Risk of Cardiovascular Disease Events in Patients With Type 2 Diabetes Prescribed the Glucagon-Like Peptide 1 (GLP-1) Receptor Agonist Exenatide Twice Daily or Other Glucose-Lowering Therapies

A retrospective analysis of the LifeLink database

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OBJECTIVE — To test the hypothesis that exenatide twice daily reduces the relative incidence of cardiovascular disease (CVD) events among patients with type 2 diabetes compared with other glucose-lowering agent(s).

RESEARCH DESIGN AND METHODS — A retrospective database analysis was performed of the LifeLink database of medical and pharmaceutical insurance claims for June 2005 through March 2009. Patients with no history in the preceding 9 months of myocardial infarction, ischemic stroke, or coronary revascularization procedure were assigned to the exenatide-initiated or non–exenatide-initiated cohorts based on the first new prescription filled and reassigned if exenatide was prescribed or discontinued. Incident CVD events (myocardial infarction, ischemic stroke, or coronary revascularization procedure) were identified by ICD-9-CM diagnosis codes. Patient outcomes were adjusted for differences in clinical and demographic characteristics and compared using propensity score–weighted discrete time survival analysis with time-varying exposure to exenatide.

RESULTS — A total of 39,275 patients with type 2 diabetes were treated with exenatide twice daily, and 381,218 patients were treated with other glucose-lowering therapies. Patients who initiated exenatide were more likely to have prior ischemic heart disease, obesity, hyperlipidemia, hypertension, and/or other comorbidities at baseline. Exenatide-treated patients were less likely to have a CVD event than non–exenatide-treated patients (hazard ratio 0.81; 95% CI 0.68–0.95; $P = 0.01$) and lower rates of CVD-related hospitalization (0.88; 0.79–0.98; $P = 0.02$) and all-cause hospitalization (0.94; 0.91–0.97; $P < 0.001$).

CONCLUSIONS — Exenatide twice-daily treatment was associated with a lower risk of CVD events and hospitalizations than treatment with other glucose-lowering therapies.

Diabetes Care 34:90–95, 2011

The risk of cardiovascular disease (CVD) is increased two- to fivefold in patients with type 2 diabetes compared with patients without diabetes. Observational studies have reported that hyperglycemia (even below the current diabetes diagnostic threshold) is associated with increased cardiovascular risk (1–3), but the effects of glucose-lowering strategies on CVD events in clinical trials have been mixed (4–9). Intervention studies have shown modest benefit (6,8), no benefit (4,7,9), or a suggestion of harm (5). Furthermore, aggregating data via meta-analyses (10–12) or systemic review (13) have provided evidence of benefit and suggestion of harm. Few data exist on "real world" experience.

Medications such as exenatide twice daily, which have been available to patients for much shorter periods of time than sulfonylureas and metformin, have not yet been tested in clinical trials of CVD outcomes. One of the best interval approaches is to assess the effect of exenatide on CVD outcomes in a "real world" cohort using well-established glucose-lowering agents as comparators. This study retrospectively analyzed the risk of a first CVD event among patients with type 2 diabetes treated with exenatide or other glucose-lowering therapies in the LifeLink database.

Exenatide is an injectable GLP-1 receptor agonist that was approved in June 2005 in the U.S. as an adjunct to diet and exercise for the treatment of patients with type 2 diabetes who have not achieved adequate glycemic control without drug therapy, on monotherapy, or on combination therapy with metformin and a sulfonylurea or thiazolidinedione. Exenatide improves glycemic control, reduces body weight, and has been associated with improvements in CVD risk factors including hypertension and dyslipidemia in some but not all patients (14). This study was designed to test the hypothesis that exenatide use reduces the risk of CVD events and hospitalization compared with other glucose-lowering therapies.

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Received 19 July 2010 and accepted 28 September 2010. Published ahead of print at http://care.diabetesjournals.org on 7 October 2010. DOI: 10.2337/dc10-1393.

RESEARCH DESIGN AND METHODS

Source population

Data were obtained from the IMS LifeLink Program: Health Plan Claims (U.S.) Database (formerly known as PharMetrics), which is comprised of medical and pharmaceutical claims for over 36 million unique patients from 98 health plans across the U.S for the period June 2005 through March 2009. The database includes inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in Current Procedural Terminology, 4th Edition [CPT-4], and Healthcare Common Procedure Coding System [HCPCS] formats) and both retail and mail-order prescription records. Available data on prescription claims include the National Drug Code (NDC), days' supply, and quantity dispensed. Dates are available for all services rendered. Additional data include demographic variables (age, sex, geographic region), type of insurance (e.g., HMO, preferred provider organization), payer type (e.g., commercial, self-pay), provider specialty, and eligibility dates related to plan enrollment and participation. In compliance with the Health Insurance Portability and Accountability Act (HIPAA), patient data used in the analysis were de-identified; therefore, this study was exempt from Institutional Review Board review.

Cohort formation and exposure definition

Patients entered the study cohort if they had type 2 diabetes and filled any new glucose-lowering medications on or after 1 June 2005. A new agent was defined as a prescription filled with no evidence of a previous prescription for that agent in the prior 9 months. Patients were assigned to the exenatide or nonexenatide cohort based on the first new prescription filled on or after 1 June 2005. Patients were defined as having type 2 diabetes if they had a claim for an oral glucose-lowering medication or exenatide and met at least one additional criterion during the study period: *1*) an ICD-9-CM diagnosis code of 250.xx on a medical, facility, or surgical claim or *2*) a claim for insulin or pramlintide. Patients were excluded from the study if *1*) they were not continuously enrolled in a health plan with both medical and pharmacy coverage for a minimum of 9 months precohort entry date and at least 1 day postcohort entry date or *2*) had acute myocardial infarction (MI), ischemic stroke, or coronary revascularization procedures during the 9 months before the cohort entry date (Fig. 1).

Patients were followed from cohort entry date until the end of their observation period, which was defined as the date of disenrollment, the first occurrence of a CVD event of interest, or end of data stream (31 March 2009). To capture complex treatment patterns (e.g., exposure to glucose-lowering therapy) over time, patients were allowed to change cohort membership during the study period. Patients' cohort membership was evaluated at intervals of 31 days. A patient was assigned to the exenatide cohort if the day's supply for an exenatide prescription plus 31 days covered the end point of the time interval. As a result, each patient could have contributed multiple 31-day intervals to the analysis. Patients were designated as exenatide patients as long as a prescription for exenatide was found despite the addition or discontinuation of other glucose-lowering agents, including insulin. Similarly, nonexenatide patients were so designated despite switching or adding glucose-lowering agents different from the initial agent (except exenatide).

Definition of study events

CVD events of interest were defined as the first occurrence of MI, ischemic stroke, or coronary revascularization procedure (angioplasty/atherectomy, percutaneous transluminal coronary angioplasty/stenting, or coronary artery bypass graft). Incident MI was defined as a hospitalization with an ICD-9-CM diagnosis code (410.xx excluding 410.7x) in the primary position. Similarly, ischemic stroke was defined as a hospitalization with an ICD-9-CM diagnosis code (433.x1, 434.x1, 435.9, 436, 437.1x, 437.9x) in the primary position. Coronary revascularization procedure was defined as a hospitalization or an outpatient visit with one of the following CPT procedure codes (35450–35459, 35470–35475, 35480–35495; 92980, 92981, 92982, 92984, 92995, 92996, G0290, G0291, S2211, S2222; 33510–33536, 33572, S2204–S2209).

Baseline covariates

Baseline covariates were derived from the pharmacy and medical claims rendered during the 9 months preceding cohort entry, inclusive of claims rendered during the day of cohort entry. The following variables were included: patient demographics; the calendar quarter of study entry; indicators of diabetes severity (number of glucose-lowering medications used, diabetic retinopathy, peripheral neuropathy, renal impairment, and dialysis); indicators of preexisting CVD (ischemic heart disease, congestive heart failure, acute coronary syndrome, deep vein thrombosis, arrhythmia/conduction-related events); CVD risk factors (hyperlipidemia, hypertriglyceridemia, and hypertension); other comorbidities (malignant neoplasms, obesity, depressive disorders, alcohol dependence/abuse, smoking, hyperthyroidism, cardiomyopathy, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, other chronic kidney disease, arthritis, osteoporosis, and open heart surgery), filled prescriptions for concomitant therapies (ACE inhibitors, angiotensin-receptor blockers, vasodilators, anti-arrhythmic agents, fibrates, HMG-CoA reductase inhibitors [statins], anti-obesity agents, antiplatelet agents, nonsteroidal anti-inflammatory drugs, antithrombolytic agents, and immunomodulating drugs); and patients' Charlson comorbidity index score (15). The analyses included (and adjusted for) variables that occurred most frequently (top 50) in the database (primary and secondary diagnosis codes for most recent hospitalization pre-exposure, procedures, ICD-9 diagnosis codes, and medications), whether they were thought to be causal or not, to optimize balance between the study groups.

Data analysis

A propensity score–weighted discrete time survival analysis with time-varying exposure to exenatide (16) was used to compare the hazard of incident CVD events between patients treated with exenatide versus other glucose-lowering therapies, which included all formulations of metformin, thiazolidinediones, sulfonylureas, dipeptidyl-peptidase inhibitors, α-glucosidase inhibitors, and insulin. A dataset was compiled from all 31-day intervals contributed by each patient.

A propensity score model was developed to predict patients' assignment at cohort entry to ensure cohort balance. The propensity score model included >300 variables and the interaction effects derived from the baseline covariates (online appendices 1–4, available at http://care.diabetesjournals.org/cgi/content/full/dc10-1393/DC1). The final propensity model was then used to generate a patient-specific propensity score that was used to ad-

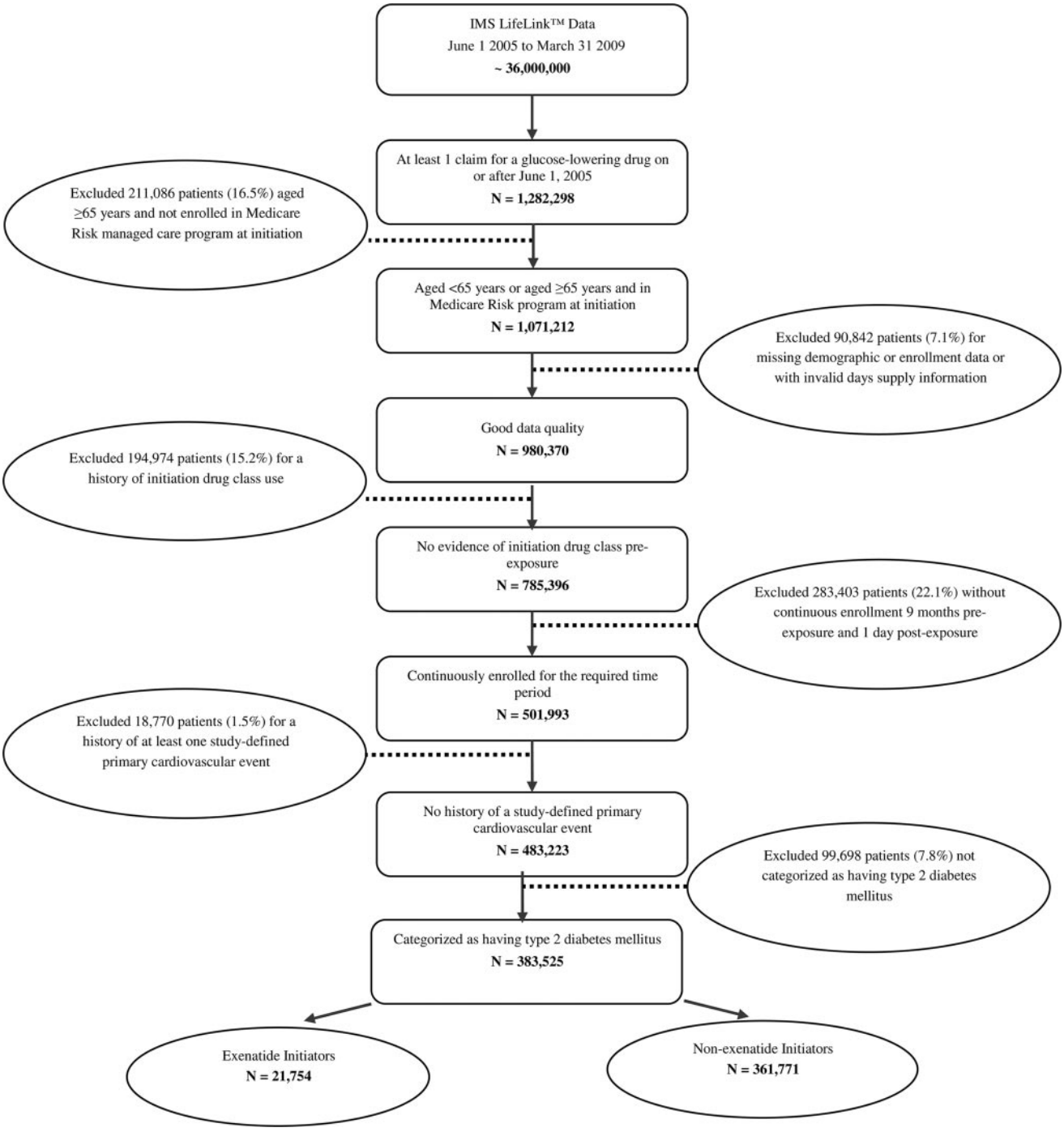

Figure 1—*Patient selection and sample attrition.*

just for potential selection bias in the final analyses.

To ensure the stability of results with regard to methodological choices, we completed a primary analysis and sensitivity analyses that used various designs and adjustment techniques.

Primary analyses

The primary analysis was a discrete time survival analysis using time-varying exposure to exenatide. We estimated the main effect using a propensity score–weighted pooled logistic regression. The estimation procedure was completed using generalized estimating equations to account for the multiplicity of observations within patients. The standardized propensity score weights were calculated for each patient by the inverse of the propensity score, adjusted for the sample size of each cohort.

Sensitivity analyses

As a sensitivity analysis for the adjustment technique, the same model as in the base case was estimated using propensity score stratification as the method of adjustment. Patients were grouped into deciles based on their estimated propensity score, and patients were then compared within each stratum using the pooled logistic regression. The summary hazard ratio (HR) was calculated as a weighted

average of all point estimates within each stratum, the weight being the inverse of the variance of each estimate. The variance of the weighted average was the inverse of the sum of the weights.

As a sensitivity analysis for the design, we estimated and compared the rate of CVD events using intent-to-treat analysis. The intent-to-treat analysis provides a good benchmark to the general practice in a clinical trial and is known to preserve the null hypothesis.

All data management and analyses were performed using Statistical Analysis Software (versions 8.2 and 9.1; SAS, Cary, NC). For all analyses, statistical significance was evaluated at a type 1 error of 5%.

RESULTS — More than 1.2 million patients were identified with evidence of at least one glucose-lowering prescription on or after 1 June 2005. After applying all study criteria, a total of 383,525 patients prescribed glucose-lowering medications were included in the analysis (Fig. 1; Table 1), including 21,754 exenatide initiators and 361,771 nonexenatide initiators. Exenatide initiators appeared to have more severe diabetes based on indicators of diabetes severity (Table 1). Specifically, exenatide initiators had evidence of greater use of other glucose-lowering therapies before the initial exenatide prescription and a greater proportion of the exenatide initiators had evidence of diabetic retinopathy, peripheral neuropathy, hyperlipidemia, hypertension, and ischemic heart disease than nonexenatide initiators. Medications used to treat CVD risk factors were more commonly listed for exenatide initiators than nonexenatide initiators, including antihypertensive agents, antihyperlipidemic agents, and specifically ACE inhibitors, angiotensin-receptor blockers, statins, and fibrates. Arthritis was the most common comorbidity in exenatide initiators, and associated nonsteroidal anti-inflammatory drug use was also greater. Obesity (ICD-9-CM code 278.0x) was more prevalent in exenatide initiators than in nonexenatide initiators.

Table 1—*Baseline clinical characteristics and demographics for patients initiating exenatide twice daily and other glucose-lowering medications*

	Exenatide b.i.d.	Non-exenatide
Total (*n*)	21,754	361,771
Mean age (years)	52.7 ± 8.7	53.2 ± 11.2*
Male	43.8	51.5*
Geographic region*		
Northeast	29.3	31.1
Midwest	26.7	34.4
South	35.5	24.6
West	8.5	9.9
Health plan type*		
Preferred provider organization (PPO)	56.0	46.8
Health maintenance organization (HMO)	24.0	32.7
Point of service (POS)	11.3	13.3
Other/unknown	8.8	7.2
Comorbidities		
Indicators of diabetes severity		
Diabetic retinopathy	11.2	5.5*
Peripheral neuropathy	4.9	2.7*
Renal impairment	2.8	2.6
Indicators of cardiovascular disease		
Hyperlipidemia	66.3	51.7*
Hypertension	65.4	56.3*
Arrhythmia/conduction-related events	30.4	30.3
Ischemic heart disease	12.7	10.4*
Congestive heart failure	3.5	3.3
Hypertriglyceridemia	3.0	2.0*
Acute coronary syndrome	1.1	1.0
Other comorbidities		
Arthritis	16.6	13.7*
Obesity	16.2	9.1*
Mean Charlson Comorbidity Index (CCI) (%)	1.6 ± 1.1	1.3 ± 1.3*
Mean total number of glucose-lowering agents used in pre-exposure period (%)	1.9 ± 1.1	0.6 ± 0.9*
Use of glucose-lowering medication (within 30 days before index date)		
Combination therapy	57.4	15.4*
Metformin only	13.6	10.3*
Sulfonylurea only	3.2	6.6*
TZD only	3.1	3.6*
Insulin only	5.3	2.9*
Use of other medications (recorded prescription)		
Antihypertensive agents	77.8	57.8*
Antihyperlipidemic agents	63.8	39.3*
HMG-CoA reductase inhibitors (statins)	49.4	30.9*
ACE inhibitors	36.0	24.1*
Nonsteroidal anti-inflammatory drugs	23.2	18.7*
Angiotensin-receptor blockers	16.6	8.9*
Fibrates	12.9	6.6*

Data are percent or means ± SD unless otherwise indicated. *$P < 0.001$ exenatide vs. non-exenatide.

Cardiovascular events and rate of hospitalizations

Over the course of the study, 39,275 patients and 381,218 patients were "exposed" to (treated with) exenatide and nonexenatide therapies, respectively. The HR for CVD events among the exenatide-treated patients compared with the non–exenatide-treated patients is shown in Fig. 2. In the primary analysis, exenatide-treated patients were significantly less likely to have a CVD event (HR 0.81; 95% CI 0.68–0.95; $P = 0.01$) compared with non–exenatide-treated patients. Results were robust with respect to the statistical method used. In a propensity score–stratified analysis, exenatide-treated patients were less likely to have a CVD event (HR 0.80; 0.74–0.86; $P < 0.001$) compared with non–exenatide-treated patients. In the intent-to-treat analysis, exenatide initiators were less likely to

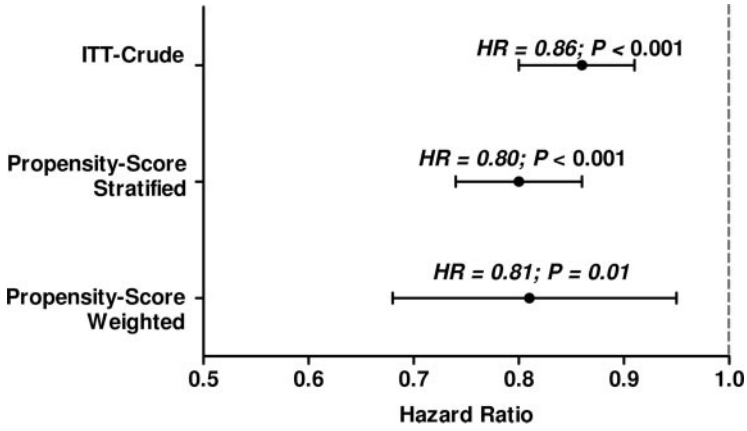

Figure 2—*HRs for cardiovascular events among the exenatide twice daily study cohort versus nonexenatide study cohort resulting from various methodological techniques. Error bars represent 95% CIs. Propensity-Score Stratified, propensity score, stratified by decile; ITT, intention to treat.*

have a CVD event (HR 0.86; 0.81–0.92; $P < 0.001$) compared with non-exenatide initiators.

Consistent with the reduced frequency of CVD events, exenatide initiators had lower rates of hospitalization for CVD-related events (HR 0.88; 0.79–0.98; $P = 0.02$) during the follow-up period compared with the non-exenatide initiators and had a lower rate of all-cause hospitalization (HR 0.94; 0.91–0.97; $P < 0.001$).

CONCLUSIONS — In a "real world" cohort of patients with type 2 diabetes, use of exenatide twice daily was associated with a reduced risk for CVD events and CVD-related hospitalization. The finding that the associated risk reduction is robust using multiple statistical approaches gives credibility to the observation of reduced CVD risk. The observation that lipid levels, blood pressure, obesity, and evidence of prior CVD were higher in patients initially treated with exenatide than in patients initially treated with other agents lends additional support to the concept that exenatide use is associated with favorable effects on CVD outcomes and hospitalization compared with other therapies. These data are consistent with the hypothesis that the GLP-1 receptor agonist exenatide may reduce the risk for CVD in patients with type 2 diabetes.

Several factors may explain the observed reduction in CVD events and hospitalization in exenatide versus non–exenatide-treated patients: greater reduction of hyperglycemia with less hypoglycemia and/or improvement in CVD risk factors, including weight, lipids, and blood pressure (14). A randomized controlled clinical trial of the cardiovascular outcomes associated with long-term use of exenatide is needed to demonstrate whether exenatide treatment reduces CVD risk and to determine whether changes in A1C, the incidence of hypoglycemia, and/or reductions in CVD risk factors are associated with improved cardiovascular outcomes.

Although observational studies have generally shown a relationship between hyperglycemia (even below the threshold for the diagnosis of type 2 diabetes) and CVD (1–3), clinical trials have not consistently confirmed that reducing hyperglycemia reduces CVD (4–9). The UK Prospective Diabetes Study (UKPDS) reported a significant reduction in MI in the small cohort treated with metformin (6), but effects with sulfonylureas and insulin did not achieve statistical significance until the 10-year follow-up study (7,8). Three large recently completed intervention trials (Veterans Affairs Diabetes Trial [VADT], Action to Control Cardiovascular Risk in Diabetes [ACCORD], and Action in Diabetes and Vascular Disease: Preterax and Diamicron–MR Controlled Evaluation [ADVANCE]) did not show evidence of CVD risk reduction in the primary outcome (nonfatal MI, nonfatal stroke, or death from cardiovascular causes) (4,5,9). In fact, ACCORD was terminated early because of increased all-cause mortality in the intensive glycemic treatment arm (5). Of note, the increased mortality in each of the ACCORD arms was associated with hypoglycemia (17). Although the systematic review by Kelly et al. (13) suggests that when the data from UKPDS, ACCORD, ADVANCE, and VADT are combined, the reduction in CVD events becomes statistically significant, the effect is small. These observations from ACCORD and VADT suggest that when there is a need to intensify glucose control, hypoglycemia may increase CVD risk and counter the benefits of reducing hyperglycemia.

The primary strength of this study was the inclusion of patients with type 2 diabetes who received glucose-lowering therapy in a real-world population, a large and broadly representative source population. This study reflects common clinical practice across the U.S. and provides for more than adequate statistical power and information to adjust for potential confounders. However, the administrative data used in this real-world study present challenges of accurately ascertaining variables of interest. Although we sought to mitigate potential sources of bias in the conduct of this study, some limitations remain, including potential misclassification of exposure and/or outcome, and the potential for residual confounding. Diagnosis of CVD using ICD-9-CM codes may not always represent a clinical diagnosis of the disease; however, prior publications indicate that the estimated predictive value of administrative data for identifying cardiovascular end points are high (95% for acute MI and stroke), suggesting that ICD-9-CM codes have good positive predictive value (18,19). In studies based on administrative data, the misclassification might be assumed to be nondifferential with respect to exposure, with a bias in the HR toward the null value that might obscure an association between exenatide and CVD risk. However, if physicians monitor more closely patients with severe diabetes (who are more likely to be on exenatide) for CVD, then the estimated association of exenatide with CVD would be biased away from the null.

We controlled for a large set of factors that potentially differed between the groups at baseline using propensity score methodology. Nevertheless, the incomplete capture of variables in the claims data, such as weight, smoking, alcohol consumption, and change in other variables associated with CVD risk (e.g., lipids, blood pressure, and A1C), is a limitation of the present analysis. Indeed, the baseline characteristics of the study cohorts suggest that exenatide initiators have a higher prevalence of potential risk factors for CVD, such as obesity, hypertension, and hyperlipidemia. The direc-

tion of imbalance in these partially captured variables suggests that remaining (unmeasured) confounding would lead to a higher risk of CVD among exenatide users. However, baseline laboratory data and measures of CVD risk markers such as weight, blood pressure, and lipids are needed to adjust for population differences, and we do not have these data. We expect that adjustment for the preindex clinical characteristics including use of antihyperlipidemic and antihypertensive medications serve as proxies for these variables.

Additionally, the linkage between pharmacy submission of claims and patients' receipt and consumption of the medication is assumed and not directly measured; prior work suggests that medication exposure measures can be accurately derived from pharmacy claims (20). As an insurance database, the results are most generalizable to similar commercially insured patients, but the results are likely to be relevant to a more general population of patients with type 2 diabetes, unless uninsured patients differ in their response to exenatide.

This study does not address potential questions about whether nonexenatide agents may be associated with increased risk (with possible absence of benefit from exenatide) or neutral risk of CVD events.

In conclusion, in this retrospective epidemiological study, exenatide-treated patients were 19% less likely to have a CVD event than patients treated with other glucose-lowering agents; exenatide-treated patients were also less likely to experience CVD-related and all-cause hospitalization. The results were robust with respect to the statistical method and support the CVD safety of exenatide twice daily for patients with type 2 diabetes. The improved CV outcomes observed in this retrospective database analysis need to be confirmed in prospective studies of treatment with exenatide.

Acknowledgments— J.H.B. and M.W. are employees and stockholders of Amylin Pharmaceuticals. W.H.H. received past funding as a consultant for Amylin and Eli Lilly. E.M.P., D.B.S., and M.A.H. are employees of IMS Health and paid consultants for Amylin. B.J.H. is an employee and stockholder of Eli Lilly. No other potential conflicts of interest relevant to this article were reported.

J.H.B., E.M.P., D.B.S., and M.A.H. researched data. J.H.B., B.J.H., W.H.H., and M.W. contributed to discussion. J.H.B., B.J.H., and M.A.H. co-wrote the manuscript. J.H.B., B.J.H., W.H.H., E.M.P., D.B.S., M.W., and M.A.H. participated in development of the statistical plan and reviewed/edited the manuscript.

The authors thank Prafulla Girase, IMS Health, for assistance with data analysis and Mary Beth DeYoung, Amylin Pharmaceuticals, for editorial assistance.

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