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); 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, and 18.1 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.
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 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 Veterans Administration (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.×, 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 antihyperglycemic 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 code 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 a 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 Rücker 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).

**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 $>140/90$ 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 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, 10% 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 baseline CVD, inadequately controlled LDL-C was associated with 20% of observed MI/ACS and 14% of strokes. More than 4% of CV events were associated with smoking. Inadequately controlled BP was associated with nearly 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
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 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 attributable to 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).

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 attributable to 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).

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 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.
Table 2 shows the hazard ratios (95% CI) of inadequate control of factors as described in the table. The hazard ratios are adjusted for age, sex, race/ethnicity, diabetes medication, smoking, blood pressure medication, chronic kidney disease at baseline, incidence diabetes at baseline, and other inadequately controlled factors as described in the table.
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 mm Hg), 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 Modified-Release 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 (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

| Table 3—Five-year event rates and all-cause mortality and percentage of preventable CV events among adults with diabetes with and without baseline CVD |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Outcomes        | No CVD (n = 593,167) | CVD (n = 266,450) |
|                 | S-year rates per 100 persons | Preventable events (%) | S-year rates per 100 persons | 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 |
percentage for CV events and total mortality that reflect current levels of A1C, BP, 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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