A1C and Cardiovascular Outcomes in Type 2 Diabetes

A nested case-control study

Danielle C. Colayco, pharmd, ms[1]
Fang Niu, ms[2]

Jeffrey S. McCombs, phd[1]
T. Craig Cheetham, pharmd, ms[2]

OBJECTIVE — Type 2 diabetes is associated with increased cardiovascular risk. The role of aggressive glycemic control in preventing cardiovascular events is unclear. A nested case-control study design was used to evaluate the association between average A1C and cardiovascular outcomes.

RESEARCH DESIGN AND METHODS — Adults with type 2 diabetes were identified among members of Kaiser Permanente Southern California. Type 2 diabetes was identified based on ICD-9 diagnosis codes and either A1C >7.5% or prescriptions for hypoglycemic agents. Case subjects were defined based on nonfatal myocardial infarction, nonfatal stroke, or death attributed to cardiovascular events during a 3-year window. Four type 2 diabetes control subjects were matched to each case subject based on age, sex, and index date for the corresponding case. A conditional logistic regression model was used to estimate the odds ratio of cardiovascular events and compare three patient groups based on average A1C measured in the preindex period (≤6, >6–8, >8%).

RESULTS — A total of 44,628 control subjects were matched to 11,157 case subjects. Patients with an average A1C ≤6% were 20% more likely to experience a cardiovascular event than the group with an average A1C of >6–8% ($P < 0.0001$). Patients with an average A1C >8% experienced a 16% increase in the likelihood of a cardiovascular event ($P < 0.0001$). We found evidence of statistical interaction with A1C category and LDL level ($P = 0.0002$), use of cardiovascular medications ($P = 0.02$), and use of antipsychotics ($P = 0.001$).

CONCLUSIONS — High-risk patients with type 2 diabetes who achieved mean A1C levels of ≤6% or failed to decrease their A1C to <8% are at increased risk for cardiovascular events.

Diabetes Care **34:77–83, 2011**

Type 2 diabetes is associated with an increased risk of microvascular complications, such as nephropathy, neuropathy, and retinopathy, as well as macrovascular complications including myocardial infarction (MI) and stroke. Diabetic patients who have not had a previous MI have the same risk of an infarction as nondiabetic patients who have had a previous MI (1). Cardiovascular disease complications are the most common cause of mortality in type 2 diabetic patients, accounting for 52% of deaths in this population (2).

Tighter glycemic control and lower A1C levels decrease the risk of microvascular complications (3–6). The American Diabetes Association recommends a target of A1C <7%, whereas the American Association of Clinical Endocrinologists recommends a A1C target of ≤6.5% (7,8). Despite these established guidelines, questions remain regarding the ideal A1C target for minimizing cardiovascular events in type 2 diabetes.

Observational studies (5,6,9–11) have suggested a direct association between hyperglycemia and cardiovascular events, whereas three large, randomized clinical trials failed to establish a cardiovascular benefit for intensive glycemic control. The Veterans Affairs Diabetes Trial (VADT) (10) randomly assigned diabetic subjects to intensive glycemic control (target A1C ≤6.0%) versus standard treatment (target A1C 8–9%) and found no significant difference between the treatment arms for major cardiovascular events or all-cause mortality. Similarly, the Action in Diabetes and Vascular Disease Trial (6) compared a target A1C of ≤6.5% with standard of care and found no significant difference in macrovascular events. Finally, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial (11) compared a target A1C of ≤6.0% to a target A1C of 7.0–7.9% in the standard arm. The trial was halted early because of a significant increase in all-cause death and cardiovascular death in the intensively treated arm.

We investigated whether the increased risk associated with intensive glycemic control found in the ACCORD trial is observed in a managed-care population. We define glycemic control as the mean A1C level for each patient measured over 3 years to mimic the average follow-up period in the ACCORD study.

RESEARCH DESIGN AND METHODS

We investigated the relationship between glycemic control and cardiovascular events using a nested case-control design.

Study sample

Data were derived from the Kaiser Permanente Southern California (KPSC) Health Plan, which contains information on patient demographics, diagnoses, prescriptions, laboratory results, and medical and hospital encounters. The KPSC membership includes ~3.3 million individuals, representing 15% of the underlying population in southern California. Membership is largely employer based (~5% of the KPSC population is Medicaid eligible and 11% is Medicare eligible). The racial composition is as follows: 42.9% non-Hispanic white; 23.2% Hispanic white;

14.4% black; 9.6% Asian/Pacific Islander; 0.2% American Indian/Alaskan; 9.4% other; and 0.3% two or more races.

Adult patients (aged ≥18 years) with type 2 diabetes were identified based on two recorded type 2 diabetes diagnoses between January 2002 and December 2007 and either an A1C >7.5% or a prescription for oral hypoglycemic medication or insulin. Patients with a diagnosis of polycystic ovarian syndrome, gestational diabetes, or serious illnesses including HIV/AIDS, cancer, sickle cell disease, cystic fibrosis, organ transplant, liver failure, or respiratory failure were excluded from the study.

Case subjects were defined using a primary composite end point of nonfatal MI, nonfatal stroke, or death attributed to cardiovascular causes (MI, stroke, heart failure, or arrhythmia) between January 2005 and December 2007. The date of the case-defining event was listed as the index date. Control subjects without the primary end point during the time window were eligible for matching. Each case subject was matched with four control subjects based on age and sex. Control subjects were assigned a pseudo–event date equal to the index date of their matched case subject. We excluded patients without 3 years of continuous KPSC membership plus drug benefits prior to their index date, patients whose first type 2 diabetes diagnosis occurred after their index date, and patients with no recorded A1C in the observation window.

Case and control subjects were assigned to A1C categories based on their average A1C measured over the 3 years prior to their index date. Sensitivity analyses were performed using their median A1C and most recent A1C prior to the index date. The study's A1C categories are consistent with the ACCORD study (≤6, >6–8 [comparison group], and >8%).

A power analysis indicated that 672 case subjects, matched in a one-to-four ratio to control subjects, would be necessary to have 90% power to detect an odds ratio of 1.15 between A1C categories, adopting the two-sided 0.05 significance level (12).

Statistical analyses

We compared baseline characteristics between case and control subjects using the two-sided t test for continuous variables and the χ^2 statistic for categorical variables. A conditional logistic regression model was fitted to estimate the odds ratio of the primary end point in patients with A1C ≤6 and >8%, relative to patients with A1C between >6 and 8%, adjusting for potential confounders. We used a stratified model for statistically significant interaction terms. In a post hoc analysis, we fitted a separate model for patients on antipsychotic medications. All analyses were performed using SAS version 9.1.

Covariates

We adjusted for a number of laboratory, diagnostic, and prescription covariates in the multivariate analysis. A dichotomous variable was created to indicate if the patient's A1C was measured at least six times during the 3-year preindex period. Variability in preindex A1C values was defined as the difference between the minimum and maximum A1C, with an absolute difference of 1% considered as clinically meaningful (5,10). Cholesterol levels (LDL and HDL) measured in the year prior to index date also were included as covariates in the analyses.

Concurrent diabetes medications were categorized into six commonly prescribed regimens within KPSC: insulin monotherapy; metformin monotherapy; sulfonylurea monotherapy; insulin plus oral medications; other oral medications or combinations; and no diabetes medication. Medication adherence with diabetic drugs was measured using the proportion of days covered over the year prior to index (13). Dichotomous variables also were defined to reflect the use of statins, ACE inhibitors, angiotensin receptor blockers (ARBs), other antihypertensives, antiplatelets, first- and second-generation antipsychotics, antiarrhythmics, tricyclic antidepressants, erythropoietin-stimulating agents (ESAs), and β-agonists.

Dichotomous variables were created to reflect cardiovascular events during the 3-year preindex period, including hospitalizations for MI, stroke, heart failure, or arrhythmia. Outpatient cardiovascular diagnoses included hypertension, peripheral vascular disease, or heart failure. Diagnoses of retinopathy, nephropathy, chronic kidney disease, neuropathy, and prior amputations suggesting microvascular disease were included as covariates. Finally, severe episodes of hypoglycemia requiring emergency-department services or hospitalizations were captured using dichotomous variables.

RESULTS

Study population

A pool of 254,118 type 2 diabetic patients was identified, from which a total of 16,589 case subjects met the end point of nonfatal MI, nonfatal stroke, or death attributed to cardiovascular causes. After matching and applying the exclusion criteria, a total of 44,628 control subjects were matched to 11,157 case subjects (Fig. 1).

Demographic and clinical characteristics for case and control subjects are listed in Table 1. The mean age was 65.5 ± 10.5 years, and 57% of the subjects were male. Case and control subjects differed significantly in all other characteristics. Case subjects were twice as likely as control subjects to use insulin and were less likely to use statins, ACE inhibitors, or ARBs. Case subjects were six times more likely to use antipsychotics and ESAs. Approximately 90% of the population, of both case and control subjects, had a cardiovascular diagnosis. Compared with control subjects, case subjects were four times more likely to have had a cardiovascular event in 3-year preindex period and approximately four times more likely to have had a severe episode of hypoglycemia. Case subjects also were more likely to have preexisting microvascular disease. Finally, the high percentage of β-agonist use reflects the high prevalence of asthma and chronic obstructive pulmonary disease within the population of both case and control subjects.

Primary analysis

In the unadjusted logistic model, patients with a 3-year average A1C of ≤6% were 18% more likely to experience a cardiovascular event than patients with an average A1C of >6–8% (odds ratio 1.18 [95% CI 1.11–1.25]; $P < 0.0001$). Patients with an average A1C of >8% were 31% more likely to have an event (1.31 [1.24–1.38]; $P < 0.0001$) than the comparison group.

The results of the multivariate analysis are presented in Table 2. Patients with an average A1C of ≤6% were 20% more likely to experience a cardiovascular event, and patients with an average A1C of >8% experienced a 16% increase in likelihood of a cardiovascular event compared with patients with an average A1C between >6 and 8%, after adjusting for potential confounders.

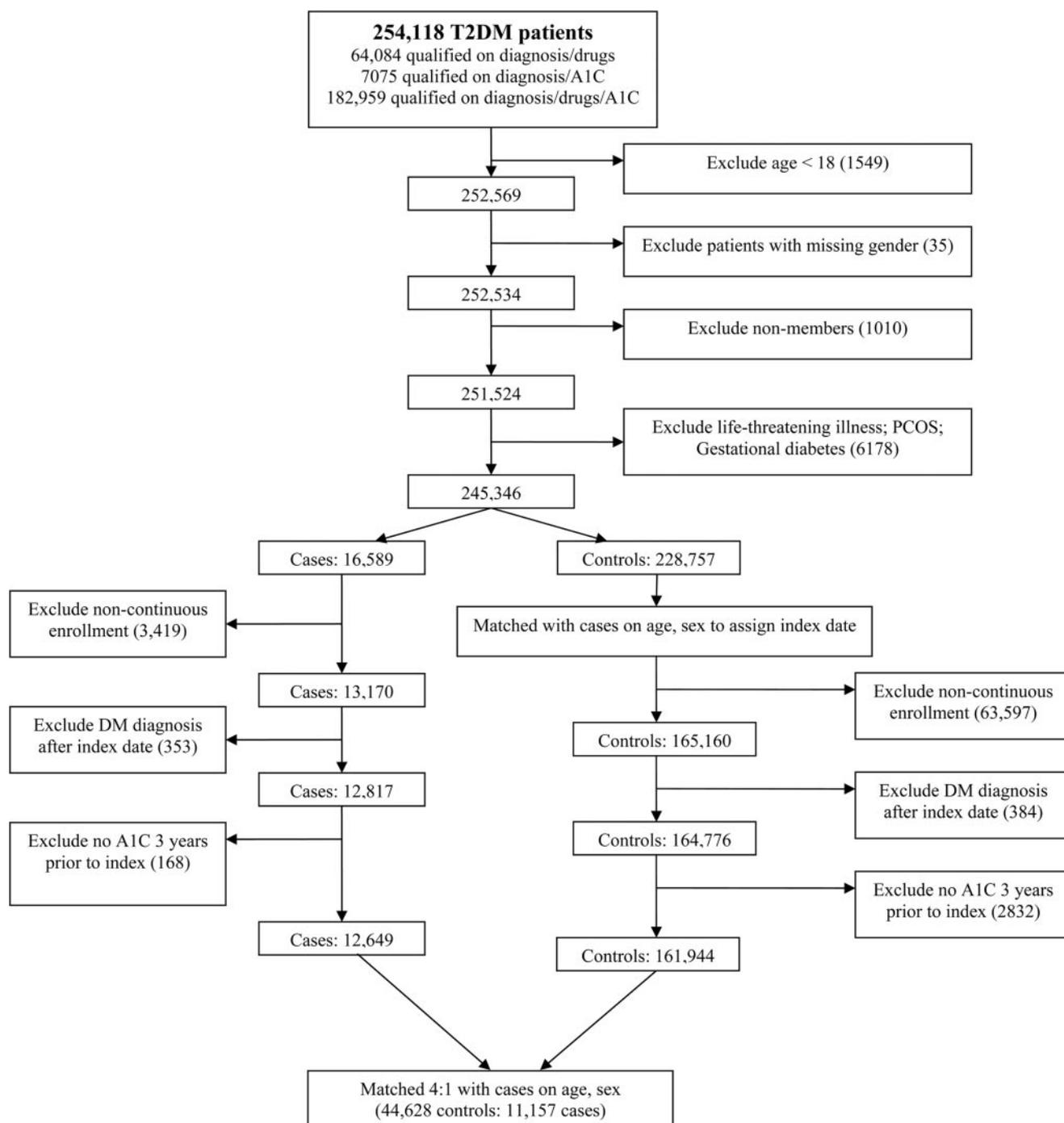Compared with the group with no diabetes medication use, patients using

254,118 T2DM patients
64,084 qualified on diagnosis/drugs
7075 qualified on diagnosis/A1C
182,959 qualified on diagnosis/drugs/A1C

Exclude age < 18 (1549)

252,569

Exclude patients with missing gender (35)

252,534

Exclude non-members (1010)

251,524

Exclude life-threatening illness; PCOS; Gestational diabetes (6178)

245,346

Cases: 16,589 | Controls: 228,757

Exclude non-continuous enrollment (3,419)

Matched with cases on age, sex to assign index date

Cases: 13,170

Exclude non-continuous enrollment (63,597)

Exclude DM diagnosis after index date (353)

Controls: 165,160

Cases: 12,817

Exclude DM diagnosis after index date (384)

Exclude no A1C 3 years prior to index (168)

Controls: 164,776

Exclude no A1C 3 years prior to index (2832)

Cases: 12,649

Controls: 161,944

Matched 4:1 with cases on age, sex
(44,628 controls: 11,157 cases)

Figure 1—*Selection of study population.*

insulin (alone or in combination) experienced a 2.5-fold increase in the risk of a cardiovascular event, whereas patients treated with sulfonylurea monotherapy and other combinations of oral medications experienced an increased risk of 55%. Metformin monotherapy was not associated with an excess cardiovascular risk. Adherence to diabetes medications conferred a significant protective effect, with each 10% increase in proportion of

days covered being associated with a 44% decrease in the risk of a cardiovascular event.

Statins, ACE inhibitors, and ARBs were associated with a decrease in odds, whereas antipsychotics, ESAs and tricyclic antidepressants were associated with an increased risk of cardiovascular events. Complications such as prior amputations, severe hypoglycemia, and history of previous cardiovascular events were significantly associated with cardiovascular events, as were indicators of microvascular disease (including nephropathy, neuropathy, and retinopathy). High LDL (>100 mg/dl) also was significantly associated with cardiovascular events, whereas high HDL (>40 mg/dl) was protective.

The stratified analysis evaluating the impact of A1C categories on cardiovascular outcomes within selected populations

are presented in Table 3. For all subgroups, an average A1C of >8% was associated with an increased risk of cardiovascular events; however, for those with high LDL or those taking cardiovascular medications other than ACE inhibitors and ARBs, an A1C ≤6% was not significantly associated with event risk.

The final two groups in Table 3 reflect that 2,539 patients taking antipsychotics had a different risk profile from those not taking antipsychotics. For patients taking antipsychotics, an A1C >8% was associated with a threefold-increased odds of cardiovascular events, whereas A1C ≤6% was not significantly associated with cardiovascular events. For those not taking antipsychotics, the risk profile resembled that of the overall study, with both A1C categories showing statistically significant increases in cardiovascular risk relative to the >6–8% group.

Sensitivity analysis
Our model was robust to changes in the definition of glycemic control. Defining glycemic categories based on the median A1C yielded similar results in which the risk of cardiovascular events in patients with median A1C ≤6% was 21% higher than for patients with a A1C between >6 and 8%. Patients with median A1C >8% were at 10% increased risk of cardiovascular events. Using the most recent A1C prior to index, patients with A1C ≤6% were 41% more likely to have an event than those near target, whereas those with A1C >8% were at a 5% increased odds of a cardiovascular event.

CONCLUSIONS — In this study, patients with type 2 diabetes who achieved mean A1C levels of ≤6% or who failed to decrease their A1C to <8% over a 3-year period were at increased risk for cardiovascular events compared with patients with mean A1C levels between >6 and 8%. Although treatment effects varied across subgroups with different risk profiles, these subgroup analyses are consistent with the core results.

These results are consistent with the ACCORD trial, which found a significant increase in all-cause death and cardiovascular death in the intensively treated arm (11). Our study also lends support to the results of a recent retrospective cohort study by Currie et al. (14), which found a U-shaped association between survival and A1C. In this study, patients with the lowest A1C levels (median 6.4%) were at a 52% increased risk of all-cause mortality

Table 1—Patient characteristics

Variable	Case subjects	Control subjects	P
n	11,157	44,628	
Mean age (years)	65.5 ± 10.5	65.5 ± 10.5	Matching variable
Male sex	6,359 (57)	25,436 (57)	Matching variable
Mean A1C level (%)			
≤6	1,580 (14.2)	5,801 (13.0)	0.001
>6–8	6,818 (61.1)	29,564 (66.3)	<0.001
>8	2,759 (24.7)	9,263 (20.8)	<0.001
Measured ≥6 A1Cs over 3-year follow-up	6,055 (54.3)	22,150 (49.6)	<0.001
A1C range >1.0%	8,186 (73.4)	29,251 (65.5)	<0.001
Diabetes medications			
Insulin only	2,102 (18.8)	3,386 (7.6)	<0.001
Metformin only	681 (6.1)	5,908 (13.2)	<0.001
Sulfonylurea only	2,230 (20.0)	10,142 (22.7)	<0.001
Insulin and oral medications	2,579 (23.1)	5,747 (12.9)	<0.001
Other oral medications/oral combination	2,444 (21.9)	14,413 (32.3)	<0.001
No diabetes medications	1,121 (10.1)	5,032 (11.3)	<0.001
Mean proportion of days covered of diabetes medications	0.69 ± 0.35	0.71 ± 0.35	<0.001
Other medications			
Statins	7,787 (69.8)	33,602 (75.3)	<0.001
ACE inhibitors/ARBs	8,624 (77.3)	35,731 (80.1)	<0.001
Other antihypertensives/antiplatelets	4,241 (38.0)	11,195 (25.1)	<0.001
Antipsychotics	1,822 (16.3)	1,102 (2.5)	<0.001
Antiarrhythmics	423 (3.8)	510 (1.1)	<0.001
Tricyclic antidepressant	505 (4.5)	468 (1.1)	<0.001
ESAs	1,385 (12.4)	911 (2.0)	<0.001
β-Agonists	2,292 (20.5)	4,905 (11.0)	<0.001
Prior cardiovascular event	2,604 (23.3)	2,601 (5.8)	<0.001
MI only	293 (11.3)	428 (16.5)	
Stroke only	224 (8.6)	289 (11.1)	
Heart failure only	1,436 (55.1)	899 (34.6)	
Arrhythmia only	491 (18.9)	911 (35.0)	
MI and stroke	7 (0.3)	5 (0.2)	
MI and heart failure	60 (2.3)	24 (0.9)	
MI and arrhythmia	15 (0.6)	22 (0.8)	
Stroke and heart failure	6 (0.2)	2 (0.1)	
Stroke and arrhythmia	6 (0.2)	2 (0.1)	
Heart failure and arrhythmia	66 (2.5)	19 (0.7)	
Cardiovascular diagnosis	10,297 (92.3)	38,761 (86.9)	<0.001
Hypertension only	5,342 (51.9)	30,495 (78.7)	
Peripheral vascular disease only	88 (0.8)	235 (0.6)	
Heart failure only	123 (1.3)	144 (0.3)	
Peripheral vascular disease and heart failure	34 (0.3)	26 (0.1)	
Hypertension and heart failure	1,861 (18.1)	3,025 (7.8)	
Hypertension and peripheral vascular disease	1,423 (13.8)	3,590 (9.3)	
Hypertension, peripheral vascular disease, and heart failure	1,426 (13.8)	1,246 (3.2)	
LDL >100 mg/dl	3,499 (31.4)	15,465 (34.7)	<0.001
LDL ≤100 mg/dl	6,478 (58.0)	25,768 (57.7)	
Missing LDL	1,180 (10.6)	3,395 (7.6)	
HDL >40 mg/dl	5,278 (47.3)	27,409 (61.4)	<0.001

(continued)

Table 1—*Continued*

Variable	Case subjects	Control subjects	P
HDL ≤40 mg/dl	4,669 (41.8)	13,760 (30.8)	
Missing HDL	1,210 (10.8)	3,459 (7.8)	
Retinopathy	3,886 (34.8)	10,062 (22.6)	<0.001
Nephropathy	8,005 (71.8)	23,194 (52.0)	<0.001
Neuropathy	4,487(40.2)	12,016 (26.9)	<0.001
Prior amputations	466 (4.2)	274 (0.6)	<0.001
Prior severe hypoglycemia	447 (4.0)	520 (1.2)	<0.001

Data are *n* (%) or means ± SD. Prior cardiovascular event = hospitalization for MI, stroke, heart failure, or arrhythmia in the 3-year preindex period. Cardiovascular diagnosis = hypertension, heart failure, and/or peripheral vascular disease. Prior severe hypoglycemia = emergency-room visit or hospitalization with a primary diagnosis of hypoglycemia.

relative to patients with a median A1C of 7.5%. In addition, patients in the highest A1C group (median A1C 10.5%) were at 79% increased relative risk. However, our results differ from that of the UK Prospective Diabetes Study (UKPDS) 10-year follow-up, which demonstrated that intensive treatment was associated with a

Table 2—*Conditional logistic regression model of cardiovascular events*

Covariate	Odds ratio (95% CI)	P
Mean A1C level (%)		
≤6.0	1.20* (1.10–1.31)	<0.001
>6.0–8.0	Reference	—
>8.0	1.16* (1.09–1.25)	<0.001
≥6 A1C tests over prior 3 years	0.84 (0.80–0.89)	<0.001
A1C range >1.0%	1.29 (1.21–1.38)	<0.001
Diabetes medications		
Insulin only	2.65 (2.31–3.05)	<0.001
Metformin only	1.06 (0.92–1.23)	0.41
Sulfonylurea only	1.55 (1.36–1.76)	<0.001
Insulin and oral medications	2.56 (2.19–3.00)	<0.001
Other oral medications/oral combination	1.55 (1.33–1.80)	<0.001
No diabetes medications	Reference	—
Mean proportion of days covered of diabetes medications	0.56 (0.49–0.63)	<0.001
Statins	0.75 (0.70–0.80)	<0.001
ACE inhibitors/ARBs	0.80 (0.74–0.86)	<0.001
Other antihypertensives/antiplatelets	1.34 (1.25–1.43)	<0.001
Antipsychotics	7.10 (6.24–8.09)	<0.001
Antiarrhythmics	1.54 (1.30–1.83)	<0.001
Tricyclic antidepressant	2.91 (2.44–3.46)	<0.001
ESAs	2.75 (2.46–3.08)	<0.001
β-Agonists	1.63 (1.52–1.75)	<0.001
Prior cardiovascular event	3.10 (2.87–3.36)	<0.0001
Cardiovascular diagnosis	1.41 (1.28–1.56)	<0.0001
LDL >100 mg/dl	1.14 (1.06–1.22)	0.0033
HDL > 40 mg/dl	0.67 (0.63–0.71)	<0.0001
Retinopathy	1.13 (1.07–1.21)	<0.0001
Nephropathy	1.68 (1.58–1.79)	<0.0001
Neuropathy	1.19 (1.12–1.26)	<0.0001
Prior amputations	3.28 (2.52–4.26)	<0.0001
Prior severe hypoglycemia	1.67 (1.40–1.99)	<0.0001

*Odds ratio estimated using multivariate analysis controlling for all covariates listed in table. Prior cardiovascular event = hospitalization for MI, stroke, heart failure, arrhythmia in the 3-year preindex period. Cardiovascular diagnosis = hypertension, heart failure, and/or peripheral vascular disease. Prior severe hypoglycemia = emergency-room visit or hospitalization with primary diagnosis of hypoglycemia.

15% relative risk reduction in MI (relative risk 0.85 [95% CI 0.74–0.97]; *P* = 0.01) (5).

The characteristics of our patient population are comparable with the ACCORD trial and the study by Currie et al. (14) in terms of age and cardiovascular risk profile and less comparable with the UKPDS. Our study sample was composed of mostly elderly subjects (mean age 65.5 years), whereas the UKPDS recruited younger, newly diagnosed patients (mean age 53 years), with <8% of the population having a history of cardiovascular disease. By contrast, 90% of our study population had comorbid hypertension and ~60% had microvascular disease. The ACCORD trial also included patients with previous cardiovascular events or multiple cardiovascular risk factors. The study by Currie et al. included patients with a history of medication escalation, and 63% of the population had a smoking history. These results suggest that in elderly patients with a high cardiovascular risk profile, intensive glycemic control should be initiated with caution.

The medication regimens used in the different studies also warrant discussion. In our study, metformin monotherapy was not associated with excess cardiovascular risk, whereas other combinations of oral drugs, including sulfonylureas, exhibited an increased risk of events. Similarly, in the UKPDS, the relative risk reductions for death and MI were greater for patients receiving metformin-based regimens than for those on sulfonylurea-based regimens. In our study, insulin use alone or in combination with oral medications was associated with a >2.5-fold–increased risk of cardiovascular events. These findings are consistent with Currie et al. (15), which identified a lower survival rate in insulin users compared with oral medication users. The mechanism for the excess risk associated with insulin and sulfonylurea use is not clearly understood; however, it is possible that hypoglycemia plays a role. It has been proposed that hypoglycemia may precipitate cardiac arrhythmias through hypokalemia and sympatho-adrenal activation (15,16). In addition, glucose variability has been implicated as a factor in oxidative stress and vascular inflammation (17). Alternatively, insulin use may reflect more advanced disease.

Taking antipsychotics also appeared to confer an increased risk of cardiovascular events, primarily driven by the use of first-generation antipsychotics, which

Table 3—*Conditional logistic regression model of cardiovascular events, stratified by subgroup*

Subgroup	n	A1C (%)	Odds ratio (95% CI)*	P
LDL <100, no other CV drug†	20,871	≤6	1.39 (1.15–1.67)	0.0006
		>8	1.20 (1.03–1.40)	0.02
LDL >100, no other CV drug†	13,983	≤6	1.05 (0.79–1.39)	0.74
		>8	1.41 (1.18–1.69)	0.0002
On other cardiovascular drug, LDL <100†	9,555	≤6	1.10 (0.85–1.43)	0.45
		>8	1.25 (0.95–1.63)	0.11
On other cardiovascular drug, LDL >100†	4,038	≤6	0.89 (0.39–2.01)	0.78
		>8	1.32 (0.70–2.49)	0.39
Patients using antipsychotics‡	2,539	≤6	1.05 (0.53–2.07)	0.90
		>8	3.15 (1.18- 8.44)	0.02
Patients not using antipsychotics†	53,246	≤6	1.26 (1.15–1.38)	<0.0001
		>8	1.17 (1.09–1.26)	<0.0001

LDL units are in mg/dl. Other cardiovascular drugs include antiplatelets and antihypertensives other than ACE inhibitors and ARBs.*Odds ratio for A1C category compared with A1C 6–8% (reference). †Not on antipsychotics. Model controlled for number of A1C tests in the 3-year index period, A1C range, diabetes medications, proportion of days covered of diabetes medications, use of statins, ACE inhibitors, ARBs, antiarrhythmics, tricyclic antidepressants, ESAs, β-agonists, diagnosis of hypertension, heart failure or peripheral vascular disease, retinopathy, nephropathy, neuropathy, prior cardiovascular events in 3-year preindex period, and severe hypoglycemia. ‡Model controlled for prior cardiovascular events, HDL level, use of β-agonists, and ESAs.

are associated with cardiac rhythm disturbances and QTc prolongation (18). To a lesser extent, second-generation antipsychotics, which are associated with weight gain and metabolic disturbances, also contributed to this effect (19). As expected, our data show that patients taking antipsychotics differed significantly in all clinical characteristics from those not taking antipsychotics; thus, it is likely that the two subgroups have different risk profiles. The secondary analysis revealed that intensive glycemic control in patients taking antipsychotics was associated with cardiovascular events to a lesser extent than in patients not taking antipsychotics. The effect of antipsychotics on cardiovascular risk in diabetic patients deserves further investigation.

Our study is subject to a number of limitations. First, the preindex time window was limited to 3 years. It is possible that any cardiovascular benefits of intensive glycemic control may take longer to become apparent, as shown in UKPDS. However, even short-term cardiovascular risk associated with average A1C levels <6% is a significant finding with clinical implications. Second, the use of conditional logistic regression in our analysis resulted in odds ratios that may overestimate relative risk when the absolute rate of events is high (20). Although the magnitude of risk may be overestimated, the direction of risk associated with intensive glycemic control is valid. Third, the non-

randomized design may subject the results to treatment selection bias; however, the completeness of the KPSC database allowed us to control for multiple potential confounders, including laboratory results and hospitalization data. Still, some key demographic data were missing, including race and socioeconomic status. Additionally, BMI data were not available for 66% of the study population and smoking status data generally are missing. Finally, duration of diabetes was not available, which was an important determinant of risk associated with intensive treatment based on post hoc analyses of VADT (21).

Our findings suggest that with respect to A1C control, aggressive lowering may not be appropriate for all type 2 diabetic patients. Although the potential for selection bias precludes us from drawing causal conclusions about the relationship between mean A1C and cardiovascular risk, our findings, together with those of the ACCORD trial and the study by Currie et al., have implications for clinical practice. Whereas uncontrolled hyperglycemia is an established risk factor for microvascular and macrovascular disease, intensive A1C control may not be the best approach for all type 2 diabetic patients. Initiation of intensive glycemic control warrants careful consideration of individual cardiovascular risk profiles. For a given individual, aggressive treatment strategies should carefully weigh the ben-

efits of preventing microvascular complications with the risk of precipitating cardiovascular events. Further research is needed to identify the types of patients for whom intensive glycemic control would be most appropriate, as well as selection of appropriate medication regimens. Ultimately, mitigating cardiovascular risk requires a multifactorial approach, glycemic control coupled with lipid lowering and blood pressure control, as well as lifestyle interventions (22).

References
1. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
2. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. Diabetologica 2001;44(Suppl. 2):S14–S21
3. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized

prospective 6-year study. Diabetes Res and Clin Pract 1995;28:103–117

4. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837–853

5. Stratton IM, Adler AJ, Neil AW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412

6. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572

7. American Diabetes Association. Standards of Medical Care in Diabetes: 2010. Diabetes Care 2010;33(Suppl. 1):S11–S61

8. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, Hellman R, Jellinger PS, Jovanovic LG, Levy P, Mechanick JI, Zangeneh F. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocrine Practice 2007;13(Suppl. 1):3–68

9. Yang X, Kong APS, So WY, Ma RC, Ho CS, Lam CW, Chow CC, Cockram CS, Tong PC, Chan JC. Effects of chronic hyperglycaemia on incident stroke in Hong Kong Chinese patients with type 2 diabetes. Diabetes Metab Res Rev 2007;23:220–226

10. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139

11. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358(24):2545–2559

12. Lachin JM. Sample size evaluation for a multiply matched case-control study using the score test from a conditional logistic (discrete Cox PH) regression model. Statistics in Medicine 2007;27:2509–2523

13. Leslie RS, Gwadry-Sridhar F, Thiebaud P, Patel BV. Calculating medication compliance, adherence and persistence in administrative pharmacy claims databases. Pharmaceutical Programming 2008;1(1):13–19

14. Currie CJ, Peters JR, Tynan A, Evans M, Heine R, Bracco O, Zagar T, Poole C. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375(9713):481–489

15. Davies JS, Hinds NP, Millward Em, McDowell I, Scanlon MF. Hypokalaemia during insulin-induced hypoglycemia in hypopituitary adults with and without growth hormone deficiency. Clin Endocrinol (Oxf) 1998;49:217–220

16. Lee SP, Yeoh L, Harris ND, Davies CM, Robinson RT, Leathard A, Newman C, Macdonald IA, Heller SR. Influence of autonomic neuropathy on QTc interval lengthening during hypoglycemia in type 1 diabetes. Diabetes 2004;53:1535–1542

17. Choi SW, Benzie IF, Ma SW, Strain JJ, Hannigan BM. Acute hyperglycemia and oxidative stress: direct cause and effect? Free Radic Biol Med 2008;44:1217–1231

18. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001;158:1774–1782

19. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27(2):596–601

20. Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ 1998;316:989–991

21. Riddle M, Bonds D, Duckworth W. New Analyses of ACCORD and VADT (late-breaking presentation). American Diabetes 69th Scientific Sessions, New Orleans, LA, 5–9 June 2009

22. Gaede P, Vedel P, Larsen N, Jensen GVH, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–393