The Association Between Different A1C-Based Measures of Glycemia and Risk of Cardiovascular Disease Hospitalization

OBJECTIVE
We tested whether average monthly glycemic burden (AMGB), a marker of hyperglycemia that is a function of the extent and duration that A1C exceeded 7%, indicated greater risk of cardiovascular disease (CVD) than traditional A1C measures.

RESEARCH DESIGN AND METHODS
Using a case-control design, we studied 2,456 members of Kaiser Permanente Northwest with type 2 diabetes: 1,228 who experienced a CVD hospitalization, matched on age, sex, and duration of diabetes to 1,228 patients who were not hospitalized for CVD. We calculated AMGB from diabetes diagnosis until CVD hospitalization as a function of the difference between each actual or interpolated A1C measurement and 7%, resulting in an area under the curve estimate of hyperglycemic exposure, adjusted for number of months of observation. We used conditional logistic regression to compare the association between several A1C-based measures of glycemia and CVD, controlling for clinical characteristics and comorbidities.

RESULTS
AMGB was associated with increased CVD risk of 29% (odds ratio 1.29 [95% CI 1.16–1.44]; \(P < 0.001\)), while mean A1C was associated with a 22% risk increase (1.22 [1.09–1.37]; \(P < 0.001\)). A1C ever exceeding 7% was associated with increased CVD risk of 39% (1.39 [1.08–1.79]; \(P = 0.010\)). No model with a glycemia measure provided substantially more information than an identical model without a glycemia measure.

CONCLUSIONS
AMGB demonstrated somewhat greater CVD risk than mean A1C, but its clinical usefulness may be limited. A1C ever rising above 7% (53 mmol/mol) was a simple predictor of CVD risk that may have important clinical ramifications for newly diagnosed patients.

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Despite significant reductions in cardiovascular disease (CVD) over the past six decades (1–3), patients with type 2 diabetes remain at approximately twofold greater risk of developing CVD than similar patients without diabetes (1,3,4). The logical assumption is that the hyperglycemia that characterizes diabetes is a major cause of the higher relative risk, but supporting evidence is lacking. Although epidemiologic analysis of the UK Prospective Diabetes Study (UKPDS) data suggested that each 1% reduction in A1C was associated with a 14% reduced risk of myocardial infarction (MI) (5), the intensive control arm on-trial did not experience significantly lower rates of MI (6). More recent clinical trials were also unable to demonstrate that intensive glycemic control reduced CVD risk (7–9). The marginal benefit of tight control may not be sufficient to reduce CVD events after controlling for other CVD risk factors (10).

One hypothesis that would explain the weak association between A1C level and CVD risk is that cardiac damage resulting from exposure to hyperglycemia is a slow process that cannot be assessed with single point-in-time measurements or even mean measurements that do not span a sufficient time period. This hypothesis is consistent with the notion that a diabetes duration of at least 8 years is needed before it can be considered a coronary heart disease risk equivalent (11) and the UKPDS findings of a significant reduction in MI only after long-term follow-up (12). Moreover, glycemic lowering after damage has accumulated may not reverse the process, thereby explaining recent trial results.

A second hypothesis that would explain the weak association between A1C level and CVD is that there is large variability in A1C over time that is not adequately accounted for with mean values. In 2004, Brown et al. (13) suggested a measure of hyperglycemia termed glycemic burden that is a function of the extent and duration that A1C exceeded a predefined threshold. Such a measure would theoretically capture the cumulative effects of long-term glycemic exposure as well as the fluctuations in glycemia that may be missed by point-in-time or even mean A1C measurements. Despite its intuitive appeal, to our knowledge, glycemic burden has not been studied in association with complications of diabetes, particularly CVD. Therefore, we undertook the current study to determine whether glycemic burden suggested greater risk of CVD than traditional A1C measures after controlling for other known risk factors.

**RESEARCH DESIGN AND METHODS**

**Sample Selection**

This was a retrospective observational case-control cohort study using the electronic medical records of patients with type 2 diabetes enrolled by Kaiser Permanente Northwest (KPNW), an integrated healthcare delivery system that provides comprehensive medical services to ~480,000 individuals in a 75-mile radius around Portland, OR. We identified 1,228 patients with type 2 diabetes who experienced a CVD hospitalization (primary ICD-9-CM diagnosis of ischemic heart disease [410.xx–414.xx] or stroke [430.x, 431.x, 432.x, 434.x, 435.x, 436.x, 437.1]) and met all of the following criteria: 1) diagnosed with diabetes between 1998 and 2009; 2) age ≥18 years; 3) 1-year health plan eligibility prior to diabetes diagnosis; 4) 1-year health plan eligibility following diabetes diagnosis (to allow adequate time to accumulate glycemic burden); 5) no known CVD hospitalization before or up to 1 year following diabetes diagnosis; and 6) had at least three A1C measurements between diagnosis and the CVD event. We matched these 1,228 patients to the same number of diabetic patients who also met the above criteria but did not experience a CVD hospitalization prior to the match on year of birth, sex, and duration of diabetes, calculated as the difference between the date of the case’s CVD event and diabetes diagnosis date. These matching variables were selected to demographically standardize the groups while ensuring identical time periods for accumulation of glycemic burden for each case-control pair.

**Glycemic Burden**

The concept of glycemic burden was proposed by Brown et al. (13), defined as the cumulative amount by which A1C has exceeded a specified treatment goal. It is calculated as the sum of the differences between a patient’s A1C and the treatment threshold (Fig. 1). We used the threshold of 7% (53 mmol/mol) and all A1C measurements recorded in the KPNW electronic medical record system between date of diabetes diagnosis and event date to estimate total glycemic burden. We assumed the change between each pair of A1C measurements represented a linear function and included a monthly estimate of burden for the assumed values so that the resulting total glycemic burden approximated an area under the curve measurement. Actual or estimated measurements below the 7% threshold neither increased nor decreased the cumulative burden. To account for differential time over which glycemic burden was calculated, we divided total burden by the number of months of observation to yield average monthly glycemic burden (AMGB). Therefore, each unit of total glycemic burden represents 1 month of an A1C that is one percentage point higher than the threshold, and AMGB is adjusted for the number of months over which the burden was accumulated. For example, an A1C of 8% that remained unchanged for 10 months would produce 10 units of glycemic burden, but the AMGB would be 1. We compared AMGB of case subjects with control subjects and also examined other A1C-based measures of glycemia, including first A1C after diagnosis, last A1C of observation, mean A1C over the entire observation period, and whether A1C ever exceeded 7% (53 mmol/mol) during observation.

**Covariates**

We assessed a number of potentially confounding variables that could contribute to CVD risk. In addition to the matching variables of age, sex, and diabetes duration, we collected data on race (white/nonwhite), smoking status, other clinical CVD risk factors (systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, and BMI), comorbidities (nonhospitalized CVD diagnosed in the outpatient setting, heart failure, depression, retinopathy, neuropathy, or chronic kidney disease defined by glomerular filtration rate <60 mL/min/1.73 m²), and use of
antihypertensive medications (ACE inhibitors, angiotensin receptor blockers, diuretics, and β-blockers), antihyperglycemic agents (metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, meglitinides, dipeptidyl peptidase-4 inhibitors, and insulin), and statins.

Statistical Analyses
We compared the measures of glycemia and the covariates between patients with and without CVD events using signed-rank tests for continuous variables and Mantel-Haenszel tests for categorical variables. To isolate the effects of the glycemia measures, covariates that were significant at \( P < 0.05 \) at the univariate level were entered into a multivariable conditional logistic regression model. We then tested each of the glycemia measures one at a time into a multivariable conditional logistic regression model. We then tested each of the glycemia measures after adjustment for significantly different covariates shown in Table 1. Each additional 1% (11 mmol/mol) of A1C at diagnosis was associated with a 12% greater probability of a CVD hospitalization (odds ratio 1.12 [95% CI 1.06–1.18]; \( P < 0.001 \)). Each additional 1% (11 mmol/mol) of mean A1C during observation was associated with a 22% greater probability of an event (1.22 [1.09–1.37]; \( P < 0.001 \)), while each unit of AMGB was associated with a 29% higher probability (1.29 [1.16–1.45]; \( P < 0.001 \)). Ever crossing above the threshold of 7% (53 mmol/mol) was associated with a 39% increased probability of CVD (1.39 [1.08–1.79]; \( P = 0.010 \)). The standardized coefficients show that AMGB produced the highest CVD risk estimate, followed by first A1C and mean A1C. All models provided approximately the same fit, as evidenced by similar values of the Akaike Information Criterion. However, an identical model without any glycemia measure provided at least 98% of the information included in each of the models that included a glycemia measure. The results of the complete models are shown in Supplementary Table 1. The covariates performed similarly in all models.

RESULTS
The characteristics of the patients who did and did not experience a CVD hospitalization are displayed in Table 1. By matching on year of birth, we found a small but significant difference in age (69.9 vs. 69.8 years; \( P = 0.001 \)), but the matching variables of sex (57.7% men) and diabetes duration (5.3 years of observation) did not differ. Case subjects had more adverse risk factors, more comorbidities, and more aggressive pharmacotherapy than control subjects.

A1C at diagnosis was significantly higher among case subjects compared with control subjects (7.7 [61 mmol/mol] vs. 7.4% [57 mmol/mol]; \( P < 0.001 \)), but last A1C during observation was similar (Table 2). Mean A1C was statistically but not clinically greater among case subjects (7.1 [54 mmol/mol] vs. 7.0% [53 mmol/mol]; \( P = 0.012 \)). Patients in both groups averaged \( \sim 10 \) A1C measurements during observation. Total glycemic burden was somewhat higher among case subjects, and AMGB was significantly greater (1.0 vs. 0.8; \( P < 0.001 \)). Patients who experienced a CVD event were less likely to have remained <7% (53 mmol/mol) for the entire observation period, thus accumulating zero glycemic burden (23.4 vs. 27.0%; \( P < 0.001 \)).

Table 3 displays the probability of a CVD hospitalization associated with each of the glycemia measures after adjustment for significantly different covariates shown in Table 1. Each additional 1% (11 mmol/mol) of A1C at diagnosis was associated with a 12% greater probability of a CVD hospitalization (odds ratio 1.12 [95% CI 1.06–1.18]; \( P < 0.001 \)). Each additional 1% (11 mmol/mol) of mean A1C during observation was associated with a 22% greater probability of an event (1.22 [1.09–1.37]; \( P < 0.001 \)), while each unit of AMGB was associated with a 29% higher probability (1.29 [1.16–1.45]; \( P < 0.001 \)). Ever crossing above the threshold of 7% (53 mmol/mol) was associated with a 39% increased probability of CVD (1.39 [1.08–1.79]; \( P = 0.010 \)). The standardized coefficients show that AMGB produced the highest CVD risk estimate, followed by first A1C and mean A1C. All models provided approximately the same fit, as evidenced by similar values of the Akaike Information Criterion. However, an identical model without any glycemia measure provided at least 98% of the information included in each of the models that included a glycemia measure. The results of the complete models are shown in Supplementary Table 1. The covariates performed similarly in all models.

CONCLUSIONS
In this case-control study of 1,228 diabetic patients who experienced CVD hospitalization matched with 1,228 diabetic patients who did not have such an event over 5.3 years of follow-up, we found that after controlling for other CVD risk factors, AMGB was the strongest predictor of developing CVD, but was only modestly stronger than other A1C-based measurements. The amount of information added to each model was approximately equivalent, and minimal, for all glycemia measures.
Interestingly, we also found that patients who never exceeded the A1C threshold of 7% (53 mmol/mol) were significantly less likely to be hospitalized for CVD than those who ever exceeded this threshold.

As a dichotomous measure, this last finding is not directly comparable to the other continuous measures studied. Moreover, any threshold-based dichotomous measure is of no value once the threshold is crossed. Nevertheless, this result has potentially important clinical ramifications. First, all patients in the current study were diagnosed in 2009 or earlier when fasting plasma glucose tests rather than A1C assays were the diagnostic standard. This may have allowed us to identify patients at a different, earlier stage of hyperglycemia than would now be possible. In any case, to prevent A1C from ever rising >7% (53 mmol/mol), early diagnosis would be essential; this in turn may require targeted screening of patients at high risk of diabetes. It would also require aggressive initiation and intensification of therapies for hyperglycemia concurrent with rather than following lifestyle-change efforts. Nevertheless, when taken together with the finding that the first A1C after diagnosis demonstrated a strong association with CVD, it appears that early diagnosis and treatment of diabetes using A1C may be an important strategy for CVD prevention. Indeed, previous studies have shown that metformin, the recommended first-line therapy for diabetes (14), is most effective and has greater durability when initiated at low A1C levels and at diabetes diagnosis (15,16), suggesting that attainment and maintenance of low A1C levels is indeed possible when therapy is not delayed. Furthermore, the legacy effect of low A1C levels early in the course of diabetes may endure even after A1C subsequently rises (12).

A1C is a measure of average glucose levels over the life of the erythrocyte that does not account well for the day-to-day or hour-to-hour glycemic variability that increases oxidative stress and may be associated with macrovascular complications (17). We hypothesized that the glycemia measure of AMGB would be more strongly associated with higher risk of CVD than traditional measures such as mean A1C or point-in-time A1C measurements because it would be increased by large glycemic excursions not captured in other measures. AMGB did in fact produce the highest odds ratio of these measures, the largest standardized coefficient, and the lowest P value, but provided only a small amount of additional information to the multivariable model. Indeed, based on the Akaike Information Criterion, none of the glycemia variables added meaningfully to other information contained in the models. Thus, AMGB may still not be sensitive enough to daily or hourly glycemic variation. In a study of a more general diabetic population in this setting, A1C was not significantly associated with CVD hospitalization, but control of blood pressure and cholesterol demonstrated strong associations (10). To reduce CVD risk, emphasis should be placed on lipid-lowering (with statins) and blood pressure control (18).

The current study sample had mean diabetes duration approximately midway between the newly diagnosed patients in the UKPDS and those of long duration (8–11 years) in recent clinical trials (7–9), which may partially account for the modest A1C/CVD association we report. Mean duration of diabetes over which AMGB and mean A1C was assessed in our study was 5.3 years. This time period may be too short to adequately capture glycemia-related CVD risk. The on-trial findings from the UKPDS, which followed newly diagnosed patients for a median of 10

| Table 1—Characteristics of 1,228 people with diabetes who experience a CVD event compared with 1,228 people with diabetes who remained event free, matched on age, sex, and duration of diabetes at time of the event | Had CVD event (case subjects, n = 1,228) | No CVD event (control subjects, n = 1,228) | P value* |
|---|---|---|---|
| Age (years) | 69.9 ± 12.0 | 69.8 ± 11.9 | 0.001 |
| Percent men | 57.7 | 57.7 | — |
| Diabetes duration | 5.3 ± 2.9 | 5.3 ± 2.9 | — |
| Percent white | 92.6 92.2 0.302 |
| Percent smokers | 12.1 9.0 0.010 |
| BMI (kg/m²)† | 32.4 ± 6.2 32.6 ± 6.6 0.247 |
| Systolic blood pressure (mmHg)† | 137 ± 13 135 ± 11 <0.001 |
| LDL cholesterol (mg/dL)† | 108 ± 29 104 ± 25 <0.001 |
| HDL cholesterol (mg/dL)† | 42 ± 10 44 ± 12 <0.001 |
| Triglycerides (mg/dL)† | 212 ± 135 200 ± 128 0.009 |
| Established CHD | 63.2 24.8 <0.001 |
| History of heart failure | 24.6 | 14.3 <0.001 |
| GFR <60 mL/min/1.73 m² | 26.8 | 21.2 0.001 |
| Neupathy | 35.8 | 30.3 0.004 |
| Retinopathy | 8.6 | 6.0 0.016 |
| Depression | 30.1 | 26.6 0.049 |
| Metformin use | 29.0 | 37.2 <0.001 |
| Sulfonylurea use | 33.3 | 35.6 0.235 |
| Insulin use | 9.0 | 7.5 0.186 |
| Other antihyperglycemic | 0.7 | 0.7 0.808 |
| ACE/ARB use | 56.4 | 57.3 0.684 |
| Diuretic use | 38.0 | 35.5 0.209 |
| β-Blocker use | 52.0 | 36.4 <0.001 |
| Calcium channel blocker use | 23.6 | 16.8 <0.001 |
| Statin use | 51.4 | 52.1 0.716 |

Data are mean ± SD or percent. ARB, angiotensin receptor blocker; CHD, coronary heart disease; GFR, glomerular filtration rate. *P values based on signed-rank tests for continuous variables and Mantel-Haenszel tests for categorical variables. †Data missing for <2% of observations.
years, did not show a CVD benefit to intensive treatment despite achieving an A1C of 7.0 vs. 7.9% in the conventional therapy group (6). However, an additional 10 years of follow-up showed risk reductions in MI despite an equalizing of A1C over time (12). Moreover, other evidence suggests that diabetes does not reach a cardiovascular risk-equivalent state for at least 8 years following diagnosis (11). Thus, glycemia-related cardiac damage may take many years to manifest. The benefits of good glycemic control may not be apparent in patients of relatively short diabetes duration, while among patients with long diabetes duration, cardiac damage may have already occurred, negating the benefits of current tight control.

Another important factor complicating the association between A1C-derived measures of glycemia and CVD is that the relationship may not be linear. Epidemiologic analysis from the UKPDS suggested there was no threshold below which additional A1C lowering would not provide benefit (5), a finding that was also demonstrated in the Swedish Diabetes Register (19). However, two other recent studies did find a threshold effect (20,21), and other studies found a U-shaped relationship, such that CVD risk was elevated at both high and low A1C values (22–26). Our AMGB measure does not consider that low A1C might increase CVD risk nor does its calculation include negative burden for A1C values <7% (53 mmol/mol).

There are other limitations to our study that warrant mention. As an observational study, we cannot conclude that the significant associations between any of the glycemic measures we tested and CVD are causal. Although our study was strengthened by the large number of covariates, residual confounding could remain. In particular, we could not account for differences in dietary intake, physical activity, or socioeconomic status, all of which would likely contribute to CVD risk. In addition, implementing the study criteria resulted in a sample with mean age of 70 years and a mean duration of 5 years, so mean age at diagnosis was ~65 years. Whether the associations we report would also be found in contemporary populations that are typically diagnosed at younger ages is unknown (27). Moreover, we did not attempt to account for glycemic burden that occurred prior to diagnosis. Although we required 1 year of prior eligibility to ensure diabetes had not been recognized, undiagnosed diabetes or even subdiagnostic levels of hyperglycemia could have affected our burden calculations and biased our results. Finally, a glycemia measure such as glycemic burden that accounts for the time and extent to which a treatment level is exceeded is intuitively appealing but difficult to calculate. Because it provided little information beyond mean A1C, its value as a clinical tool may therefore be limited.

In summary, we found that the AMGB accumulated over time was a somewhat better marker of CVD risk than mean A1C. Trials would be needed to determine its usefulness in diabetes care, but the marginal increase in the association with CVD hospitalization probably does not warrant such an investment. Furthermore, no model with a glycemia measure provided substantially more information than an identical model without a glycemia measure. Therefore, our results further support the notion that CVD risk reduction in diabetes remains most effective by targeting blood pressure and LDL cholesterol (18). However, the fact that A1C ever rising >7% (53 mmol/mol) was associated with CVD hospitalization may have important implications.

### Table 2—Univariate comparisons of measures of glycemia

| Glycemia measure | Had CVD event (case subjects, n = 1,228) | No CVD event (control subjects, n = 1,228) | P value* |
|------------------|----------------------------------------|------------------------------------------|----------|
| A1C at diagnosis (%) | 7.7 ± 2.0 | 7.4 ± 1.8 | <0.001 |
| A1C at diagnosis (mmol/mol) | 60.2 ± 21.6 | 57.6 ± 19.7 | 0.168 |
| Last A1C of observation (%) | 7.1 ± 1.4 | 7.0 ± 1.2 | 0.012 |
| Last A1C of observation (mmol/mol) | 54.0 ± 15.7 | 53.0 ± 13.6 | 0.012 |
| Mean A1C during observation (%) | 7.1 ± 1.1 | 7.0 ± 1.0 | 0.128 |
| Mean A1C during observation (mmol/mol) | 54.5 ± 11.9 | 53.2 ± 10.4 | 0.128 |
| Mean number of A1C measurements | 10.2 ± 6.7 | 10.1 ± 6.6 | 0.060 |
| Total glycemic burden | 36.3 ± 67.6 | 31.0 ± 53.7 | 0.001 |
| Mean adjusted monthly glycemic burden | 1.0 ± 1.2 | 0.8 ± 0.9 | <0.001 |

*Percent with zero AMGB

*P values based on signed-rank tests for continuous variables and Mantel-Haenszel tests for categorical variables.

### Table 3—Results of conditional logistic regression models

| Glycemia measure | Odds ratio (95% CI) | Standardized coefficient (exponentiated) | P value | Akaike Information Criterion* |
|------------------|---------------------|-----------------------------------------|---------|------------------------------|
| First A1C (per % or 11 mmol/mol) | 1.12 (1.06–1.08) | 1.24 (1.11–1.38) | 0.0001 | 1,191 |
| Last A1C (per % or 11 mmol/mol) | 1.09 (1.00–1.18) | 1.12 (1.00–1.25) | 0.0442 | 1,202 |
| Mean A1C (per % or 11 mmol/mol) | 1.22 (1.09–1.37) | 1.22 (1.09–1.37) | 0.0008 | 1,194 |
| AMGB | 1.29 (1.16–1.45) | 1.31 (1.17–1.47) | <0.0001 | 1,184 |
| A1C ever >7% (53 mmol/mol) | 1.39 (1.08–1.79) | 1.15 (1.04–1.29) | 0.0102 | 1,199 |

*The Akaike Information Criterion for a model without any glycemia measure was 1,204.
clinical ramifications for newly diagnosed patients.

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