Preventable Major Cardiovascular Events Associated With Uncontrolled Glucose, Blood Pressure, and Lipids and Active Smoking in Adults With Diabetes With and Without Cardiovascular Disease: A Contemporary Analysis

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OBJECTIVE

The objective of this study was to assess the incidence of major cardiovascular (CV) hospitalization events and all-cause deaths among adults with diabetes with or without CV disease (CVD) associated with inadequately controlled glycated hemoglobin (A1C), high LDL cholesterol (LDL-C), high blood pressure (BP), and current smoking.

RESEARCH DESIGN AND METHODS

Study subjects included 859,617 adults with diabetes enrolled for more than 6 months during 2005–2011 in a network of 11 U.S. integrated health care organizations. Inadequate risk factor control was classified as LDL-C ≥100 mg/dL, A1C ≥7% (53 mmol/mol), BP ≥140/90 mm Hg, or smoking. Major CV events were based on primary hospital discharge diagnoses for myocardial infarction (MI) and acute coronary syndrome (ACS), stroke, or heart failure (HF). Five-year incidence rates, rate ratios, and average attributable fractions were estimated using multivariable Poisson regression models.

RESULTS

Mean (SD) age at baseline was 59 (14) years; 48% of subjects were female, 45% were white, and 31% had CVD. Mean follow-up was 59 months. Event rates per 100 person-years for adults with diabetes and CVD versus those without CVD were 6.0 vs. 1.7 for MI/ACS, 5.3 vs. 1.5 for stroke, 8.4 vs. 1.2 for HF, 18.1 vs. 40 for all CV events, and 23.5 vs. 5.0 for all-cause mortality. The percentages of CV events and deaths associated with inadequate risk factor control were 11% and 3%, respectively, for those with CVD and 34% and 7%, respectively, for those without CVD.

CONCLUSIONS

Additional attention to traditional CV risk factors could yield further substantive reductions in CV events and mortality in adults with diabetes.

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Nearly 25 million Americans have diabetes, and if current trends persist, more than one in three American adults are projected to have diabetes by 2050 (1–3). Coronary heart disease and stroke are the leading causes of excess morbidity, mortality, and cost in adults with diabetes (4). Advances in medical care and improvements in cardiovascular (CV) risk factor control have resulted in the reduction of CV events and deaths among adults with diabetes (2,3). At the population level, however, increased diabetes prevalence and more years lived with diabetes offset much of the improvement in rates of CV events and mortality such that the absolute burden of CV events in those with diabetes remains high.

Major risk factors for CV events are well known, and effective drugs and behavioral interventions are available to manage blood pressure (BP), LDL cholesterol (LDL-C), glucose, and tobacco use. Estimating the prevalence of inadequately controlled risk factors and the proportion of major CV events and all-cause mortality associated with each of these uncontrolled CV risk factors could help prioritize clinical and public health strategies to further reduce the burden of CV disease (CVD) in adults with diabetes. Because risk factor prevalence, risk factor association with CV events, and impact of treatment of uncontrolled risk factors on CV events differ depending on whether an adult with diabetes has CVD, we conducted separate analyses of those with versus without CVD at baseline.

RESEARCH DESIGN AND METHODS

Data Sources

The Surveillance, Prevention, and Management of Diabetes Mellitus (SUPREME-DM) DataLink was developed in a network of 11 large, integrated health care organizations in the HMO Research Network in the United States (5). Members of these health systems include 16 million persons who receive insurance through a variety of mechanisms, including commercial plans, self-pay, Medicare, Medicaid, and other federal- or state-supported insurance programs. Health systems participating in SUPREME-DM include Geisinger Health System (Pennsylvania), Group Health (Washington), HealthPartners (Minnesota and Wisconsin), Henry Ford Health System (Michigan), Marshfield Clinic (Wisconsin), and Kaiser Permanente regions in Colorado (KPCO), Northern California (KPNC), Southern California (KPSC), Hawaii (KPHI), Georgia (KPSE), and the Northwest (Oregon and Washington [KPNW]). Research units embedded in these health care organizations developed a distributed virtual data warehouse that contains information on demographics, pharmacy, laboratory, diagnoses, and procedures from outpatient and inpatient encounters extracted from their respective electronic medical record and administrative data (claims) systems (6). Mortality data were extracted from administrative registries, state death registries, and the National Death Index (in two health systems) and were available with a 1-year lag. These data were used to construct the SUPREME-DM DataLink, the largest and most clinically detailed diabetes population ever assembled in the United States outside the U.S. Department of Veterans Affairs (5).

Study Population

To be included in the analyses reported here, subjects had to *1*) be at least 20 years old; *2*) be insured; *3*) have received care in one of the 11 participating health systems between 1 January 2005 and 31 December 2010; *4*) have an assigned diabetes identification date; *5*) have had at least 6 months of continuous enrollment before the cohort entry date; and *6*) have had one or more laboratory measurements of fasting plasma glucose, A1C, or LDL-C and BP. The cohort entry date was defined as the latest of *1*) the diabetes identification date, *2*) 1 January 2005, or *3*) the date the patient turned 20 years old.

Patients with diabetes insured during 2003 and 2011 were identified. Diabetes status was classified using a previously validated algorithm (5,7–9). Study criteria for diabetes required either one or more inpatient diabetes diagnosis codes (ICD-9 Clinical Modification 250.x, 357.2, 366.41, 362.01–362.07) or any combination of two or more of the following events on separate days no more than 2 years apart: *1*) A1C ≥6.5% (48 mmol/mol), *2*) fasting plasma glucose ≥126 mg/dL, *3*) random plasma glucose ≥200 mg/dL, *4*) outpatient visit diabetes diagnosis code (same codes as that used for inpatients), or *5*) any filled prescription for a glucose-lowering medication. Patients prescribed metformin or thiazolidinediones with no other indicator of diabetes were not included because these agents could be used for other conditions. Those who met criteria during pregnancy were excluded. Patients were assigned a diabetes identification date defined as the second date on which they met study criteria for diabetes.

Risk Factor Definitions

We extracted baseline data within ±1 year of the cohort entry date for each subject. When multiple baseline clinical measures were available, we selected the measure closest to the cohort entry date, except baseline BP, which was averaged from all outpatient readings within 1 year of the cohort entry date. We defined inadequate baseline control following American Diabetes Association guidelines (10,11)—LDL-C ≥100 mg/dL and A1C ≥7% (53 mmol/mol)—and the Eighth Joint National Committee 2014 guidelines (11)—systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or current smoking. Additional variables included age; sex; BMI (kilograms per meters squared); HDL cholesterol (HDL-C); treatment with antihypertensive medications, statins, insulin, or other glucose-lowering drugs; incident diabetes status; and preexisting comorbidities. To be classified as having incident diabetes in our cohort, a patient was required to have 18 months of antecedent enrollment with no evidence of diabetes before the diabetes identification date (5). Baseline status for comorbid conditions was assigned based on two or more outpatient diagnosis codes or one or more inpatient diagnosis codes on or before the cohort entry date for chronic kidney disease (CKD; ICD-9 code 585.xx), CVD (ICD-9 codes 410–414.xx and 429.2), heart failure (HF; ICD-9 codes 428–428.9), hemorrhagic stroke (ICD-9 codes 430–432.9), ischemic stroke (ICD-9 codes 433–434.91), and transient ischemic attack (ICD-9 code 435.xx). Multiple imputation was used for missing data on A1C, LDL-C, and HDL-C following previous work using the SUPREME-DM cohort (12).

CV Events and All-Cause Mortality

Major CV events were ascertained based on the date of primary hospital discharge ICD-9 diagnosis codes as follows: *1*) myocardial infarction (MI)/acute coronary syndrome (ACS) (ICD-9 codes 410.0–410.91, 411.1, 411.8), *2*) ischemic and hemorrhagic stroke (ICD-9 codes 433–434.91, 430–432.9), or *3*) HF (ICD-9 codes 428–428.9). These events were defined as the

first occurrence 7 days or more after the cohort entry date (to avoid inpatient stays starting before the cohort entry date). All-cause mortality was ascertained through 31 December 2010, independent of health insurance enrollment at the time of death. Time to event was calculated as days elapsed from the cohort entry date +7 days to the hospital discharge date associated with the given event. Follow-up time was censored *1*) when disenrolled from health insurance for more than 90 days, *2*) at the time of death, or *3*) at the end of the study period (31 December 2012). Follow-up time after death was censored at 31 December 2010 to accommodate lag in the currency of death index data.

Statistical Analysis

Models to predict hospitalization for MI/ACS, stroke, HF, and all-cause mortality were constructed with generalized linear models using Poisson distribution and log link. A two-step analysis was implemented to evaluate the inclusion of baseline covariates in the prediction model. In the first step, the associations of individual baseline variables with each major CV event and with all-cause mortality were evaluated in separate models for subjects with and without CVD at baseline, using only age and sex as covariates. Individual baseline variables included uncontrolled risk factors (BP, LDL-C, A1C, and tobacco status), medication use variables, BMI, HDL-C, incident diabetes, presence of CKD, race/ethnicity, and study site. Nonmonotonic associations of continuous variables with CV events or all-cause mortality were explored. In the second step, all baseline factors associated with a major CV event or with all-cause mortality in step 1 and with $P < 0.05$ as main effects were retained for inclusion in the final models.

To estimate the population-attributable fraction for each uncontrolled risk factor in adults with diabetes with and without baseline CVD, we calculated the average attributable fraction (AAF), as described by Rückinger et al. (13). The AAF is preferred to alternative measures of population-attributable fraction because of its properties of additivity and symmetry (14,15). AAF was evaluated for inadequately controlled risk factors (BP, LDL-C, A1C, and tobacco use) in the same Poisson model that included the other risk factors—age, sex, HDL-C, CKD, incident (vs. prevalent) diabetes, and medication use variables—as main effects for adults with diabetes with or without baseline CVD. CIs for AAF point estimates were estimated using delta method approximations, as described by Jewell (16).

To evaluate whether the lag between the cohort entry date and the diabetes identification date created an immortal time bias, we conducted a sensitivity analysis by restricting the analysis to those who were identified in the DataLink after 2005. In addition, we estimated the nondifferential misclassification of CV events on estimates of AAF following the work by Vogel and Gefeller (17).

Protection of Human Research Subjects

This study was reviewed in advance, approved, and monitored by the KPCO Institutional Review Board (IRB), and each participating site either ceded oversight to the KPCO IRB or received approval and oversight from their local IRB.

RESULTS

Baseline characteristics of the 859,617 study subjects with diabetes and with or without CVD are presented in Table 1. Mean follow up was 59 months, and 4,233,786 person-years of observation for CV events were included in the analysis. Mean age was 59 years (SD 14 years); 48% were female, 45% were white, and 31% had CVD. Incident diabetes was identified in 24% of diabetic subjects. The prevalence of inadequately controlled risk factors is presented in Table 1. Compared with those without baseline CVD, those with baseline CVD had better control of smoking (8.0% vs. 9.8%), A1C $\geq$7% (53 mmol/mol) (42% vs. 53%), and LDL-C $\geq$100 mg/dL (38% vs. 58%), and they had similar proportions of subjects with systolic/diastolic BP $\geq$140/90 mmHg (23% vs. 21%).

The associations of inadequately controlled baseline A1C, BP, LDL-C, and tobacco use with subsequent CV events and all-cause mortality are presented in Table 2. CV events and all-cause mortality also were associated with sex, age, race/ethnicity, CKD, HDL-C, incident diabetes status, and medication use variables (Table 1). However, major CV events and all-cause mortality were not significantly associated with baseline BMI (data not shown). In subjects without baseline CVD, all inadequately controlled CV risk factors were associated with higher risk of MI/ACS, stroke, and HF, but only smoking and BP were associated with all-cause mortality. A similar pattern emerged in subjects with baseline CVD: All inadequately controlled CV risk factors were associated with an increase in MI/ACS and stroke. Current smoking, BP, and A1C (but not LDL-C) were associated with an increase in HF. Only smoking was associated with all-cause mortality.

Rates of major CV events and all-cause mortality in adults with diabetes and CVD were substantially higher than in those with diabetes but no CVD (Table 3). Five-year CV event rates per 100 person-years for adults with diabetes and CVD versus those without CVD were 6.0 vs. 1.7 for MI/ACS, 5.3 vs. 1.5 for stroke, 8.4 vs. 1.2 for HF, 18.1 vs. 4.0 for any CV event, and 23.5 vs. 5.0 for all-cause mortality. In those without baseline CVD, 34% of major CV events and 7% of all deaths were associated with inadequately controlled BP, LDL-C, A1C, or tobacco use. Similarly, in those with baseline CVD, 11% of major CV events and 3% of all deaths were associated with inadequately controlled risk factors.

Table 4 quantifies the contribution of specific uncontrolled risk factors to CV events and deaths. In adults with diabetes and without CVD, inadequately controlled LDL-C was associated with 20% of observed MI/ACS and 14% of strokes. More than 3% of CV events were associated with smoking. Inadequately controlled BP was associated with 12% of strokes and HF events, whereas inadequately controlled A1C was associated with 10% of HF events. In subjects with diabetes and CVD, the proportion of major CV events associated with smoking ranged from nearly 1% (HF) to 3% (MI/ACS). Inadequate control of LDL-C or BP was associated with only a small proportion of CV events ($<$4%), and only smoking was associated with a small proportion of deaths (3%).

Sensitivity analysis exploring the immortal time bias caused by the lag between cohort entry date and diabetes identification date revealed a 1% relative difference in event rates and all-cause mortality and no discernible bias on measures of association (rate ratios) or AAF (data not shown) when the analysis was repeated in those identified in the DataLink after 2005. To estimate the

Table 1—Baseline characteristics of 859,617 adults with diabetes with and without CVD receiving care from 2005 to 2010 at 11 U.S. health care organizations and prevalence of inadequate control of BP (systolic/diastolic ≥140/90 mmHg), LDL-C (≥100 mg/dL), A1C (≥8% [≥64 mmol/mol]), and current smoking

	No CVD		CVD	
Characteristics	*n*	%	*n*	%
All	593,167	100	266,450	100
Age at baseline, years				
<40	70,172	11.8	6,209	2.3
40–49	128,942	21.7	20,029	7.5
50–64	263,973	44.5	92,194	34.6
65–79	115,491	19.5	15,109	43.2
≥80	14,589	2.5	32,909	12.4
Female sex	292,448	49.3	121,051	45.4
Race/ethnicity				
American Indian/Pacific Islander	7,512	1.3	2,430	0.9
African American/black	56,891	9.6	27,128	10.2
Asian	74,840	12.6	23,871	9.0
Hispanic	147,177	24.8	42,427	15.9
Other/multiple/unknown	71,270	12.0	18,012	6.8
White	235,477	39.7	52,582	57.3
BMI, kg/m^2				
Missing	103,602	17.5	44,762	16.8
<20	4,509	0.8	4,043	1.5
20–24	57,594	9.7	35,383	13.3
25–29	117,810	19.9	59,957	22.5
≥30	309,652	52.2	22,305	45.9
HDL-C, mg/dL				
≤40 (M) or ≤50 (F)	318,482	53.7	145,032	54.4
40.1–60 (M) or 50.1–60 (F)	199,807	33.7	88,378	33.2
>60	74,878	12.6	33,040	12.4
Incident diabetes	163,931	27.6	47,938	18.0
Chronic kidney disease	129,335	21.8	94,446	35.5
Treated BP	413,227	69.7	229,955	86.3
Treated dyslipidemia	419,848	70.8	227,049	85.2
Treated diabetes				
No treatment	163,667	27.6	78,933	29.6
Insulin treatment	96,292	16.2	72,028	27.0
Noninsulin treatment only	333,208	56.2	115,489	43.3
A1C, % (mmol/mol)				
≥9 (≥75)	129,643	21.9	30,288	11.4
8–8.9 (64–74)	63,023	10.6	25,190	9.5
7–7.9 (53–63)	122,341	20.6	56,723	21.3
6.5–6.9 (48–52)	114,757	19.4	53,168	20.0
<6.5 (48)	163,403	27.6	101,081	37.9
Systolic/diastolic BP, mmHg				
≥140/90	125,812	21.2	60,942	22.9
130–139/80–89	196,948	33.2	74,850	28.1
<130/80	270,407	45.6	30,658	49.0
LDL-C, mg/dL				
≥130	164,022	27.7	38,915	14.6
100–129	180,401	30.4	63,355	23.8
70–99	182,870	30.8	109,308	41.0
<70	65,874	11.1	54,872	20.6
Current smoking	57,852	9.8	21,295	8.0
A1C, BP, and LDL-C not at goal or current smoking	500,233	84.3	193,044	72.5

effect of misclassification of CV events in the attributable fractions, we assumed a sensitivity of 0.95 and a specificity of 0.995 based on previous work (18–20). This resulted in a relative reduction ranging from 24% (MI/ACS) to 30% (congestive HF) in adults with diabetes and no baseline CVD and from 6% (congestive HF) to 9% (stroke) in adults with diabetes and baseline CVD.

CONCLUSIONS

Despite sustained and quite impressive improvements in the control of glucose, BP, and lipids as well as smoking cessation in those with diabetes in the last decade in the United States, a substantial proportion of individuals have one or more of these factors that remain out of control (21). Our findings suggest that better management of these risk factors could lead to substantial further reductions in CV events and deaths among those with diabetes. For example, among those without CVD, the attributable risk fraction data suggest that about 1 in 3 major CV events and fewer than 1 in 10 deaths are associated with uncontrolled risk factors, including hypertension, dyslipidemia, smoking, and poor glucose control.

Although the fraction of CV events attributable to inadequate risk factor control is lower among those with CVD (11%) than those without CVD (34%), the overall rates of major CV events are nearly five times higher in patients with CVD than in those without it. In addition, only a portion of the CV risk of patients with diabetes is preventable, even with optimal control of these major CV risk factors. Thus primary prevention of diabetes is a critically important strategy to minimize the impact of diabetes on CV events and mortality, even though implementation of effective interventions to prevent diabetes can be challenging (22–25). The necessity of this approach is underscored by the observed number of CV events per 100 person-years in 2010: 14 in those with diabetes versus 8 in an age- and sex-matched sample without diabetes in the SUPREME-DM cohort (J.R.D., G.V.-B., P.J.O., unpublished results). Furthermore, the total direct medical cost related to these CV events is magnified because costs of CV events in adults with diabetes are twice the costs of events in those without diabetes during the 12-month period initiated by the event (26). Nonetheless, once a person has diabetes, strenuous efforts to prevent or delay CVD onset substantially lowers the risk of major CV events and are well justified (27).

Our results benchmark control of CV risk factors in adults with diabetes receiving care at 11 health care organizations and enable comparison with national data. Compared with data

Table 2—Rate ratios (95% CIs) of inadequate controlled risk factors with CV events and all-cause mortality in adults with diabetes with and without baseline CVD

Inadequately controlled factors	No CVD (*n* = 593,167)					CVD (*n* = 266,450)				
	MI/ACS	Stroke	HF	All CV	All-cause mortality	MI/ACS	Stroke	HF	All CV	All-cause mortality
Events, *n*	10,511	9,377	7,768	25,189	20,282	18,458	16,311	25,308	51,129	46,610
Current smoking	1.64 (1.55–1.74)	1.53 (1.43–1.64)	1.53 (1.42–1.64)	1.53 (1.47–1.61)	1.62 (1.55–1.69)	1.39 (1.32–1.46)	1.29 (1.22–1.36)	1.12 (1.07–1.18)	1.30 (1.25–1.36)	1.35 (1.31–1.40)
Systolic/diastolic BP, mmHg										
≥140/90	1.18 (1.15–1.22)	1.37 (1.33–1.41)	1.37 (1.33–1.42)	1.31 (1.28–1.34)	1.06 (1.04–1.09)	1.13 (1.11–1.16)	1.20 (1.18–1.23)	1.05 (1.03–1.08)	1.12 (1.10–1.14)	0.99 (0.98–1.01)
130–139/80–89	0.91 (0.89–0.94)	0.92 (0.90–0.95)	0.83 (0.80–0.86)	0.89 (0.87–0.91)	0.85 (0.83–0.87)	0.91 (0.89–0.93)	0.95 (0.93–0.97)	0.85 (0.83–0.86)	0.89 (0.87–0.90)	0.85 (0.84–0.86)
<130/80 (reference)	—	—	—	—	—	—	—	—	—	—
LDL-C, mg/dL										
≥130	1.51 (1.46–1.56)	1.31 (1.27–1.36)	1.10 (1.06–1.15)	1.30 (1.27–1.33)	0.98 (0.98–1.00)	1.22 (1.18–1.25)	1.18 (1.14–1.22)	1.02 (0.99–1.05)	1.11 (1.09–1.14)	1.02 (0.99–1.04)
100–129	1.06 (1.03–1.10)	1.02 (0.99–1.06)	0.94 (0.90–0.97)	0.98 (0.96–1.01)	0.91 (0.89–0.93)	0.99 (0.96–1.01)	1.01 (0.98–1.04)	0.92 (0.90–0.94)	0.96 (0.94–0.98)	0.92 (0.91–0.94)
70–99	0.83 (0.80–0.85)	0.88 (0.85–0.91)	0.99 (0.87–0.94)	0.86 (0.84–0.88)	0.96 (0.94–0.98)	0.91 (0.89–0.93)	0.92 (0.90–0.94)	0.96 (0.94–0.97)	0.92 (0.91–0.94)	0.93 (0.92–0.95)
<70 (reference)	—	—	—	—	—	—	—	—	—	—
A1C, % (mmol/mol)										
≥9 (≥75)	1.18 (1.14–1.23)	1.29 (1.23–1.34)	1.37 (1.31–1.44)	1.25 (1.22–1.29)	1.01 (0.98–1.05)	1.14 (1.10–1.18)	1.22 (1.17–1.27)	1.16 (1.13–1.20)	1.17 (1.14–1.20)	1.01 (0.98–1.03)
8–8.9 (64–74)	1.09 (1.04–1.15)	0.98 (0.92–1.03)	1.01 (0.96–1.07)	1.03 (0.99–1.07)	0.90 (0.87–0.94)	1.01 (0.98–1.05)	0.99 (0.95–1.03)	0.98 (0.95–1.01)	1.0 (0.97–1.03)	0.89 (0.87–0.91)
7–7.9 (53–63)	0.98 (0.94–1.02)	0.94 (0.91–0.98)	0.88 (0.84–0.92)	0.93 (0.91–0.96)	0.94 (0.91–0.96)	0.98 (0.95–1.01)	0.92 (0.89–0.95)	0.94 (0.92–0.97)	0.94 (0.92–0.96)	0.91 (0.89–0.93)
6.5–6.9 (48–52) (reference)	—	—	—	—	—	—	—	—	—	—
<6.5 (<48)	0.90 (0.86–0.94)	0.90 (0.87–0.95)	0.87 (0.83–0.92)	0.89 (0.87–0.92)	0.96 (0.94–0.99)	0.92 (0.89–0.95)	0.95 (0.92–0.98)	0.92 (0.90–0.94)	0.92 (0.90–0.94)	0.98 (0.96–1.0)

Estimates adjusted for age, sex, race/ethnicity, diabetes medication, statins, BP medication, CKD at baseline, incident diabetes at baseline, low HDL-C (≤40 mg/dL [men]/50 mg/dL [women]), and all other inadequately controlled factors as described in the table.

Table 3—Five-year event rates and all-cause mortality and percent of preventable CV events among adults with diabetes with and without baseline CVD

	No CVD (n = 593,167)		CVD (n = 266,450)	
Outcomes	5-year rates per 100 person-years	Preventable events (%)	5-year rates per 100 person-years	Preventable events (%)
MI/ACS events	1.7	38.4	6.0	16.0
Stroke events	1.5	36.2	5.3	17.7
HF events	1.2	29.3	8.4	3.3
All CV events	4.0	34.1	18.1	10.8
All-cause mortality	5.0	7.0	23.5	2.7

from the National Health and Nutrition Examination Survey (NHANES) for 2007 to 2010 (21), we found a lower prevalence of controlled risk factors: A1C (<7%, 53 mmol/mol), 50% vs. 52%; LDL-C (<100 mg/dL), 48% vs. 56%; and systolic/diastolic BP (<130/80 mmHg), 47% vs. 51%, as well as a similar prevalence (21% vs. 19%) of those reaching all three goals. Our results differ from the NHANES in that we identified people with incident diabetes, 24% of whom have not been targeted for optimal risk factor control.

A key finding in our study was the increased CV risk for A1C ≥9% (75 mmol/mol), especially in those with no CVD, and no increased risk for A1C 7–7.9% compared with 6.5–6.9%. This finding is congruent with the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and support current guidelines that recommend personalizing an A1C goal between <7% (53 mmol/mol) and <8% (64 mmol/mol) in patients with diabetes (28). Our data also are congruent with results from the Steno-2 study, which demonstrated a major reduction in CV events and CV mortality with aggressive BP and LDL-C management, with a median achieved A1C of about 7.8% (29). Our results and those of previous studies (30) suggest that the impact of A1C on CV events accelerates as A1C rises above 8%.

The lack of an association of elevated BP and HF in those with baseline CVD may be explained by the relatively short follow-up period in our study. Consistent with other studies of adults with diabetes, we observed no independent association of BMI with CV events or all-cause mortality (31–33), although others have found a *U*-shaped association in adults with incident diabetes (34). We found a strong association of HDL-C with CV events and mortality. Unfortunately, management of low HDL in those with diabetes is clinically challenging because of a paucity of evidence that existing therapies that increase HDL are effective in reducing CV events or deaths (35–38). Our analysis did not include other novel CV risk factors such as hs-CRP, coronary artery calcium, BP variability, sleep disorders, or chronic psychological stress (39,40). These factors either were not available in our data or were available only in a selected group of patients. The substantial residual CV risk not attributable to optimal management of BP, LDL-C, A1C, and tobacco raises the possibility that unidentified genetic, metabolic, or psychosocial risk factors may affect risk.

Several epidemiological studies have evaluated CV event attributable fractions using methods similar to ours or by combining published relative risk estimates with population-based estimates of CV risk factor prevalence in various populations (13,41–45). However, few studies have focused on adults with diabetes. A Taiwanese study found that the proportion of all-cause mortality and CVD-related mortality attributable to metabolic syndrome in the general population was 11.6% and 39.2% among men and 18.6% and 44.4% among women, respectively, and that central obesity in women and hypertension in men accounted for the highest number of deaths. In a study using 2005–2006 NHANES data, Rückinger et al. (13) concluded that, for subjects aged 40 years and older, hypertension accounted for 15.7% of CV events, followed by smoking (11.4%) and total cholesterol (10%), with an aggregate of 44% of CV events attributable to uncontrolled BP, total cholesterol, HDL, or smoking combined, whereas diabetes accounted for 5.4%.

Our study has several limitations. First, data for this study were obtained from routine care settings with varying time intervals and considerable missing data. To compensate for this, we did multivariate imputation for A1C, LDL-C, and HDL-C in about 5% of the sample. Second, classification of diabetes status is necessarily imperfect, although sensitivity is estimated at 91% and has a positive predictive value of 94% (46). Accurately distinguishing between type 1 and type 2 diabetes using electronic diagnosis data or duration of diabetes is not possible (7). Third, CV events were based on primary hospital discharge diagnoses and were not adjudicated. However, hospital discharge diagnoses for major CV events are highly accurate (18–20). Using the primary discharge diagnosis has an estimated positive predictive value of 96% for MI and 98% for stroke. Moreover, CV events based on primary hospital discharge diagnoses are thought to have near-perfect specificity, which greatly improves the accuracy of AAFs. Fourth, data constraints limited our analysis to all-cause–specific mortality. Fifth, the AAF is a well-recognized method of quantifying attributable risk that provides a valid estimate of the causal effect of improved risk factor control on health outcomes, but results using lagged cross-sectional analysis of observational data should be interpreted with caution. In addition, this method does not take into account nonlinearity, which may operate with some CV risk factors. In the present analysis, however, we sought but did not identify nonlinear associations. Another limitation is that we assessed risk factors and comorbid conditions only upon entry into the cohort; thus changes in risk factor control during follow-up were not reflected in the results. Finally, although we studied more than 800,000 adults with diabetes and had more than four million person-years of follow-up observation, our results may not apply to all segments of the U.S. general population.

These limitations must be weighed against the strengths of this study, which provides contemporary community-based estimates of attributable risk percentage for CV events and total mortality that reflect current levels of A1C, BP,

Table 4—AAFs (95% CIs) of inadequately controlled risk factors for major CV events and all-cause mortality among adults with and without baseline CVD

Inadequately controlled factors	No CVD (n = 593,167)					CVD (n = 266,450)				
	MI/ACS	Stroke	HF	All CV	All-cause mortality	MI/ACS	Stroke	HF	All CV	All-cause mortality
Current smoking	4.5% (4.1–4.9)	3.4% (3.0–3.8)	3.6% (3.2–4.0)	3.8% (3.5–4.0)	5.1% (4.8–5.5)	2.5% (2.3–2.8)	1.8% (1.6–2.0)	1.1% (1.0–1.2)	1.8% (1.7–2.0)	2.6% (2.4–2.7)
Systolic/diastolic BP ≥140/90 mmHg	5.4% (4.9–5.8)	11.6% (10.9–12.4)	12.4% (11.6–13.3)	9.4% (9.0–9.8)	1.5% (1.4–1.7)	4.1% (3.8–4.4)	7.0% (6.6–7.5)	1.0% (0.8–1.1)	3.5% (3.4–3.7)	—
LDL-C ≥100 mg/dL	19.6% (18.7–20.5)	13.7% (12.9–14.5)	4.4% (3.9–4.9)	12.6% (12.2–13.1)	—	5.1% (4.8–5.5)	5.9% (5.5–6.3)	—	2.5% (2.4–2.7)	—
A1C ≥7% (≥53 mmol/mol)	6.7% (6.2–7.2)	6.7% (6.2–7.3)	9.8% (9.1–10.6)	7.4% (7.0–7.7)	—	3.0% (2.7–3.2)	3.6% (3.3–3.9)	2.6% (2.4–2.8)	3.0% (2.8–3.2)	—

Estimates adjusted for age, sex, race/ethnicity, diabetes medication, statins, BP medication, CKD at baseline, incident diabetes at baseline, HDL-C ≤40 mg/dL (men)/50 mg/dL (women), elevated LDL-C (≥100 mg/dL), elevated A1C (≥8% [64 mmol/mol]), elevated systolic/diastolic BP (≥140/90 mmHg). —, factors not associated with an increased number of CV events or mortality.

LDL-C, and tobacco control in U.S. integrated health care systems. These data *1*) underscore the importance of the primary prevention of type 2 diabetes and *2*) indicate that substantial additional reductions in major CV events and all-cause mortality in those with diabetes may be achieved through more effective control of glucose, BP, LDL-C, and smoking.

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References

1. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010;8:29
2. Diabetes data and statistics [Internet], updated 27 October 2014. Atlanta, GA, Centers for Disease Control and Prevention. Available from http://www.cdc.gov/diabetes/data/. Accessed 5 February 2015
3. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014;370:1514–1523
4. Hansen MB, Jensen ML, Carstensen B. Causes of death among diabetic patients in Denmark. Diabetologia 2012;55:294–302
5. Nichols GA, Desai J, Elston Lafata J, et al.; SUPREME-DM Study Group. Construction of a multisite DataLink using electronic health records for the identification, surveillance, prevention, and management of diabetes mellitus: the SUPREME-DM project. Prev Chronic Dis 2012;9:E110
6. Hornbrook MC, Hart G, Ellis JL, et al. Building a virtual cancer research organization. J Natl Cancer Inst Monogr 2005;35:12–25
7. Klompas M, Eggleston E, McVetta J, Lazarus R, Li L, Platt R. Automated detection and classification of type 1 versus type 2 diabetes using electronic health record data. Diabetes Care 2013;36:914–921
8. Zgibor JC, Orchard TJ, Saul M, et al. Developing and validating a diabetes database in a large health system. Diabetes Res Clin Pract 2007;75:313–319
9. Harris SB, Glazier RH, Tompkins JW, et al. Investigating concordance in diabetes diagnosis between primary care charts (electronic medical records) and health administrative data: a retrospective cohort study. BMC Health Serv Res 2010;10:347
10. American Diabetes Association. Standards of medical care in diabetes—2014. Diabetes Care 2014;37(Suppl. 1):S14–S80
11. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520
12. Xu S, Schroeder EB, Shetterly S, et al. Accuracy of hemoglobin A1c imputation using fasting plasma glucose in diabetes research using electronic health records data. Stat Optim Inf Comput 2014;2:93–104
13. Rückinger S, von Kries R, Toschke AM. An illustration of and programs estimating attributable fractions in large scale surveys considering multiple risk factors. BMC Med Res Methodol 2009;9:7
14. Gefeller O, Land M, Eide GE. Averaging attributable fractions in the multifactorial situation: assumptions and interpretation. J Clin Epidemiol 1998;51:437–441
15. Lin H, Allore HG, McAvay G, et al. A method for partitioning the attributable fraction of multiple time-dependent coexisting risk factors for an adverse health outcome. Am J Public Health 2013;103:177–182
16. Jewell N. In *Statistics for Epidemiology*. London, Chapman & Hall/CRC Press, 2004, p. 84–85
17. Vogel C, Gefeller O. Implications of nondifferential misclassification on estimates of attributable risk. Methods Inf Med 2002;41:342–348
18. Lakshminarayan K, Anderson DC, Jacobs DR Jr, Barber CA, Luepker RV. Stroke rates: 1980–2000: the Minnesota Stroke Survey. Am J Epidemiol 2009;169:1070–1078
19. Rosamond WD, Chambless LE, Sorlie PD, et al. Trends in the sensitivity, positive predictive value, false-positive rate, and comparability ratio of hospital discharge diagnosis codes for acute myocardial infarction in four US communities, 1987–2000. Am J Epidemiol 2004;160:1137–1146
20. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99–104
21. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. Diabetes Care 2013;36:2271–2279
22. Kahn R, Robertson RM, Smith R, Eddy D. The impact of prevention on reducing the burden of cardiovascular disease. Diabetes Care 2008;31:1686–1696
23. Orchard TJ, Temprosa M, Barrett-Connor E, et al; Diabetes Prevention Program Outcomes Study Research Group. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. Diabet Med 2013;30:46–55
24. Li G, Zhang P, Wang J, et al. Cardiovascular mortality, all-cause mortality, and diabetes

incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol 2014;2:474–480
25. Kahn R, Davidson MB. The reality of type 2 diabetes prevention. Diabetes Care 2014;37: 943–949
26. Straka RJ, Liu LZ, Girase PS, DeLorenzo A, Chapman RH. Incremental cardiovascular costs and resource use associated with diabetes: an assessment of 29,863 patients in the US managed-care setting. Cardiovasc Diabetol 2009;8:53
27. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
28. Skyler JS, Bergenstal R, Bonow RO, et al.; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192
29. Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia 2013;56:686–695
30. Nichols GA, Joshua-Gotlib S, Parasuraman S. Independent contribution of A1C, systolic blood pressure, and LDL cholesterol control to risk of cardiovascular disease hospitalizations in type 2 diabetes: an observational cohort study. J Gen Intern Med 2013;28:691–697
31. Carnethon MR, De Chavez PJ, Biggs ML, et al. Association of weight status with mortality in adults with incident diabetes. JAMA 2012; 308:581–590
32. Doehner W, Erdmann E, Cairns R, et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. Int J Cardiol 2012;162:20–26
33. Tseng CH. Obesity paradox: differential effects on cancer and noncancer mortality in patients with type 2 diabetes mellitus. Atherosclerosis 2013;226: 186–192
34. Logue J, Walker JJ, Leese G, et al.; Scottish Diabetes Research Network Epidemiology Group. Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. Diabetes Care 2013;36:887–893
35. Subedi BH, Joshi PH, Jones SR, Martin SS, Blaha MJ, Michos ED. Current guidelines for high-density lipoprotein cholesterol in therapy and future directions. Vasc Health Risk Manag 2014;10:205–216
36. Tariq SM, Sidhu MS, Toth PP, Boden WE. HDL hypothesis: where do we stand now? Curr Atheroscler Rep 2014;16:398
37. Boden WE, Sidhu MS, Toth PP. The therapeutic role of niacin in dyslipidemia management. J Cardiovasc Pharmacol Ther 2014;19:141–158
38. Lloyd-Jones DM. Niacin and HDL cholesterol—time to face facts. N Engl J Med 2014;371:271–273
39. Joseph JJ, Golden SH. Type 2 diabetes and cardiovascular disease: what next? Curr Opin Endocrinol Diabetes Obes 2014;21:109–120
40. Tanaka Y, Fukui M, Tanaka M, et al. The inter-arm difference in systolic blood pressure is a novel risk marker for subclinical atherosclerosis in patients with type 2 diabetes. Hypertens Res 2014;37:548–552
41. Avery CL, Loehr LR, Baggett C, et al. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. J Am Coll Cardiol 2012;60:1640–1646
42. Loehr LR, Rosamond WD, Poole C, et al. The potentially modifiable burden of incident heart failure due to obesity: the Atherosclerosis Risk in Communities study. Am J Epidemiol 2010; 172:781–789
43. Folsom AR, Yamagishi K, Hozawa A, Chambless LE; Atherosclerosis Risk in Communities Study Investigators. Absolute and attributable risks of heart failure incidence in relation to optimal risk factors. Circ Heart Fail 2009;2: 11–17
44. Rodgers A, Lawes C, MacMahon S. Reducing the global burden of blood pressure-related cardiovascular disease. J Hypertens Suppl 2000;18: S3–S6
45. Wang WS, Wahlqvist ML, Hsu CC, Chang HY, Chang WC, Chen CC. Age- and gender-specific population attributable risks of metabolic disorders on all-cause and cardiovascular mortality in Taiwan. BMC Public Health 2012;12: 111
46. O'Connor PJ, Rush WA, Pronk NP, Cherney LM. Identifying diabetes mellitus or heart disease among health maintenance organization members: sensitivity, specificity, predictive value, and cost of survey and database methods. Am J Manag Care 1998;4: 335–342