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Association between extended-release niacin treatment and glycemic control in patients with type 2 diabetes mellitus: analysis of an administrative-claims database

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ABSTRACT

The aim of the study was to evaluate trends in antihyperglycemic agents (AHAs) use in patients with type 2 diabetes mellitus (T2DM) newly initiating extended-release niacin (ERN) compared with other lipid-modifying therapy (LMT). United States administrative-claims data identified adults with T2DM on AHAs who received a new prescription for ERN or another LMT between January 2001 and June 2003 (index date), and these adults were followed for 12 months. Inclusion criteria were (1) stable T2DM as defined by *International Classification of Diseases, Ninth Revision,* codes and also receiving at least 2 AHA prescriptions 12 to 24 months before initiating ERN or LMT treatment and (2) at least 2 prescriptions within 12 months before the onset of ERN or LMT. Trends in AHA prescriptions 12 months before (baseline) and after (follow-up) index date were defined as (1) no change (ie, stable T2DM), (2) increased (ie, worsening T2DM), or (3) reduced (ie, improved T2DM). Among 3799 patients with T2DM, 392 (10.3%) were treated with ERN and 3407 (89.7%) were treated with other LMT. In the ERN cohort, 82.1% of patients experienced no change in AHA prescriptions between baseline and follow-up compared with 79.4% of patients in the LMT cohort ($P = .20$); 13% of the ERN cohort and 16% of the LMT cohort ($P = .17$) experienced a dose increase or the addition of another AHA; and 5% of both cohorts were prescribed fewer AHAs or switched to a lower dose ($P = .92$). Treatment with ERN (vs other types of LMT) did not significantly increase AHA use, implying that T2DM status did not worsen in this cohort.

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1. Introduction

Elevated low-density lipoprotein (LDL) cholesterol remains the principal treatment target in patients with cardiovascular disease or increased risk [1,2]. As the prevalences of type 2 diabetes mellitus (T2DM) and other insulin-resistant syndromes have increased [3], so has appreciation of these conditions as contributors to the development of cardiovascular disease [4] and the need to address other lipid abnormalities [5,6].

In this context, niacin (nicotinic acid) is the most effective lipid-modifying therapy (LMT) available for raising high-density lipoprotein cholesterol [7]. Niacin also (1) confers potentially beneficial effects on total cholesterol, LDL cholesterol, triglycerides, and large buoyant high-density lipoprotein cholesterol; (2) reduces small, dense LDL; and (3) is the only available therapy that lowers lipoprotein(a) [8]. Treatment with niacin-containing regimens has been associated with beneficial effects on inflammation, endothelial function, and indices of atherosclerotic progression [9]. Niacin therapy has

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also been associated with decreases in mortality and morbidity on long-term follow-up in patients with coronary heart disease (CHD) [10]. In general, increases in fasting glucose and hemoglobin A_{1c} (HbA_{1c}) with niacin treatment have been minor [11]; however, such treatment can reduce insulin sensitivity and elicit potentially significant glucose excursions in patients with T2DM [12,13].

The present study evaluated trends in the use of antihyperglycemic agents (AHAs) among patients with T2DM newly initiating extended-release niacin (ERN) therapy (vs other LMT).

2. Methods

2.1. Data source

This study used data from the proprietary (i3 Global, Cary, NC; www.i3global.com) Ingenix LabRx Database, which is an automated US health care administrative-claims database capturing anonymized (deidentified) information. The database is composed of approximately 32 million prescriptions in 14 million patients. This database includes laboratory data that allow for comparisons between claims-based, prescription data, and laboratory-based definitions of diseases. These prescriptions encompass paid-facility, professional-service, and retail (ie, outpatient) pharmacy claims for the commercially insured, Medicaid, and Medicare populations. The Ingenix I3 database is representative of the US population. [14-16].

2.2. Data extraction

A retrospective database analysis was performed on patients at least 20 years old who were continuously enrolled for at least 36 months in the I3 database with a diagnosis of T2DM (*International Classification of Diseases, Ninth Revision* [*ICD-9*]) and who were on active treatments with AHAs. Patients had to receive their first prescriptions for ERN or another LMT (statins, fibrates, resins, ezetimibe) on a date (index date) from January 1, 2001, to June 30, 2003. The index date indicated the onset of treatment with ERN (alone or in combination with other LMT) or indicated the use of another LMT besides ERN. For patients on ERN therapy, the average daily dose at index date was calculated by multiplying the dose prescribed by the quantity dispensed then dividing this total by the duration (days) of use ([formulation*quantity]/duration). Eligible patients were followed for 12 months after initiating ERN or another LMT. Patient characteristics, including age, sex, and diabetes-related resource utilization, were summarized and compared for all patients on ERN vs other LMT. Measures of resource utilization included hospitalizations, emergency department visits, and physician visits 1 year before the baseline period.

Identification of the 2 cohorts (ERN and other LMT) required a 2-step process to verify T2DM diagnosis and active treatment with AHAs before initiation of ERN or another LMT. The first step occurred in the prebaseline period (12-24 months before the index date); patients had to have been diagnosed with stable T2DM, as defined by *ICD-9* codes (250.00, 250.02, 2501.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, and 250.92.), and received at least 2 prescriptions for AHAs (metformin, sulfonylureas, thiazolidinediones, insulin, and other). In the second step known as the *baseline period* (12 months before index date), all patients with T2DM were required to have been prescribed at least 2 prescriptions for AHAs (Fig. 1`). Only patients with stable use of AHA prescriptions during the baseline period were included in the analyses. As such, 19 patients in the ERN and 204 patients in the LMT groups were excluded because of increases in the daily dose of their AHA prescriptions at baseline.

Changes in diabetes status were inferred from trends in AHA prescriptions filled between the baseline (12 months before index date) and follow-up periods (12 months after index date). Outcomes comprised one of the following: (1) no change in AHA prescriptions, which was taken as a proxy for stable diabetes status; (2) increase in AHA prescriptions, which was captured as (*a*) a higher daily dose of the initial AHA, (*b*) addition of another AHA, or (*c*) progression to insulin (including addition or switch) and which was taken as proxy for worsened diabetes status; and (3) decrease in AHA prescriptions, which was taken as a proxy for improved diabetes status. Patients who were taking multiple AHAs (>1) during the baseline period and who switched to only one AHA prescription, but increased the daily dose at follow-up (n = 3 on ERN, n = 34 on other LMT), were also excluded because there was no reliable means of categorizing diabetes status.

2.3. Statistical analysis

χ^2 and Fisher exact tests were used to compare proportions of patients with each possible change (no change, increased, decreased) in AHA treatment. Multivariate analyses, using multivariate logistic regression, examined the association between type of LMT (ERN vs other LMT) and an increase in AHA prescriptions, controlling for age, sex, insulin use, and prior diabetes-related hospitalizations, emergency department visits, and physician visits 1 year before the baseline period. Measures of prior diabetes-related resource use were used as a proxy for disease severity. All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC), with significance defined at a 2-tailed $\alpha = .05$.

Fig. 1 – Schematic of study design.

3. Results

A total of 3799 patients with stable T2DM receiving ERN or another LMT from 2001 through 2003 met the eligibility criteria. Of these, 392 (10.3%) received prescriptions for ERN and 3407 (89.7%) received other forms of LMT (Fig. 2). Among patients taking ERN, the majority were on a 0- to 500-mg dose (69.1%) at the index date, 25.8% reached a 501- to 1000-mg dose, whereas a small minority were on greater than 1000 mg (5.1%). Patients on ERN tended to be older compared with patients on other LMT (56.5 ± 8.8 vs 55.2 ± 10.0 years, $P = .006$), and significantly more were men (74% vs 59%, $P < .0001$) (Table 1). Patients on ERN were also associated with a significantly higher number of hospitalizations and physician visits 1 year before the baseline period as compared with patients on other LMT ($P = .01$); on the other hand, emergency department visits were similar.

Most patients experienced no changes from baseline in AHA prescriptions in either the ERN cohort (82.1%) or the other LMT group cohort (79.4%, $P = .20$) during the 1-year follow-up. Approximately 13% of the ERN patients vs 16% of other LMT patients ($P = .17$) experienced a dose increase in their current AHA regimens, an addition of another AHA, or progression to insulin. An equal proportion (~5%) of patients in both groups ($P = .92$) received fewer AHAs or switched to lower doses of their current AHAs (Table 2). In summary, there were no significant differences in T2DM status among the ERN and the other LMT cohorts as measured through change in AHA prescriptions, dose change, or progression to insulin (Table 2).

Results of multivariate analyses further revealed that ERN therapy, as compared with other LMT, was not significantly associated with an increase in AHA prescriptions, holding other factors constant ($P = .17$, Table 3). In contrast, the number of diabetes-related hospitalizations 1 year before the baseline period was significantly associated with an approximately 21% increase in the odds of having an increase in AHA prescriptions (odds ratio, 1.21; $P = .021$). Increased age was associated with a modest 2% decrease in the likelihood of having an increase in AHA prescriptions ($P = .0001$), whereas all other factors did not show a significant association.

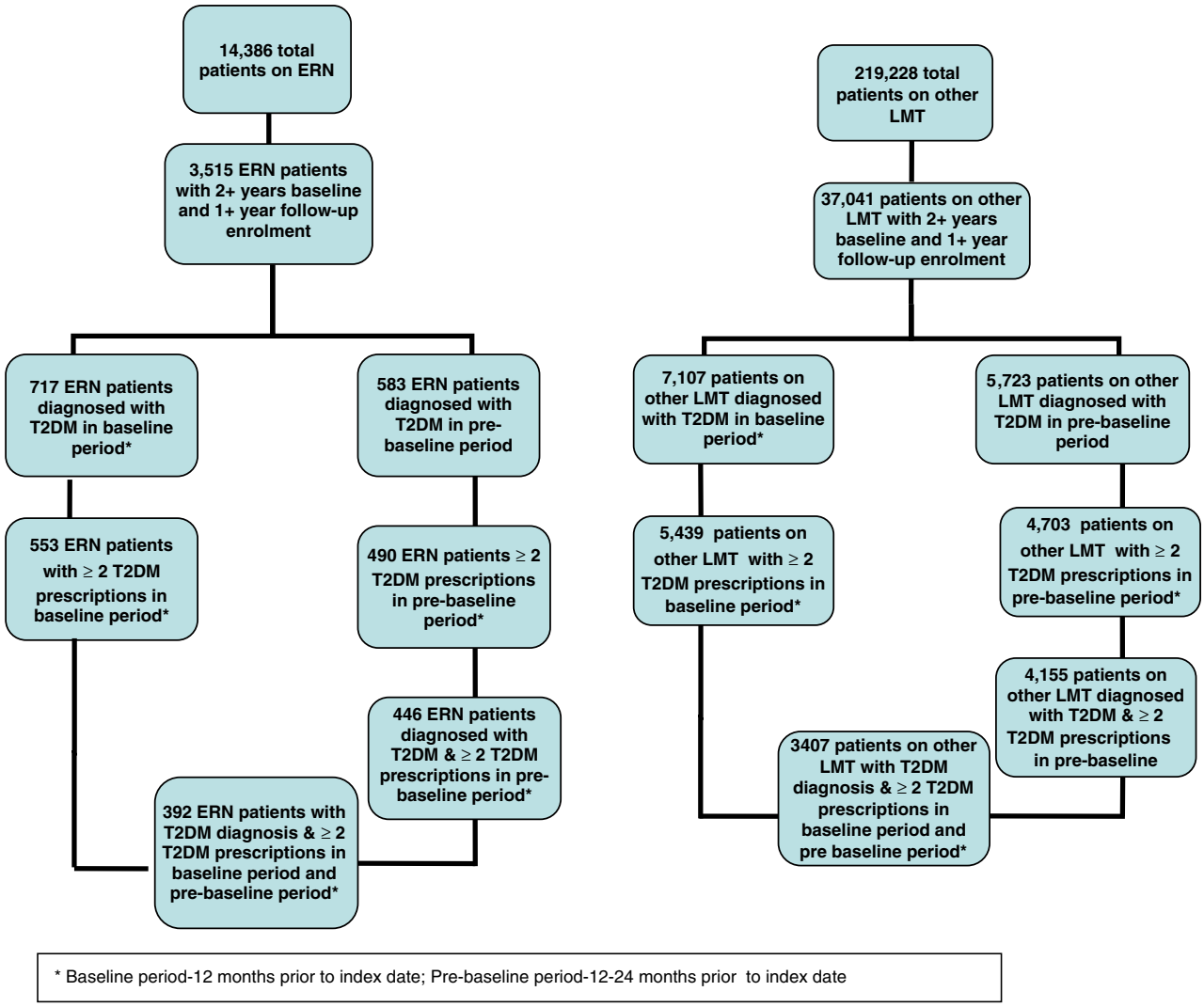

Fig. 2 – Sample selection: ERN vs other LMT.

4. Discussion

Within a few years after a 1955 publication on niacin [7], anecdotal reports surfaced regarding erosion in glycemic regulation following niacin treatment (often at high doses) in patients having dyslipidemia with [17] or without [18] T2DM. The mechanism for these effects may involve a rebound rise in free fatty acids with or without changes in β-cell insulin secretory responses [12,13,19]. In a clinical trial involving 7 healthy subjects studied with the hyperinsulinemic-euglycemic clamp method, there was a moderate (18%) decline in short-term insulin sensitivity without fasting hyperinsulinemia after treatment with low-dose immediate-release niacin for up to 7 days [20]. In a meta-analysis by Birjmohun et al [21], patients receiving niacin were significantly more likely than those without such treatment to experience hyperglycemia (2.3% vs 0.4, relative risk = 3.04, 95% confidence interval = 1.28-7.21, $P = .01$).

Table 1 – Comparison of characteristics of patients treated with ERN compared with other LMTs

Characteristics	ERN (n = 392)		Other LMTs (n = 3407)		P value
	n	%	n	%	
Daily dose of ERN (mg)					
0-500	271	69.1			
501-1000	101	25.8			
>1000	20	5.1			
Type of other LMT					
Statin [a]			2457	72.1	
Ezetimibe			33	1.0	
Resins (bile acid)			230	6.8	
Fibrates			687	20.2	
Sex					
Male	290	74.0	2,030	59.6	<.0001
Female	102	26.0	1,377	40.4	
Age at index date					
20-34	3	0.8	73	2.1	.030
35-54	157	40.1	1,507	44.2	
55-74	222	56.6	1,703	50.0	
75+	10	2.6	124	3.6	
Mean age (SD)	56.5	(8.83)	55.2	(10.0)	.0062
No. of prior emergency visits [c]					
0	370	94.4	3,187	93.5	.34 [b]
1-2	21	5.4	208	6.1	
≥3	1	0.3	13	0.3	
No. of prior hospitalizations [c]					
0	327	83.4	2,912	85.5	.012
1-2	55	14.1	453	13.3	
≥3	10	2.6	42	1.2	
No. of prior physician visits [c]					
0	313	79.8	2,829	83.0	.010
1-2	71	18.1	558	16.3	
≥ 3	8	2.0	20	0.7	
AHA therapy at baseline					
Single AHA	99	25.3	899	26.4	
Metformin	53	53.6	447	49.7	
Sulfonylureas	32	32.3	360	40.0	
Thiazolidinedione	9	9.1	85	9.5	
Other	5	5.0	7	0.8	
Multiple AHAs (>1)	186	47.4	1536	45.1	
AHAs = 2	121	65.1	965	62.8	
Metformin/sulfonylureas	54	44.6	507	52.5	
Metformin/thiazolidinedione	23	19.0	213	22.1	
Sulfonylureas/thiazolidinedione	31	25.6	190	19.7	
Other	13	10.7	55	5.6	
AHAs = 3	55	29.6	478	31.1	
Metformin/sulfonylureas/thiazolidinedione	35	63.6	353	73.8	
Other	20	36.4	125	26.2	
AHAs ≥4	10	5.3	93	6.1	
Insulin use	107	27.3	972	28.5	

[a] Includes statin monotherapy and combination therapy with other LMTs, excluding ERN.
[b] Fisher exact test.
[c] Diabetes-related resource use 1 year before baseline period.

Table 2 – Changes in prescriptions for AHAs from baseline to 1-year follow-up

Distribution of outcomes at 1-y follow-up by baseline outcomes	ERN (n = 392)		Other LMT (n = 3407)		P value
	n	%	n	%	
Single AHA (=1) at baseline (no dose changes at baseline)	99		899		
Reduced: no AHA used in 1-y follow-up	1	1.0	20	2.2	.71[a]
No change: AHA = 1 without dose change at 1-y follow-up	64	64.6	511	56.8	.14
Increased: AHA = 1 with dose increase at 1-y follow-up	7	7.1	101	11.2	.21
Increased: AHA >1 at 1-y follow-up	25	25.3	234	26.0	.87
Increased: insulin addition or replacement at 1-y follow-up	2	2.0	33	3.7	.57[a]
Multiple AHAs (>1) at baseline	186		1536		
Reduced: no AHA used in 1-y follow-up period	0	0.0	7	0.4	1.00[a]
Reduced: AHA = 1 without dose change at 1-y follow-up	15	7.9	103	6.6	.49
No change: same multiple AHAs (>1) at 1-y follow-up	154	81.5	1,261	80.3	.81
Increased: insulin addition or replacement at 1-y follow-up	17	9.0	165	10.5	.50
Insulin only at baseline	107		972		
Reduced: no AHA or insulin used in 1-y follow-up	0	0.0	8	0.8	1.00[a]
Reduced: AHA = 1 without dose change at 1-y follow-up	2	1.9	9	0.9	.30[a]
Reduced: AHA = 1 with dose increase at 1-y follow up	1	0.9	1	0.1	.19[a]
Reduced: AHA >1 at 1-y follow-up	0	0.0	21	2.2	.26[a]
No change: Insulin use at 1-y follow-up	104	97.2	933	96.0	.79[a]
Summary of results					
Reduced (improved)	19	4.8	169	5.0	.92
No change (remained stable)	322	82.1	2705	79.4	.20
Increased (worsened)	51	13.0	533	15.6	.17

[a] Statistical differences were measured using Fisher Exact test. In all other instances, χ^2 tests were used.

Our findings suggest no adverse consequences of ERN (vs other forms of LMT) on glycemic control as assessed by changes in prescribed T2DM regimens. Consistent with these findings, a recent review of the literature suggested that (1) changes in fasting glucose and HbA_{1c} with niacin treatment (≤3.0 g/d) tend to be modest (+4% to +5%), transient, and reversible; (2) these changes are infrequently caused by niacin treatment discontinuation and are typically amenable to alterations in AHA regimens; (3) niacin treatment infrequently causes incident T2DM in individuals initially free of this condition; and, importantly, (4) cardioprotective benefits of long-term niacin offset any short-term changes in glucose control. Patients on niacin with CHD in the Coronary Drug Project experienced significant decreases in myocardial infarction, CHD-specific death, and/or all-cause mortality irrespective of baseline fasting glucose levels or number of components of metabolic syndrome [11].

4.1. *Potential study limitations*

Our study cannot rule out potential sources of bias, including the inherently limited patient-level data in an administrative-claims database. For example, the significantly higher mean age of the ERN vs the other LMT cohort and higher incidence of prior hospitalizations and physician visits may be a surrogate for more advanced T2DM and/or more frequent cardiovascular disease, treatment of which can alter glucose control [22-27]. Interestingly, our analyses also identified a higher percentage of male patients in the ERN vs the other LMT cohort. Prior studies of ERN utilization patterns using administrative claims data have also identified a high proportion of male vs female patients on ERN therapy [28-30], whereas an additional study noted that this proportion was higher among ERN users as compared with those on other LMT [30]. Although there is no prevailing theory to explain this observation, results of the

Table 3 – Multivariate analyses of factors associated with increased use of AHA prescriptions from baseline to 1-year follow-up (N = 3799)

Patient characteristic	Odds ratio	95% Confidence interval	P value
ERN therapy (vs other LMT)	0.80	(0.58-1.10)	.17
Age	0.98	(0.97-0.99)	.0001
Sex (male)	1.01	(0.84-1.23)	.90
Insulin use	1.00	(0.92-1.17)	.94
No. of hospitalizations[a]	1.21	(1.03-1.43)	.021
No. of emergency department visits[a]	1.06	(0.82-1.37)	.68
No. of physician visits[a]	0.82	(0.66-1.02)	.08

[a] Diabetes-related resource use 1 year before baseline period.

multivariate analyses conducted in this study suggest that male sex is not significantly associated with increases in AHA prescriptions ($P = .90$). Therefore, there is little evidence suggesting that the higher incidence of male patients in the ERN group would confound comparisons of changes in AHA prescriptions between the 2 treatment groups.

In addition, our definitions of glycemic status according to changes in AHA prescriptions were indirect. More direct measures of diabetes status, such as measurements of fasting blood glucose or HbA_{1c}, would provide a more accurate means of measuring changes in glycemic control. Unfortunately, the Ingenix LabRx Database does not contain complete information on fasting blood glucose or HbA_{1c} for all subjects included in the study. However, prior research has suggested that changes in antihyperglycemic therapies provide a meaningful comparison of glycemic control before and after initiation of LMT. Clinical trials have shown that patients treated with lower daily doses of niacin (1-2.5 g of immediate-release formulation) showed no significant changes in the use of insulin and AHAs [31] and no clinically relevant changes in HbA_{1c} [31,32]. The results of this study provide further evidence that the use of low doses of ERN is not significantly associated with increases in the use of AHAs in regular clinical practice.

Administrative records of ERN prescriptions are also indirect measures of prescription-filling and medication-taking behaviors. Potential *ICD-9* coding errors, the limited baseline period, and the fact that many cases of T2DM are undiagnosed may have resulted in our underestimating the true number of patients with T2DMs receiving ERN or another LMT. Niacin is also available over the counter in other formulations. Based on a Canadian observational study, ERN is used primarily at lower daily doses (up to 1 g), with less than 7% of patients reaching 2 g within a 1-year treatment period [33]. At such doses, hyperglycemia-triggering treatment may not be an issue.

Our findings cannot necessarily be generalized to individuals with advanced T2DM and/or with less access to care, including those hospitalized with microvascular and/or macrovascular complications. A number of consensus treatment panels, including the National Lipid Association, recommend monitoring glucose control when niacin therapy is initiated or intensified [11]. Finally, the index period of our study preceded the advent of other forms of AHA therapy, including incretin mimetics and enhancers.

5. Conclusions

Therapy with ERN in US patients with stable T2DM identified from an administrative-claims database was not associated with a significant increase in the use of AHAs, suggesting that T2DM status did not worsen in the ERN cohort compared with patients on another LMT.

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