The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study)

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Diabetes Care 2019;42:416–426 | https://doi.org/10.2337/dc17-1144

EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To examine for a legacy effect of early glycemic control on diabetic complications and death.

RESEARCH DESIGN AND METHODS

This cohort study of managed care patients with newly diagnosed type 2 diabetes and 10 years of survival (1997–2013, average follow-up 13.0 years, *N* = 34,737) examined associations between HbA_{1c} <6.5% (<48 mmol/mol), 6.5% to <7.0% (48 to <53 mmol/mol), 7.0% to <8.0% (53 to <64 mmol/mol), 8.0% to <9.0% (64 to <75 mmol/mol), or ≥9.0% (≥75 mmol/mol) for various periods of early exposure (0–1, 0–2, 0–3, 0–4, 0–5, 0–6, and 0–7 years) and incident future microvascular (end-stage renal disease, advanced eye disease, amputation) and macrovascular (stroke, heart disease/failure, vascular disease) events and death, adjusting for demographics, risk factors, comorbidities, and later HbA_{1c}.

RESULTS

Compared with HbA_{1c} <6.5% (<48 mmol/mol) for the 0-to-1-year early exposure period, HbA_{1c} levels ≥6.5% (≥48 mmol/mol) were associated with increased microvascular and macrovascular events (e.g., HbA_{1c} 6.5% to <7.0% [48 to <53 mmol/mol] microvascular: hazard ratio 1.204 [95% CI 1.063–1.365]), and HbA_{1c} levels ≥7.0% (≥53 mmol/mol) were associated with increased mortality (e.g., HbA_{1c} 7.0% to <8.0% [53 to <64 mmol/mol]: 1.290 [1.104–1.507]). Longer periods of exposure to HbA_{1c} levels ≥8.0% (≥64 mmol/mol) were associated with increasing microvascular event and mortality risk.

CONCLUSIONS

Among patients with newly diagnosed diabetes and 10 years of survival, HbA_{1c} levels ≥6.5% (≥48 mmol/mol) for the 1st year after diagnosis were associated with worse outcomes. Immediate, intensive treatment for newly diagnosed patients may be necessary to avoid irremediable long-term risk for diabetic complications and mortality.

In the U.S., an estimated 1.4 million adults are newly diagnosed with diabetes every year and present an important intervention opportunity for health care systems. In patients newly diagnosed with type 2 diabetes, the benefits of maintaining an HbA_{1c} <7.0% (<53 mmol/mol) are well established. The UK Prospective Diabetes Study (UKPDS) found that a mean HbA_{1c} of 7.0% (53 mmol/mol) lowers the risk of

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Received 8 June 2018 and accepted 7 July 2018

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1144/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

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diabetes-related end points by 12–32% compared with a mean HbA_{1c} of 7.9% (63 mmol/mol) (1,2). Long-term observational follow-up of this trial revealed that this early glycemic control has durable effects: Reductions in microvascular events persisted, reductions in cardiovascular events and mortality were observed 10 years after the trial ended, and HbA_{1c} values converged (1). Similar findings were observed in the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes (2–4). These posttrial observations have been called legacy effects (also metabolic memory) (5), and they suggest the importance of early glycemic control for the prevention of future complications of diabetes. Although these clinical trial long-term follow-up studies demonstrated legacy effects, whether legacy effects exist in real-world populations, how soon after diabetes diagnosis legacy effects may begin, or for what level of glycemic control legacy effects may exist are not known.

In a previous retrospective cohort study, we found that patients with newly diagnosed diabetes and an initial 10-year HbA_{1c} trajectory that was unstable (i.e., changed substantially over time) had an increased risk for future microvascular events, even after adjusting for HbA_{1c} exposure (6). In the same cohort population, this study evaluates associations between the duration and intensity of glycemic control immediately after diagnosis and the long-term incidence of future diabetic complications and mortality. We hypothesized that a glycemic legacy effect exists in real-world populations, begins as early as the 1st year after diabetes diagnosis, and depends on the level of glycemic exposure.

RESEARCH DESIGN AND METHODS

Source Population

Since 1993, the Kaiser Permanente Northern California (KPNC) Diabetes Registry has maintained a cohort of patients with diabetes (7,8). Patients with diabetes are identified through an algorithm that is based on any of the following: *1*) inpatient diagnosis (principal diagnosis of ICD-9 code 250), *2*) outpatient diagnosis (two or more diagnoses with ICD-9 code 250, excluding diagnoses collected in the emergency, optometry, or ophthalmology departments), *3*) two abnormal outpatient laboratory results (fasting glucose ≥126 mg/dL, random or post-challenge [75-g] glucose ≥200 mg/dL, HbA_{1c} ≥6.5% [≥48 mmol/mol] tested on separate days within a 3-year period), or *4*) pharmacy use (prescription for insulin or oral antihyperglycemic medications) (9). This algorithm has been compared internally with chart review, and its sensitivity was 96% for identifying patients with diabetes (8). This study, a substudy of the National Institute of Diabetes and Digestive and Kidney Diseases–funded Diabetes & Aging Study, used KPNC Diabetes Registry data to examine the epidemiology of diabetes across the life course (6,10–13). The study received institutional review board approval from the Kaiser Foundation Research Institute (Oakland, CA) and The University of Chicago (Chicago, IL).

The current study is a follow-up to our previous analysis describing associations between 10-year HbA_{1c} trajectories and risk of diabetic complications in patients with newly diagnosed diabetes (6). We used the same initial cohort, defined as patients diagnosed with type 2 diabetes between 1997 and 2003 who had continuous membership in KPNC for at least 2 years before diagnosis and at least 10 years of survival after diagnosis (Supplementary Fig. 1). It was necessary to include patients who survived for at least 10 years to study the effects of various periods of early HbA_{1c} exposure on outcomes. All patients received standard diabetes care from KPNC while enrolled in the health system. We excluded patients with anemia during the study period because of potential inaccuracies of HbA_{1c} in assessing glycemic exposure in these patients (14–16). We also excluded patients who did not have any HbA_{1c} results during the first 3 months after diagnosis and who did not have a second HbA_{1c} result during the first 2 years after diagnosis because we were unable to classify their levels of early HbA_{1c} exposure. In addition, we excluded patients who had missing HbA_{1c} results for more than one-half of the follow-up years after year 3 because patients with frequent missing HbA_{1c} values may have been receiving care outside of Kaiser and may be missing clinical outcome data.

Design

This study used survival analysis methods to examine associations of various periods of early glycemic exposure and various levels of glycemic exposure with the risks for subsequent diabetic complications and death. Figure 1 defines the seven early exposure periods and subsequent follow-up periods. In total, 21 Cox proportional hazards models (seven early exposure periods multiplied by three outcomes of interest) were used to analyze these associations. For each outcome, because the seven models differed in the number of years of early

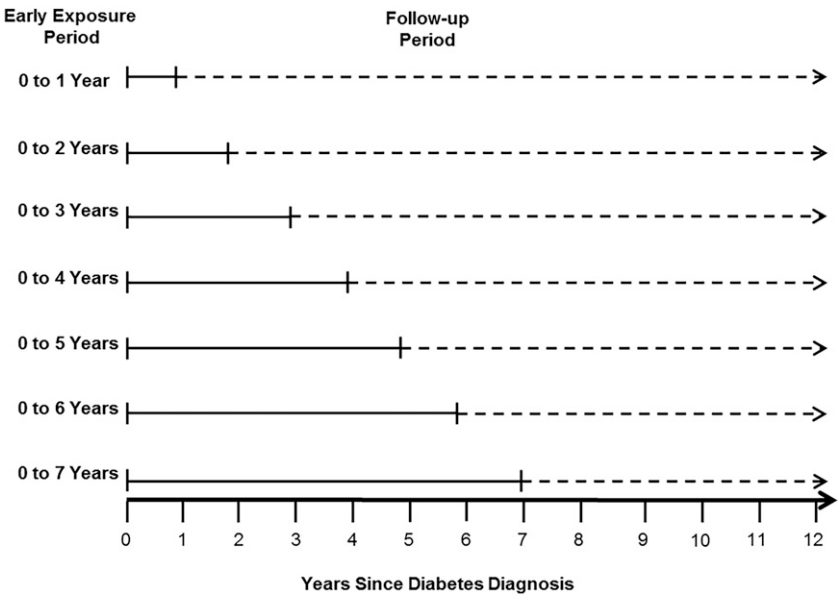

Figure 1—Definitions of early exposure periods and subsequent follow-up periods for the research design.

glycemic exposure, differences in hazard ratios (HRs) across models reflect additional hazards as a result of longer durations of early HbA_{1c} exposure compared with an HbA_{1c} <6.5% (<48 mmol/mol) for the same duration of exposure.

Exposure

To explore the effects of various periods of early glycemic exposure, we defined a family of seven early exposure periods (0–1, 0–2, 0–3, 0–4, 0–5, 0–6, and 0–7 years), beginning with 3 months after the first measured HbA_{1c} result (Fig. 1). The mean HbA_{1c} value was calculated for each early exposure period by using all HbA_{1c} results except those measured within 3 months after diagnosis. These initial values were excluded because they reflect control before treatment was initiated, and the glycemic legacy effect has been demonstrated only in populations receiving diabetes treatment.

To explore the effects of various levels of glycemic exposure, the mean HbA_{1c} value for each of the seven early exposure periods was categorized into either HbA_{1c} <6.5% (<48 mmol/mol), 6.5% to <7.0% (48 to <53 mmol/mol), 7.0% to <8.0% (53 to <64 mmol/mol), 8.0% to <9.0% (64 to <75 mmol/mol), or ≥9.0% (≥75 mmol/mol) or as missing if no values were available. All HbA_{1c} assays were conducted at KPNC's centralized laboratory, which is certified by the NGSP (16).

Outcomes

The outcomes of interest were incident future advanced microvascular events, macrovascular events, and death. Advanced microvascular events included end-stage renal disease, diabetic eye disease, and lower-extremity amputation; macrovascular events included cerebrovascular disease, heart disease, heart failure, and vascular disease. Events were ascertained on the basis of a combination of outpatient, emergency department, or inpatient primary diagnostic or procedure codes (Supplementary Table 1). Advanced diabetic eye disease was identified by diagnostic codes for proliferative diabetic retinopathy, diabetic macular edema, or blindness/low vision and procedure codes for destruction of a localized retinal lesion, destruction or treatment of extensive/progressive retinopathy, or photocoagulation. We included only the first occurrence of microvascular and macrovascular events. Mortality data were obtained from the California state mortality file, social security death records, and Kaiser administrative records.

Covariates

We adjusted for potentially confounding variables. Models adjusted for sex, race/ethnicity, age at diagnosis, and year of diagnosis as well as for cardiovascular risk factors (total and HDL cholesterol, BMI, blood pressure, smoking status), using the last observed value for each of the seven early exposure periods. When there were issues with missing data, the last observation was carried backward. Certain cardiovascular risk factors were more likely to be missing than other variables, reflecting systematic differences in how variables were collected in clinical practice during the study period. For example, BMI and smoking data were available in only one-half of patients in years 4 and 6 after diabetes diagnosis, respectively, whereas cholesterol and blood pressure data were available in 85% of patients in years 1 and 3 after diabetes diagnosis.

In addition, models adjusted for the Charlson comorbidity index (17). We calculated the Charlson comorbidity index using several years of data because of concerns about missing diagnostic codes in the administrative database. The Charlson comorbidity index for the 0-to-1- and 0-to-2-year early exposure periods was calculated using 3 years of data, starting with data from 2 years before diagnosis. For the 0-to-3- and 0-to-4-year early exposure periods, the Charlson comorbidity index was calculated using 5 years of data, starting with data from 2 years before diagnosis, and for the 0-to-5-, 0-to-6-, and 0-to-7-year early exposure periods, it was calculated using data from the first 5 years after diabetes diagnosis.

Finally, models adjusted for glycemic exposure after each of the seven early exposure periods. This variable was defined similarly to how glycemic exposure was defined during the early exposure periods. For each patient, the mean HbA_{1c} value was calculated for the time period after each early exposure period and before incidence of the outcome under study for each of the 21 Cox proportional hazards models. These 21 mean values were then categorized as HbA_{1c} <6.5% (<48 mmol/mol), 6.5% to <7.0% (48 to <53 mmol/mol), 7.0% to <8.0% (53 to <64 mmol/mol), 8.0% to <9.0% (64 to <75 mmol/mol), or ≥9.0% (≥75 mmol/mol).

Statistical Analysis

We summarized data for patient characteristics using means and SDs for continuous variables and counts and percentages for categorical variables stratified by the 0-to-1-year early exposure period. We used the χ^2 test for bivariate statistics for categorical variables and the Mann-Whitney *U* test for continuous variables.

In total, 21 Cox proportional hazards models were used to examine associations between glycemic control for the seven successively longer early exposure periods and risk for subsequent microvascular or macrovascular events or death (Fig. 1). The measure of time was the number of years since diabetes diagnosis.

We adjusted for demographics (age at diagnosis, sex, race/ethnicity), diagnosis year, cardiovascular risk factors, HbA_{1c} after the early exposure period, and comorbidity. Because we were interested in incident future events, for each of the seven early exposure periods, we excluded patients who had prevalent (preexisting) microvascular (or macrovascular) complications during the relevant early exposure period for models examining microvascular (or macrovascular) complications, as appropriate. For example, if a patient had a diagnosis of end-stage renal disease in year 2 after diabetes diagnosis, the patient was included in models that examined the association between the 0- and 1-year early glycemic exposure period and incident future microvascular complications. However, this patient would be excluded from models examining associations between the 0- and 2-year early glycemic exposure period and incident future microvascular complications.

For each of the 21 models, patient follow-up was censored after the first occurrence of the outcome of interest, dropout from KPNC (for advanced microvascular and macrovascular events), or end of follow-up (31 December 2013). Overall, 1,732 patients (5.0%) dropped out, and 32,930 (94.8%) were

administratively censored at the end of follow-up. For each combination of seven early exposure periods and three outcomes, the time to event or censoring was the number of years from the beginning of the month following the end of the early exposure period to the beginning of the month of the incident outcome.

We conducted sensitivity analyses to assess how results changed with other modeling assumptions. Because the models with various early exposure periods had different follow-up periods, which may affect results, we conducted a sensitivity analysis for the microvascular and macrovascular outcomes in which we right censored patient follow-up at 5 years of follow-up. A two-sided $P < 0.05$ was considered statistically significant for all analyses. Analyses were completed using SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Overall, 34,737 eligible patients were included in the study. Mean follow-up after diagnosis was 13.0 years (SD 1.9 years) (Table 1). The mean age at diagnosis was 56.8 years (SD 11.0 years). During the 1st year after diagnosis (0-to-1-year early glycemic exposure period), 41.1% (n = 14,286) of patients had an average HbA_{1c} <6.5% (<48 mmol/mol), 16.9% (n = 5,877) had an average HbA_{1c} 6.5% to <7.0% (48 to <53 mmol/mol), 13.6% (n = 4,730) had an average HbA_{1c} 7.0% to <8.0% (53 to <64 mmol/mol), 4.1% (n = 1,418) had an average HbA_{1c} 8.0% to <9.0% (64 to <75 mmol/mol), 3.7% (n = 1,290) had an average HbA_{1c} ≥9.0% (≥75 mmol/mol), and 20.5% (n = 7,136) did not have a second HbA_{1c} value. Patients who had a mean HbA_{1c} <6.5% (<48 mmol/mol) in the 0-to-1-year early exposure period were older, more likely to be non-Hispanic white, and less likely to be current smokers and had a lower BMI and total cholesterol than those with higher mean HbA_{1c} levels. In addition, they were less likely to be taking both metformin and sulfonylureas during their 1st year after diagnosis. During the first 7 years after diabetes diagnosis, only 4.9% of patients had the same HbA_{1c} level for each of the 7 years; 50.4% of patients had >1 year with a higher HbA_{1c} level, and 30.4% of patients had >1 year with a lower HbA_{1c} level; 14.3% of patients had years with both higher and lower HbA_{1c} levels. Overall, chronic kidney disease stage 4 or 5 was present in only 53 patients.

Microvascular and Macrovascular Events

Figure 2*A* and *B* depicts HRs comparing microvascular and macrovascular event rates for the various HbA_{1c} early exposure periods and levels, compared with an HbA_{1c} <6.5% (<48 mmol/mol) for the same early exposure periods. With regard to our hypothesis that the legacy effect begins the 1st year after diagnosis, we found that patients with HbA_{1c} levels ≥6.5% (≥48 mmol/mol) for the 0-to-1-year early exposure period had a higher risk for microvascular and macrovascular events than patients with HbA_{1c} levels <6.5% (<48 mmol/mol) for the same period (e.g., HbA_{1c} 6.5% to <7.0% [48 to <53 mmol/mol]: HR 1.204 [95% CI 1.063–1.365]) (Table 2).

With regard to our hypothesis that the legacy effect depends on the level of glycemic exposure, we found that longer periods of early glycemic exposure at HbA_{1c} levels 6.5% to <8.0% (48 to <64 mmol/mol) did not increase the risk of microvascular or macrovascular events during follow-up. However, longer periods of exposure to HbA_{1c} levels ≥8.0% (≥64 mmol/mol) were associated with an increasing risk of microvascular events. HbA_{1c} levels ≥9.0% (≥75 mmol/mol) for early exposure periods >0–4 years were associated with an increasing risk of macrovascular events.

Mortality

Figure 2*C* presents the risks of mortality for various durations and levels of early glycemic exposure compared with an HbA_{1c} <6.5% (<48 mmol/mol) for the same durations of exposure. Compared with an HbA_{1c} <6.5% (<48 mmol/mol) for the 0-to-1-year early exposure period, HbA_{1c} levels of 7.0% to <8.0% (53 to <64 mmol/mol) and ≥9.0% (≥75 mmol/mol) were associated with a higher risk of mortality (HR 1.290 [95% CI 1.104–1.507] and 1.320 [1.017–1.713], respectively). HbA_{1c} 8.0% to <9.0% (64 to <75 mmol/mol) for the 0-to-2-year early exposure period was associated with a greater risk of mortality (1.240 [1.088–1.414]) compared with an HbA_{1c} <6.5% (<48 mmol/mol) for the same early exposure period. For all early exposure periods, HbA_{1c} 6.5% to <7.0% (48 to <53 mmol/mol) was not associated with a higher risk of mortality during follow-up.

Longer early exposure periods with HbA_{1c} levels <8.0% (<53 mmol/mol) were not associated with increases in mortality risk. However, longer early exposure periods with HbA_{1c} levels ≥8.0% (≥53 mmol/mol) were associated with increasing mortality risk.

Early Missing HbA_{1c}

During the 1st year after diagnosis (0-to-1-year early exposure period), patients without an HbA_{1c} value after the first 3 months after diagnosis had a higher risk of microvascular (HR 1.354 [95% CI 1.218–1.505]) and macrovascular (1.112 [1.050–1.177]) events and mortality (1.235 [1.094–1.394]) (Table 2).

Sensitivity Analyses

When follow-up time was right censored at 5 years, relationships between the duration and intensity of early glycemic exposure and microvascular and macrovascular events did not change (Supplementary Fig. 2).

CONCLUSIONS

In this large cohort study of patients with newly diagnosed diabetes and at least 10 years of survival after diagnosis, we found that diabetes control during the 1st year after diagnosis was strongly associated with future risk for diabetic complications and mortality, even after adjusting for glycemic control after the 1st year. Overall, the duration and intensity of early glycemic control were both closely aligned with outcomes. Compared with an HbA_{1c} <6.5% (<48 mmol/mol) for the 1st year after diagnosis, higher HbA_{1c} levels were associated with a higher risk for microvascular and macrovascular events, and HbA_{1c} levels ≥7.0% (≥58 mmol/mol) were associated with a higher risk for mortality. The risk of complications did not increase significantly when the early period was characterized by longer periods of HbA_{1c} levels of 6.5% to <8.0% (48 to <64 mmol/mol) (rather than just the 1st year after diabetes diagnosis). However, longer exposure to HbA_{1c} levels ≥8.0% (≥64 mmol/mol) was associated with an increased risk for microvascular events and mortality.

The current study suggests that failure to achieve an HbA_{1c} <6.5% (<48 mmol/mol)

Table 1—Characteristics of patients with newly diagnosed type 2 diabetes and 10 years of survival, stratified by mean HbA_{1c} during the 0-to-1-year early glycemic exposure period

		HbA_{1c}						
	Overall	<6.5% (<48 mmol/mol)	6.5% to <7.0% (48 to <53 mmol/mol)	7% to <8.0% (53 to <64 mmol/mol)	8.0% to <9.0% (64 to <75 mmol/mol)	≥9.0% (75 mmol/mol)	Missing	*P* value
Patients, *n* (%)	34,737 (100)	14,286 (41.1)	5,877 (16.9)	4,730 (13.6)	1,418 (4.1)	1,290 (3.7)	7,136 (20.5)	
Follow-up time (year), mean (SD)	13.0 (1.9)	12.9 (1.9)	12.6 (1.8)	12.8 (1.8)	13.1 (1.8)	13.3 (1.9)	13.3 (2.0)	<0.0001
Age at diagnosis (year), mean (SD)	56.8 (11.0)	57.9 (10.9)	57.9 (10.9)	56.2 (11.0)	53.4 (10.7)	52.0 (10.0)	55.7 (10.7)	<0.0001
Female sex, *n* (%)	16,216 (46.7)	6,329 (44.3)	3,015 (51.3)	2,451 (51.8)	706 (49.8)	588 (45.6)	3,127 (43.8)	<0.0001
Race/ethnicity, *n* (%)								<0.0001
Non-Hispanic white	17,625 (50.7)	7,996 (56.0)	2,859 (48.7)	2,177 (46.0)	591 (41.7)	506 (39.2)	3,496 (49.0)	
Non-Hispanic black	3,253 (9.4)	1,154 (8.1)	555 (9.4)	494 (10.4)	166 (11.7)	201 (15.6)	683 (9.6)	
Hispanic	4,531 (13.0)	1,831 (12.8)	703 (12.0)	596 (12.6)	197 (13.9)	218 (16.9)	986 (13.8)	
Asian	6,351 (18.3)	2,148 (15.0)	1,231 (21.0)	1,046 (22.1)	328 (23.1)	231 (17.9)	1,367 (19.2)	
Mixed	2,158 (6.2)	857 (6.0)	377 (6.4)	311 (6.6)	101 (7.1)	91 (7.1)	421 (5.9)	
Other/missing	819 (2.4)	300 (2.1)	152 (2.6)	106 (2.2)	35 (2.5)	43 (3.3)	183 (2.6)	
HbA_{1c} (%), mean (SD)	6.7 (1.2)	6.0 (0.4)	6.7 (0.1)	7.4 (0.3)	8.4 (0.3)	10.5 (1.5)	—	<0.0001
BMI (kg/m^2), mean (SD)	32.0 (6.4)	31.7 (6.2)	31.8 (6.4)	32.1 (6.5)	32.8 (6.6)	32.8 (6.9)	32.3 (6.5)	<0.0001
Systolic blood pressure (mmHg), *n* (%)								<0.0001
≤120	7,613 (21.9)	3,257 (22.8)	1,339 (22.8)	1,028 (21.7)	293 (20.7)	301 (23.3)	1,395 (19.6)	
121–129	5,119 (14.7)	2,187 (15.3)	899 (15.3)	703 (14.9)	204 (14.4)	193 (15.0)	933 (13.1)	
130–139	8,847 (25.5)	3,680 (25.8)	1,536 (26.1)	1,262 (26.7)	370 (26.1)	281 (21.8)	1,718 (24.1)	
140–159	9,492 (27.3)	3,721 (26.1)	1,554 (26.4)	1,275 (27.0)	387 (27.3)	391 (30.3)	2,164 (30.3)	
≥160	3,666 (10.6)	1,441 (10.1)	549 (9.3)	462 (9.8)	164 (11.6)	124 (9.6)	926 (13.0)	
Diastolic blood pressure (mmHg), *n* (%)								<0.0001
≤80	22,090 (63.6)	9,468 (66.3)	3,806 (64.8)	3,015 (63.7)	857 (60.4)	759 (58.8)	4,185 (58.7)	
81–84	4,357 (12.5)	1,739 (12.2)	747 (12.7)	607 (12.8)	182 (12.8)	167 (13.0)	915 (12.8)	
85–89	3,452 (9.9)	1,329 (9.3)	597 (10.2)	464 (9.8)	153 (10.8)	132 (10.2)	777 (10.9)	
90–99	3,787 (10.9)	1,364 (9.6)	576 (9.8)	506 (10.7)	178 (12.6)	187 (14.5)	976 (13.7)	
≥100	1,051 (3.0)	386 (2.7)	151 (2.6)	138 (2.9)	48 (3.4)	45 (3.5)	283 (4.0)	
TC (mg/dL), mean (SD)	205.7 (45.0)	199.0 (39.5)	204.8 (42.6)	208.2 (42.2)	212.7 (58.9)	222.6 (62.5)	213.8 (49.2)	<0.0001
HDL-C (mg/dL), mean (SD)	45.3 (11.4)	45.4 (11.6)	46.3 (11.5)	45.2 (11.2)	44.7 (11.1)	44.0 (11.3)	44.5 (11.3)	<0.0001
Smoking status, *n* (%)								<0.0001
Never	21,440 (61.7)	8,844 (61.9)	3,769 (64.1)	2,938 (62.1)	842 (59.4)	753 (58.4)	4,294 (60.2)	
Current	2,071 (6.0)	792 (5.5)	345 (5.9)	340 (7.2)	100 (7.1)	120 (9.3)	374 (5.2)	
Unknown	10,973 (31.6)	4,535 (31.7)	1,723 (29.3)	1,415 (29.9)	464 (32.7)	409 (31.7)	2,427 (34.0)	
Charlson comorbidity index, mean (SD)	1.6 (1.0)	1.6 (1.1)	1.6 (1.0)	1.6 (1.0)	1.6 (1.0)	1.6 (0.9)	1.5 (0.9)	<0.0001

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Table 1—Continued

		HbA$_{1c}$					
	Overall	<6.5% (<48 mmol/mol)	6.5% to <7.0% (48 to <53 mmol/mol)	7% to <8.0% (53 to <64 mmol/mol)	8.0% to <9.0% (64 to <75 mmol/mol)	≥9.0% (75 mmol/mol)	Missing	*P* value
Oral diabetes medication, *n* (%)								<0.0001
Biguanide only	5,383 (10)	2,024 (11)	947 (13)	935 (15)	257 (13)	215 (11)	1,005 (5)	
Sulfonylurea only	17,218 (31)	6,163 (32)	1,898 (26)	1,960 (32)	779 (40)	812 (42)	5,606 (31)	
Biguanide and sulfonylurea only	2,363 (4)	628 (3)	331 (4)	471 (8)	252 (13)	303 (16)	378 (2)	
None	29,850 (54)	10,340 (54)	4,189 (57)	2,717 (45)	667 (34)	584 (31)	11,353 (62)	
Insulin, *n* (%)	1,344 (2)	512 (3)	109 (1)	167 (3)	68 (3)	107 (6)	381 (2)	<0.0001
Statin, *n* (%)	12,578 (23)	5,257 (27)	2,471 (34)	1,727 (28)	464 (24)	314 (16)	2,345 (13)	<0.0001
Microvascular events, *n* (%)	3,185 (9.2)	1,070 (7.5)	475 (8.1)	459 (9.7)	182 (12.8)	263 (20.4)	736 (10.3)	<0.0001
Macrovascular events, *n* (%)	10,864 (31.3)	4,499 (31.5)	1,822 (31.0)	1,473 (31.1)	450 (31.7)	452 (35.0)	2,168 (30.4)	<0.0001
Death, *n* (%)	1,807 (5.2)	744 (5.2)	268 (4.6)	224 (4.7)	68 (4.8)	66 (5.1)	437 (6.1)	<0.0001

Percentages may not total 100% as a result of rounding. To convert TC and HDL-C to millimoles per liter, multiply by 0.259. HDL-C, HDL cholesterol; TC, total cholesterol.

within the 1st year after diabetes diagnosis is sufficient to establish an irremediable long-term future risk of microvascular and macrovascular complications. In addition, failure to achieve an HbA$_{1c}$ <7.0% (<53 mmol/mol) within the 1st year after diabetes diagnosis may lead to an irreversible increased risk of mortality. These findings are supported by previous cohort studies that showed that failure to intensify diabetes treatments in patients with elevated HbA$_{1c}$ values is associated with increased retinopathy and cardiovascular events (18,19).

Longer periods of early exposure to a mean HbA$_{1c}$ <8.0% (<64 mmol/mol) in the current study were not associated with an increased risk of complications; however, lower periods of early exposure to an HbA$_{1c}$ ≥8.0% (≥64 mmol/mol) were associated with an increased future risk of microvascular events and mortality. The interaction between the duration and intensity of glycemic exposure and outcomes aligns with the pathophysiologic understanding of the glycemic legacy effect and patient outcomes from the DCCT and UKPDS. In cellular and animal models, persistent harm associated with historical hyperglycemia has been attributed to mitochondrial superoxide overproduction, leading to increased advanced glycation end products, activation of protein kinase C, fructose production, and increased flux through the hexosamine pathway (20,21). In the DCCT, patients with elevated levels of advanced glycation end products had higher rates of microvascular complications (22). Furthermore, patients randomized to early intensive glycemic control in the UKPDS and DCCT had a legacy of benefits that lasted 10 and 25 additional years, respectively (1,4).

The current results suggest that the patient's lifetime history of glycemic control may be necessary to understand why patients with longstanding diabetes develop complications despite excellent control later in the course of their disease. The association between the first years of glycemic control and outcomes also should be considered when formulating public health and health care policy regarding the intensity of efforts to control hyperglycemia to improve diabetes outcomes for patients with longstanding diabetes. Young (ages 18–39 years) and

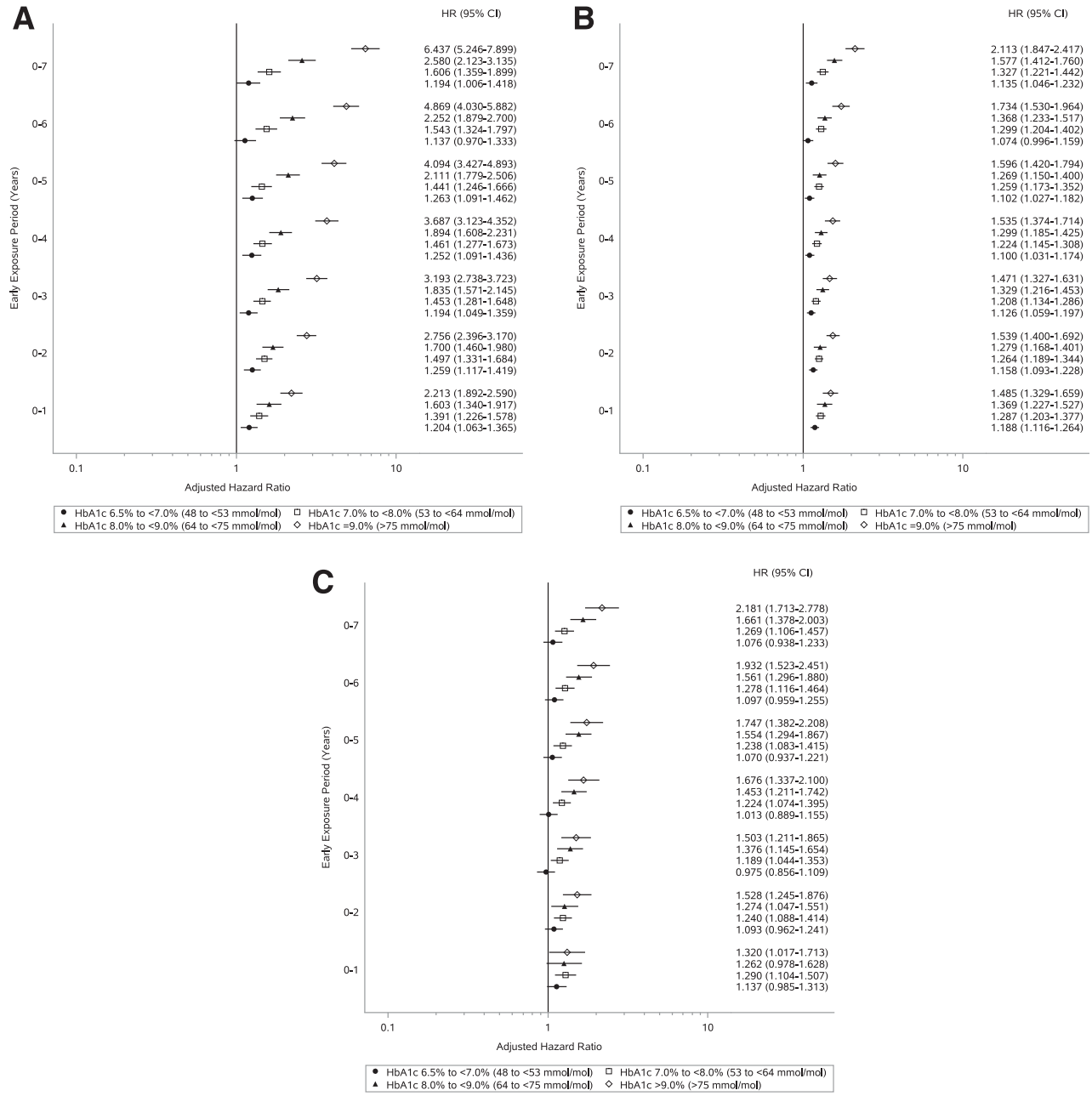

Figure 2—*A*: Microvascular events (vs. HbA_{1c} <6.5% [<48 mmol/mol]). *B*: Macrovascular events (vs. HbA_{1c} <6.5% [<48 mmol/mol]). *C*: Mortality (vs. HbA_{1c} <6.5% [<48 mmol/mol]). HRs adjusted for year of diagnosis, age at diagnosis, sex, race/ethnicity, BMI, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, smoking status, HbA_{1c} after each early exposure period, and comorbidity.

middle-aged adults (ages 40–64 years), however, have been found to have substantially higher glycemic levels than older adults (23), which is a missed opportunity; treating patients with diabetes earlier and more intensively has the potential to confer substantial, long-term improvements in public health. Our finding of a relationship between missing data in the 1st year being predictive of future events also suggests the value for aggressive follow-up or educational efforts for patients who do not use offered services. Thus, public health and health care policy should put a greater emphasis on achieving early glycemic control as an avenue for improving lifetime outcomes for patients with diabetes.

This study has several strengths and limitations. Because we studied only patients with newly diagnosed diabetes and at least 10 years of survival, the results are not generalizable to patients with established diabetes or to those with a high risk of mortality after diabetes diagnosis. It is possible that patients with established diabetes may benefit from HbA_{1c} <6.5% (<48 mmol/mol) control, but the benefits may take decades to become evident, and patients may die as a result of nondiabetes-related causes in the meantime. For example, in the Veterans Affairs Diabetes Trial (VADT), which randomized patients with established diabetes (mean 11.5 years) to intensive glycemic control or standard therapy (median HbA_{1c} 6.9% [52 mmol/mol] vs. 8.4% [68 mmol/mol]) for 5.6 years, reductions in major cardiovascular

Table 2—Associations among various early HbA_{1c} exposure periods and subsequent outcomes

	Microvascular events			Macrovascular events			Death		
Early period and mean glycemic control	*n*/total *n*	Adjusted HR (95% CI)	*P* value	*n*/total *n*	Adjusted HR (95% CI)	*P* value	*n*/total *n*	Adjusted HR (95% CI)	*P* value
0–1 year									
HbA_{1c}									
<6.5% (<48 mmol/mol)	864/14,080	Reference		3,668/13,455	Reference		744/14,286	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	372/5,774	1.204 (1.063–1.365)	0.004	1,497/5,552	1.188 (1.116–1.264)	<0.0001	268/5,877	1.137 (0.985–1.313)	0.079
7.0% to <8.0% (53 to <64 mmol/mol)	385/4,656	1.391 (1.226–1.578)	<0.0001	1,244/4,501	1.287 (1.203–1.377)	<0.0001	224/4,730	1.290 (1.104–1.507)	0.001
8.0% to <9.0% (64 to <75 mmol/mol)	154/1,390	1.603 (1.340–1.917)	<0.0001	383/1,351	1.369 (1.227–1.527)	<0.0001	68/1,418	1.262 (0.978–1.628)	0.073
≥9.0% (≥75 mmol/mol)	232/1,259	2.213 (1.892–2.590)	<0.0001	382/1,220	1.485 (1.329–1.659)	<0.0001	66/1,290	1.320 (1.017–1.713)	0.037
Missing	647/7,047	1.354 (1.218–1.505)	<0.0001	1,899/6,867	1.112 (1.050–1.177)	0.0003	437/7,136	1.235 (1.094–1.394)	0.001
0–2 years									
HbA_{1c}									
<6.5% (<48 mmol/mol)	809/14,673	Reference		3,612/13,860	Reference		817/14,940	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	451/7,517	1.259 (1.117–1.419)	0.0002	1,866/7,143	1.158 (1.093–1.228)	<0.0001	368/7,675	1.093 (0.962–1.241)	0.172
7.0% to <8.0% (53 to <64 mmol/mol)	544/7,144	1.497 (1.331–1.684)	<0.0001	1,788/6,842	1.264 (1.189–1.344)	<0.0001	368/7,295	1.240 (1.088–1.414)	0.001
8.0% to <9.0% (64 to <75 mmol/mol)	258/2,529	1.700 (1.460–1.980)	<0.0001	620/2,426	1.279 (1.168–1.401)	<0.0001	128/2,592	1.274 (1.047–1.551)	0.016
≥9.0% (≥75 mmol/mol)	408/2,159	2.756 (2.396–3.170)	<0.0001	624/2,112	1.539 (1.400–1.692)	<0.0001	126/2,235	1.528 (1.245–1.876)	<0.0001
0–3 years									
HbA_{1c}									
<6.5% (<48 mmol/mol)	619/12,475	Reference		2,931/11,635	Reference		717/12,769	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	412/7,883	1.194 (1.049–1.359)	0.007	1,818/7,347	1.126 (1.059–1.197)	0.0001	375/8,057	0.975 (0.856–1.109)	0.696
7.0% to <8.0% (53 to <64 mmol/mol)	551/8,310	1.453 (1.281–1.648)	<0.0001	1,931/7,873	1.208 (1.134–1.286)	<0.0001	433/8,541	1.189 (1.044–1.353)	0.009
8.0% to <9.0% (64 to <75 mmol/mol)	293/3,081	1.835 (1.571–2.145)	<0.0001	732/2,952	1.329 (1.216–1.453)	<0.0001	162/3,188	1.376 (1.145–1.654)	0.001
≥9.0% (≥75 mmol/mol)	406/2,084	3.193 (2.738–3.723)	<0.0001	563/2,041	1.471 (1.327–1.631)	<0.0001	120/2,182	1.503 (1.211–1.865)	0.0002
0–4 years									
HbA_{1c}									
<6.5% (<48 mmol/mol)	493/10,627	Reference		2,322/9,692	Reference		621/10,898	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	401/8,097	1.252 (1.091–1.436)	0.001	1,719/7,410	1.100 (1.031–1.174)	0.004	399/8,302	1.013 (0.889–1.155)	0.842
7.0% to <8.0% (53 to <64 mmol/mol)	542/9,306	1.461 (1.277–1.673)	<0.0001	2,019/8,710	1.224 (1.145–1.308)	<0.0001	482/9,608	1.224 (1.074–1.395)	0.002
8.0% to <9.0% (64 to <75 mmol/mol)	312/3,567	1.894 (1.608–2.231)	<0.0001	770/3,352	1.299 (1.185–1.425)	<0.0001	187/3,697	1.453 (1.211–1.742)	<0.0001
≥9.0% (≥75 mmol/mol)	412/2,115	3.687 (3.123–4.352)	<0.0001	534/2,073	1.535 (1.374–1.714)	<0.0001	118/2,232	1.676 (1.337–2.100)	<0.0001
0–5 years									
HbA_{1c}									
<6.5% (<48 mmol/mol)	399/9,209	Reference		1,862/8,226	Reference		552/9,475	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	377/8,244	1.263 (1.091–1.462)	0.002	1,596/7,389	1.102 (1.027–1.182)	0.007	423/8,465	1.070 (0.937–1.221)	0.318
7.0% to <8.0% (53 to <64 mmol/mol)	519/10,118	1.441 (1.246–1.666)	<0.0001	2,038/9,315	1.259 (1.173–1.352)	<0.0001	518/10,500	1.238 (1.083–1.415)	0.002
8.0% to <9.0% (64 to <75 mmol/mol)	331/3,841	2.111 (1.779–2.506)	<0.0001	727/3,556	1.269 (1.150–1.400)	<0.0001	200/3,984	1.554 (1.294–1.867)	<0.0001
≥9.0% (≥75 mmol/mol)	418/2,184	4.094 (3.427–4.893)	<0.0001	524/2,134	1.596 (1.420–1.794)	<0.0001	114/2,313	1.747 (1.382–2.208)	<0.0001

Continued on p. 424

Table 2—Continued

Early period and mean glycemic control	Microvascular events			Macrovascular events			Death		
	n/total *n*	Adjusted HR (95% CI)	*P* value	*n*/total *n*	Adjusted HR (95% CI)	*P* value	*n*/total *n*	Adjusted HR (95% CI)	*P* value
0–6 years									
HbA_{1c}									
<6.5% (<48 mmol/mol)	343/8,192	Reference		1,524/7,122	Reference		505/8,463	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	319/8,328	1.137 (0.970–1.333)	0.112	1,433/7,362	1.074 (0.996–1.159)	0.064	432/8,580	1.097 (0.959–1.255)	0.177
7.0% to <8.0% (53 to <64 mmol/mol)	523/10,696	1.543 (1.324–1.797)	<0.0001	1,967/9,671	1.299 (1.204–1.402)	<0.0001	547/11,120	1.278 (1.116–1.464)	0.0004
8.0% to <9.0% (64 to <75 mmol/mol)	322/4,034	2.252 (1.879–2.700)	<0.0001	713/3,683	1.368 (1.233–1.517)	<0.0001	207/4,199	1.561 (1.296–1.880)	<0.0001
≥9.0% (≥75 mmol/mol)	424/2,233	4.869 (4.030–5.882)	<0.0001	486/2,158	1.734 (1.530–1.964)	<0.0001	116/2,375	1.932 (1.523–2.451)	<0.0001
0–7 years									
HbA_{1c}									
<6.5% (<48 mmol/mol)	272/7,372	Reference		1,222/6,245	Reference		476/7,660	Reference	
6.5% to <7.0% (48 to <53 mmol/mol)	295/8,371	1.194 (1.006–1.418)	0.043	1,320/7,226	1.135 (1.046–1.232)	0.002	441/8,654	1.076 (0.938–1.233)	0.295
7.0% to <8.0% (53 to <64 mmol/mol)	481/11,178	1.606 (1.359–1.899)	<0.0001	1,783/9,959	1.327 (1.221–1.442)	<0.0001	562/11,672	1.269 (1.106–1.457)	0.001
8.0% to <9.0% (64 to <75 mmol/mol)	310/4,202	2.580 (2.123–3.135)	<0.0001	689/3,797	1.577 (1.412–1.760)	<0.0001	213/4,389	1.661 (1.378–2.003)	<0.0001
≥9.0% (≥75 mmol/mol)	414/2,201	6.437 (5.246–7.899)	<0.0001	447/2,107	2.113 (1.847–2.417)	<0.0001	115/2,362	2.181 (1.713–2.778)	<0.0001

All models adjusted for year of diagnosis, age at diagnosis, sex, race/ethnicity, BMI, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, smoking status, HbA_{1c} after each early period, and comorbidity.

events were detected only after 10 years of total follow-up (24). A long-term follow-up cohort study in a nonclinical trial population will be necessary to explore the effects of early versus later glycemic exposure in patients with established diabetes. In addition, the observed patterns between glycemic exposure and clinical outcomes may differ if we used other thresholds for defining glycemic exposure. The current study questions required a long follow-up, during which important secular changes in diabetes screening, (25) intensity of glycemic control (26), and outcomes (27) may have affected our findings. Although we adjusted for year of diagnosis to address issues with secular trends, residual confounding may still be present.

The study population was a managed care population from northern California, and this population is notable for its location, ethnic diversity, and sociodemographics. However, of note, 90% of patients with diabetes have health insurance (28), and KPNC cares for patients with a full range of insurance. In addition, because patients in KPNC are all offered uniform access to care within an integrated health care delivery system, confounding as a result of differential access to care is less of an issue by using KPNC data. Because this epidemiologic study includes all patients in KPNC with diabetes who survived 10 years after diagnosis, the predictor-outcome relationships that we identified should be widely generalizable, even if the distributions of HbA_{1c} exposure observed in this population may not apply to other settings. Furthermore, previous studies have demonstrated that quality of care at KPNC is comparable to other large health care delivery systems across the U.S. (29).

A major limitation is the inability to comment on causality. It is possible that HbA_{1c} at the time of diagnosis reflects inherent differences in baseline disease severity or patient characteristics that determine long-term outcomes. Furthermore, we relied on historical administrative databases to gather outcome data rather than a clinical adjudication of end points. Although there can be misclassification, we do not anticipate bias as a result of coding of events because that misclassification would unlikely differ systematically by timing, duration, and degree of glycemic exposure. We were

unable to study the effect of aspirin, behavioral factors, or cause of death because these are not well documented in medical records, which may have led to an overestimation of the relationships between early HbA_{1c} exposure and outcomes. We also did not analyze the effects of prescription medications because in the relationship between glycemic exposure and diabetic complications and mortality, medications can be time-dependent confounders, and using alternative modeling methods that address time-dependent confounding would preclude isolating the effects of specific early periods. Subsequent studies are necessary to explore how medications may moderate the legacy effect over time.

In conclusion, among patients with 10 years of survival after diabetes diagnosis, we found that HbA_{1c} levels $\geq$6.5% ($\geq$48 mmol/mol) for the 1st year after diagnosis was associated with a greater risk of future diabetic complications compared with an HbA_{1c} $<$6.5% for the 1st year after diagnosis. HbA_{1c} levels $\geq$7.0% ($\geq$53 mmol/mol) for the 1st year after diagnosis were associated with an increased risk of future mortality. Increasing periods of exposure to HbA_{1c} levels $\geq$8.0% ($\geq$64 mmol/mol) were associated with an increased risk of microvascular events and mortality. This study suggests that the legacy effect exists outside of trial populations, begins as early as the 1st year after diagnosis, and depends on the level of glycemic exposure. These findings underscore the urgency of early diagnosis of diabetes and the future consequences of failing to achieve near-normal glycemia soon after patients are diagnosed with diabetes.

Funding. N.L. was supported by a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant K23-DK-092783, the American Diabetes Association (1-18-JDF-037), and The University of Chicago Bucksbaum Institute for Clinical Excellence. E.S.H. is supported by NIDDK grant K24-DK-105340. N.L. and E.S.H. are members of the NIDDK Chicago Center for Diabetes Translation Research at The University of Chicago (P30-DK-092949). H.H.M., J.Y.L., and A.J.K. are members of the NIDDK Center for Diabetes Translational Research at Kaiser Permanente (P30-DK-092924). This study also was supported by the NIDDK-funded Diabetes & Aging Study (R01-DK-081796 and R56-AG-051683).

The funders had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of data; or the preparation, review, or approval of the manuscript.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. N.L. designed the study, analyzed and interpreted data, drafted the manuscript, and obtained funding. S.A.H. analyzed and interpreted data and reviewed/edited the manuscript. Y.G. contributed to the study design, analyzed and interpreted data, and reviewed/edited the manuscript. H.H.M. contributed to the study design and data interpretation, provided administrative support, and reviewed/edited the manuscript. J.Y.L. contributed to the data analysis and interpretation and reviewed/edited the manuscript. E.S.H. and A.J.K. contributed to the study design and data interpretation, reviewed/edited the manuscript, and obtained funding. N.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016.

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