)	.034
Model 3: variables from Model 2 plus change in eGFR		
GHb <9 (low GHb)	.45 (.21 – .99)	.047
Absence of DN as primary renal diagnosis	.39 (.16 – .91)	.029

* By logistic regression with only factors with $P<.1$ shown.

† Loss of renal function is expressed as negative number.

GHb= glycosylated hemoglobin; BP=blood pressure; RAS=renin angiotensin inhibitor; eGFR=estimated glomerular filtration rate; DN=diabetic nephropathy.

While evidence is growing that cardiovascular complications are now linked to levels of glycemic control,[4,5] we did not find an association with cardiovascular outcomes in this study.

DISCUSSION

In patients with diabetes and established kidney disease, BP control is considered to be a relatively more important predictor of renal survival than glycemic control.[8] In this study, we sought to examine the relationship between glycemic control and renal survival in a predominantly African American population with moderate-to-severe reductions in renal function. We found no significant association between chronic glycemic control as measured by GHb and renal survival. However, we did observe a significant association between chronic glycemic control and the presence of extrarenal microvascular complications. Moreover, the presence of DN was associated with a higher likelihood of having extrarenal microvascular complications. Our study shows that attempts to achieve glycemic control should be continued in those patients with moderate-to-severe renal disease as they may have significant complications from retinopathy, neuropathy, and amputations. While evidence is growing that cardiovascular complications are now linked to levels of glycemic control,[4,5] we did not find an association with cardiovascular outcomes in this study.

The realization that chronic hyperglycemia is directly related to microvascular diabetes complications was firmly established in the Diabetes Complications Control Trial (DCCT).[1] This

study of type 1 diabetes examined the effects of tight glycemic control, defined as target HbA1C <7%, versus conventional glycemic control on progression of established retinopathy, development of new retinopathy, development of peripheral neuropathy, and development of albuminuria. The study showed that maintaining a lower HbA1C decreased the incidence of microvascular complications of diabetes. However, data from that trial revealed a glycemic threshold for kidney protection that might have been higher than that for retinopathy and nephropathy.[9,17] The United Kingdom Prospective Diabetes Study (UKPDS) corroborated the results of the DCCT in patients with type 2 diabetes,[2] and other studies have supported a relationship between glycemic control and albuminuria/proteinuria in this population.[3,13,18]

Data from the National Health and Nutrition Examination Survey (NHANES) demonstrated that renal disease in patients with diabetes is heterogeneous.[19] In fact, classic DN is often not the primary cause of kidney disease in adults with diabetes, yet all adults with type 2 diabetes are at high risk for deteriorations in renal function. Our cohort demonstrates this heterogeneity of renal disease among patients with diabetes, since only 63% of our patients had DN as their primary renal diagnosis. The fact that almost 40% of our cohort did not have DN as their primary renal disease may be one reason why GHb was not a predictor of renal survival. To date, most studies that have examined the relationship of glycemic control to renal outcomes in patients with diabetes have been limited to those with established DN or only looked at development of nephropathy.

Our study also supports findings that show an association between DN and the other microvascular complications of diabetes.[20,21] Those patients in our study with DN were three times more likely to have extrarenal microvascular complications of diabetes than patients without DN. Why the microvascular complications of diabetes cluster is not fully understood, but genetic factors may be involved. For example, patients who have diabetes and a first-degree relative who has nephropathy or retinopathy are more likely to develop these complications.[7,12] A specific gene or group of genes that may be responsible for this increased susceptibility of diabetic complications has yet to be identified.

In type 1 diabetes, a threshold for glycemic control and development and progression of DN appears to exist. The group at the Joslin Diabetes Center examined levels of albuminuria in more than 1600 type 1 diabetic patients.[17] They measured GHb up to four years before urine testing and correlated prevalence of microalbuminuria (a marker of early DN) with GHb. They observed that risk for microalbuminuria increased very little as GHb increased, until a GHb of 10.1% was reached. At GHb >10.1%, the prevalence of microalbuminuria rose abruptly. Later they examined the relationship between chronic glycemic control and the progression of microalbuminuria to overt proteinuria in type 1 diabetes. In this analysis, they used HbA1C rather than GHb. They discovered that the risk for progression to overt proteinuria rose sharply between HbA1C values of 7.5% and 8.5% but changed little at values above or below this range.[9] Using the equations in their paper, a HbA1C of 7.5% to 8.5% is equivalent to a GHb 9.4% to 10.6%. Data from both the DCCT and the UKPDS showed that in patients with microalbuminuria, intensive control of blood sugar had no effect on progression or DN.[10,11] In those studies, the benefit of intensive therapy may not have been apparent because the threshold for benefit (HbA1C <7.5% or GHb <9.4%) was not consistently achieved.

We used a level of GHb of 9% to separate high- and low-GHb groups. The data in type 1 DN support use of this value for defining groups with potential renal benefits for glycemic control. Unfortunately, little or no data have examined the relationship between glycemic control to changes in estimated glomerular filtration rate in patients with diabetes. In the studies mentioned above, progression of DN was defined as worsening of albuminuria and not loss of glomerular filtration rate. Our study is unique in that it examines the relationship between renal survival and glycemic control in patients with significant reduction in estimated glomerular filtration rate. Clearly, glycemic control appears to be important in the development of DN and extrarenal microvascular complications in types 1 and 2 diabetes.[1,2,9,12,22] In those with early DN, glycemic control is predictive of progression to overt albuminuria/proteinuria – an established, independent risk factor for disease progression. Therefore, we can hypothesize that glycemic control is a determinant of renal survival.

While glycemic control may or may not be a predictor of loss of renal survival in patients with diabetes and significant reductions in estimated glomerular filtration rate, BP definitely is such a predictor.[7,8] We have also observed systolic BP to be a predictor of renal survival in the larger cohort used for this study.[23] Moreover, we observed an association of systolic BP with extrarenal microvascular complications in this study, which supports other observations linking retinopathy to BP.[12,24] Data from the followup to the DCCT, Epidemiology of Diabetes Intervention and Complications (EDIC), show long-term beneficial effects on intensive glycemic control on BP and development and progression of nephropathy.[25] Significantly fewer patients in the intensively treated group developed hypertension or reached a serum creatinine of 2 mg/dL, which suggests that glycemic control may help preserve estimated glomerular filtration rate. No significant differences in glycemic control were seen between the two groups during the EDIC study, which indicates that early and aggressive

therapy for glycemic control may have long-term benefits, even in the absence of sustained reductions in HbA1C. The effects on incident hypertension provide additional support for tight glycemic control in the type 1 diabetic patient with early or no nephropathy. However, as of yet a relationship between chronic glycemic control and development of new hypertension in type 2 diabetes has not been clearly established.

Our paper has several limitations. It has a relatively small sample size, is retrospective, and relies upon clinically derived data that had not been obtained by standard protocols. In addition, cardiovascular and extrarenal microvascular complications were identified through the patient's history and/or physicians' reports. In many cases, patients were not formally evaluated for retinopathy or neuropathy, and formal evaluations for nonclinical cardiovascular disease were not performed. Therefore many events may have been missed in the study population. If these subclinical complications had been diagnosed, the association between glycemic control and incident diabetic complications may have been stronger. To account for the lack of protocol-guided measurement of GHb we have developed a weighted mean GHb over followup so that the impact of values obtained within a short period of time is minimized. In addition, the use of ESRD as an endpoint for renal survival adds strength and overcomes some of the complicating issues when defining renal survival as changes in estimated glomerular filtration rate.

In summary, in a predominantly African American cohort with diabetes and moderate-to-severe reductions in renal function, we found that GHb is not an independent predictor of renal survival. However, in this group of patients, improved glycemic control lowers the likelihood of having proliferative diabetic retinopathy or diabetic neuropathy. Therefore, we believe glucose levels should be aggressively managed in patients with diabetes and moderate renal disease. While BP control may be a relatively more important factor for renal survival in this population, quality of life remains highly dependent upon chronic glycemic control, as it may lower incidence of visual deficits, diabetic foot infections, and amputations.

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AUTHOR CONTRIBUTIONS

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