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Identifying the independent effect of HbA_{1c} variability on adverse health outcomes in patients with Type 2 diabetes

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Abstract

Aims—To characterize the relationship between HbA_{1c} variability and adverse health outcomes among US military veterans with Type 2 diabetes.

Methods—This retrospective cohort study used Veterans Affairs and Medicare claims for veterans with Type 2 diabetes taking metformin who initiated a second diabetes medication (n = 50 861). The main exposure of interest was HbA_{1c} variability during a 3-year baseline period. HbA_{1c} variability, categorized into quartiles, was defined as standard deviation, coefficient of variation and adjusted standard deviation, which accounted for the number and mean number of days between HbA_{1c} tests. Cox proportional hazard models predicted mortality, hospitalization for ambulatory care-sensitive conditions, and myocardial infarction or stroke and were controlled for mean HbA_{1c} levels and the direction of change in HbA_{1c} levels during the baseline period.

Results—Over a mean 3.3 years of follow-up, all HbA_{1c} variability measures significantly predicted each outcome. Using the adjusted standard deviation measure for HbA_{1c} variability, the hazard ratios for the third and fourth quartile predicting mortality were 1.14 (95% CI 1.04, 1.25) and 1.42 (95% CI 1.28, 1.58), for myocardial infarction and stroke they were 1.25 (95% CI 1.10, 1.41) and 1.23 (95% CI 1.07, 1.42) and for ambulatory-care sensitive condition hospitalization they were 1.10 (95% CI 1.03, 1.18) and 1.11 (95% CI 1.03, 1.20). Higher baseline HbA_{1c} levels independently predicted the likelihood of each outcome.

Conclusions—In veterans with Type 2 diabetes, greater HbA_{1c} variability was associated with an increased risk of adverse long-term outcomes, independently of HbA_{1c} levels and direction of change. Limiting HbA_{1c} fluctuations over time may reduce complications.

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Competing interests
None declared.

Supporting Information
Additional Supporting Information may be found in the online version of this article:

Introduction

A substantial body of evidence shows a direct relationship between glucose control and microvascular complications (e.g. retinopathy, neuropathy and nephropathy). Higher levels of HbA_{1c} carry greater risk of such complications, and lowering HbA_{1c} prospectively reduces risk [1,2]. Diabetes also confers substantial cardiovascular disease (CVD) risk. While a relationship between higher HbA_{1c} and CVD risk exists, there is no consensus that lowering HbA_{1c} to levels < 69 mmol/mol (< 8.5%) reduces such risk. Indeed, in several major clinical trials of patients with Type 2 diabetes treated to HbA_{1c} levels < 53 mmol/mol (< 7%) [1–3], there was not only no benefit with regard to CVD disease risk but there was evidence of increased mortality [1]. The variable relationship between glucose control and diabetes complications suggests that this relationship is complex and multifaceted.

An emerging concept is that glucose variability may contribute to both microvascular and macrovascular disease risk. Several lines of evidence show that increased glucose variability carries significant risk of short-term and long-term complications. Greater day-to-day glucose variability among hospitalized patients is associated with longer length of stay, infections and in-hospital mortality [4–6] as well as risk of asymptomatic hypoglycaemia [7,8]. Glucose variability from month to month may result in HbA_{1c} variability. Increasing HbA_{1c} variability is associated with retinopathy, nephropathy, cardiovascular events and possibly mortality [9–13], and may be an independent risk predictor when compared with HbA_{1c} levels alone [9,12]. These important findings support the concept that diabetes management may be more complex than focusing only on HbA_{1c} levels. Unfortunately, previous studies have been limited either by small sample sizes or unclear distinctions between baseline and outcome periods, raising concerns of confounding by indication.

To overcome several of these limitations, we conducted an observational study using nationwide data on military veterans diagnosed with Type 2 diabetes to assess the independent effect of baseline HbA_{1c} variability on adverse health outcomes, controlling for mean baseline levels and the directional changes in HbA_{1c}.

Patients and methods

Data sources

Patient-level national data from the Veterans Health Administration were used and supplemented with data from Medicare. The study was reviewed and approved by the institutional review board at the Veterans Affairs Boston Healthcare System.

Study population

Identifying patients who are at a similar point in disease progression improves comparability among patients and helps isolate the effect of HbA_{1c} variability on health outcomes. Unfortunately, the administrative claims data used in the present study do not contain information on duration of diabetes. Nevertheless, we attempted to isolate patients who were at a similar stage in the progression of Type 2 diabetes. All prescription claims for metformin, sulphonylureas, thiazolidinediones and long-acting insulin between 2000 and 2009 were extracted from Veterans Health Administration pharmacy files. Patients were

required to have an existing metformin prescription, followed by initiation of a second diabetes medication.

Patients entered the study 12 months after starting the second diabetes medication (index date) and the preceding 36 months was considered the baseline period. The addition of a new medication may introduce HbA_{1c} variability so we included the first 12 months after that change in the calculations of baseline HbA_{1c} variability. For example, if Patient A started a second diabetes medication on 1 January 2002, their baseline period was 1 January 2000 to 31 December 2002 (Fig. 1). HbA_{1c} variability was measured during this baseline period. The individual entered the outcome period on 1 January 2003 and was followed up until 31 December 2010 because they did not experience any outcomes, resulting in 8 years of follow-up. If Patient B started their second diabetes medication on 1 July 2007, their baseline period was 1 July 2005 to 30 June 2008. This individual entered the outcome period on 1 July 2008, but died on 30 September 2009, with 1.25 years of follow-up.

Eligible individuals initiated their second diabetes medication between 2002 and 2008 (n = 301 940; Fig. 2), entered the study between 2003 and 2009 and were followed through to the end of 2010 or until they experienced any of the outcomes. We further limited the cohort to those dually enrolled in Medicare and Veterans Health Administration to ensure completeness in measures of risk adjustors and outcomes (n = 163 579), as Veterans Health Administration patients often use non-Veterans Health Administration facilities for hospital care [14]. Individuals were required to be prescribed metformin and have four or more HbA_{1c} tests during the baseline period. After excluding those with missing data on relevant covariates, the final cohort included 50 861 patients.

HbA1c variability measure

Three different HbA_{1c} variability measures were calculated for each individual during the baseline period. Each measure was categorized into quartiles. First, we measured standard deviation (SD). Since the number of HbA_{1c} measurements can influence SD value (e.g. fewer measurements making the SD greater), we accounted for this in two subsequent measures [15,16]. We calculated the coefficient of variation [(HbA_{1c} SD/ HbA_{1c} mean)*100] and an SD value adjusted for the number of HbA_{1c} measurements (#HbA_{1c}) and the mean number of days between HbA_{1c} measurements (MEAN HbA_{1c} days) [16]. We used the following linear regression: log(SD)= log(#HbA_{1c})+ log(MEAN HbA_{1c} days). Based on the coefficients and constant from this linear regression, we computed the following adjusted SD value:

$$\text{adjusted SD} = \text{SD}/\left[\exp(1.48) * \left(\#\,\text{HbA}_{1c}^{-.074}\right) * \left(\text{MEAN HbA}_{1c}\,\text{days}^{-0.36}\right)\right].$$

Baseline HbA1c levels and directional changes

We wanted to determine if HbA_{1c} variability had an independent effect on outcomes. Consequently, one key covariate of interest was the mean baseline HbA_{1c} level, categorized as < 53 mmol (< 7%), ≥ 53 and < 64 mmol/mol (7–8%), ≥ 64 and < 75 mmol/mol (8–9%) and ≥ 75 mmol/mol (≥ 9%). Following previous research, we were also interested in the

directional change in HbA_{1c}, independent of variability and mean baseline HbA_{1c} level [13]. Patients with the same mean baseline HbA_{1c} may have different risks of adverse outcomes if HbA_{1c} levels have a positive or a negative slope during the baseline period. We calculated the slope of HbA_{1c} over time for each individual using linear regression. This slope was categorized into quartiles and included as a separate covariate.

Quality controls

Individual HbA_{1c} variability may correlate with how patients with diabetes are managed at a given facility and result in biased estimates of the relationship with health outcomes; therefore, we controlled for facility-level quality of diabetes care. Three process quality variables were computed during the baseline period at the facility level. Measures were: percent of HbA_{1c} levels ≥ 75 mmol/mol (≥ 9%); percent of blood pressure readings ≥ 140/90 mm Hg; and percent of LDL cholesterol levels > 100 mg/dL [17]. Each individual's laboratory values were removed from their facility-level calculation.

Covariates

Additional control variables included age, sex, race, serum creatinine, urine microalbumin-creatinine ratio, blood pressure, LDL cholesterol, BMI (see Table S1 for categorizations) and type of second diabetes medication added (i.e. thiazolidinedione or insulin vs sulphonylurea). Indicator variables for calendar years that corresponded to the start of the outcome period were included because patients who entered the study later would be followed for shorter periods of time. Comorbidity measures included 29 indicator variables for physical and mental health conditions using the Elixhauser algorithm [18] and eight indicator variables for the components of the Young Diabetes Severity Index [19]. Indicator variables in the Young index measure microvascular and macrovascular complications [19]. All covariates were computed during the baseline period.

Outcomes

Outcomes included all-cause mortality, acute myocardial infarction (MI) or stroke, and hospital admission for any of 13 ambulatory care-sensitive conditions (ACSC) as defined by the Agency for Healthcare Research and Quality [20]. ACSC hospitalizations included diagnoses such as uncontrolled diabetes, short- and long-term diabetes complications, lower extremity amputation, angina, heart failure, pneumonia and others. The Veterans Affairs Vital Status File determines the date of death from Veterans Affairs, Medicare and Social Security Administration data and was used to determine all-cause mortality [21]. MI definitions and stroke definitions were based on previously published work [22,23]. The modelled outcome was the amount of time between the index date and the earliest date of any of the outcomes, with censoring at the end of the study period in 2010.

Statistical models

We used STATA version 10 to estimate the effects of HbA_{1c} variability on the risks of outcomes using Cox proportional hazards models. The outcome equations related HbA_{1c} variability and control variables to probabilities of death, ACSC hospitalization and stroke or MI. The Cox models assume that HbA_{1c} variability affects outcome risk by a constant

proportion over time. We tested this assumption using scaled Schoenfeld residuals from the all-cause mortality and hospitalization equations [24]. Finally, to control for facility quality differences we included a facility-level random effect.

Sensitivity tests

The study population consisted of individuals who started a second diabetes medication in the third year of their baseline period. Introducing a second medication may increase HbA_{1c} variability by lowering HbA_{1c} levels from a higher baseline, but may also reduce the HbA_{1c} variability measure if it triggers an increased number of HbA_{1c} tests. To test the robustness of our results, we also measured HbA_{1c} variability during a 2-year baseline period, with the index date changed to when the individual started the second medication (Appendices S3–S5).

Results

The study population included 50 861 individuals with Type 2 diabetes who were older (mean age 66 years) and largely male and of whom 86% were white (Table 1). Five percent had a mean $HbA_{1c} \geq 75$ mmol/mol (≥ 9%) and 19–35% had prevalent retinopathy, nephropathy, neuropathy or peripheral vascular disease during the baseline period. Patients also had high rates of CVD risk factors, including 56% with obesity, 38% with mean LDL cholesterol ≥ 100 mg/dl and 57% with cardiovascular complications based on the Young Diabetes Severity Index. In the outcome period, 9% of patients died, 18% had an ACSC hospitalization and 5% experienced a stroke or MI.

Over a mean 3.3 years of follow-up, there was a consistent relationship between greater HbA_{1c} variability and the likelihood of experiencing each health outcome (Figs 3–5). Models included HbA_{1c} variability, mean HbA_{1c} levels, the directional trend of HbA_{1c} levels, covariates and quality controls. The hazard ratio predicting each outcome generally increased throughout the quartiles for each of three HbA_{1c} variability measures. Hazard ratios for the third or fourth quartile were significantly higher for each outcome compared with individuals in the first quartile. For example, using the adjusted SD measure, the hazard ratios for mortality were 1.14 (95% CI 1.04, 1.25) and 1.42 (95% CI 1.28, 1.58) in the third and fourth quartiles, respectively (Fig. 3; see Table S2 for complete estimates from this model). For ACSC hospitalization, the hazard ratios were 1.10 (95% CI 1.03, 1.18) and 1.11 (95% CI 1.03, 1.20; Fig. 4), and for MI or stroke, third and fourth quartile hazard ratios were 1.25 (95% CI 1.10, 1.41) and 1.23 (95% CI 1.07, 1.42), respectively (Fig. 5).

Higher baseline HbA_{1c} levels also independently predicted risk of each health outcome (Figs 3–5). $HbA_{1c} \geq 53$ mmol/mol (> 7%) significantly increased the odds of both ACSC hospitalization and MI or stroke. Mean $HbA_{1c} \geq 75$ mmol/mol (≥ 9%) significantly increased the odds of mortality. In general, the hazard ratios were larger with higher mean HbA_{1c} levels. HbA_{1c} slope during the baseline period did not have a consistent and significant effect on outcomes, but there were indications that the highest quartile (i.e. more positive slope) could be associated with slightly greater risk of MI, stroke and ASCS hospitalization (data not shown).

Sensitivity analyses using similar models and a 2-year rather than a 3-year baseline period for HbA_{1c} variability resulted in a smaller study population (n = 27 398). Qualitatively similar results were noted (Tables S3–S5). Individuals in the highest quartile of HbA_{1c} variability were more likely to experience mortality, ASCS hospitalization, and MI or stroke compared with individuals in the first quartile.

Discussion

We found that greater HbA_{1c} variability significantly increased the likelihood of mortality, MI or stroke, and ACSC hospitalization for veterans with Type 2 diabetes. The effect of HbA_{1c} variability was independent of baseline HbA_{1c} levels or directional trends. As expected, the mean baseline HbA_{1c} level also significantly predicted each outcome in the same models. Our findings are consistent with those of other clinical studies that found that higher HbA_{1c} variability significantly increases the risk of incident CVD [16] and mortality [10,11,13]. We also found a previously unexamined relationship between increased HbA_{1c} variability and risk of hospitalization for ACSC.

To illustrate the effect of HbA_{1c} variability on adverse health outcomes, one can consider the risk of mortality using the adjusted SD measure. An individual with baseline $HbA_{1c} \geq 75$ mmol/mol (≥ 9%) but in the lowest quartile for HbA_{1c} variability had a 24% greater risk of death compared with an individual with baseline HbA_{1c} level < 53 mmol/mol (< 7%) who was also in the lowest quartile for HbA_{1c} variability. By contrast, an individual with baseline HbA_{1c} level < 53 mmol/mol (< 7%) but in the fourth quartile for HbA_{1c} variability had a 42% greater risk of death compared with an individual with baseline HbA_{1c} level < 53 mmol/mol (< 7%) who was also in the lowest quartile for HbA_{1c} variability. These results highlight how diabetes management may be affected by the additional risk information conveyed by HbA_{1c} variability measures.

Aspects of the study design increase its validity and strengthen the evidence for an independent effect of HbA_{1c} variability on adverse health outcomes. This study used nationwide data from electronic medical records on a large population of veterans. Consequently, the final sample size was almost five times larger than previous studies that used clinical trial data or registry information from selected facilities. We measured HbA_{1c} variability during a 3-year baseline period and used these baseline values to predict health outcomes for up to 8 years. The clearly delineated baseline and outcome periods in this study increase the likelihood that our findings are causal because variability is measured before outcomes are observed, reducing the danger of reverse causation. Additionally, we included measures of facility-level process quality to control for differences in practice style.

Despite these strengths, the main limitation of the present study was that we cannot be certain that the relationship was causal. Future research is needed to apply other experimental methods to verify whether HbA_{1c} variability causes poor health outcomes or whether the relationship is attributable to unobservable factors. The study has other limitations that could be addressed by future research. We attempted to identify patients at a similar stage in their disease progression as evidenced by the need for a second diabetes medication. Adding a new medication may alter HbA_{1c} variability so we included the first

12 months after that change in the calculations of HbA_{1c} variability. Results from sensitivity analyses that excluded this 12-month period were qualitatively similar. Nevertheless, the administrative claims data used for this study did not have reliable information on duration of diabetes. Future research could select a broader study population in whom the duration of diabetes is known, to further validate the relationship between HbA_{1c} variability and health outcomes and to determine if HbA_{1c} variability influences adverse health outcomes in different ways throughout disease progression. For example, HbA_{1c} variability could have less impact on outcomes early in the course of disease. Our study population was largely male and had low-income status so results may not be generalizable to other populations. Future studies should focus on important subpopulations to determine if the effect of HbA_{1c} variability differs among demographic groups.

The potential mechanisms underlying the observations in the present study are as yet uncertain. A few mechanistic studies have evaluated the cellular effects of glucose variability. *In vitro* and *in vivo* studies show that short-term glucose fluctuations significantly increase oxidative stress. *In vitro*, increased glucose variability enhances the release of inflammatory cytokines, and glucose oscillations induce endothelial dysfunction in both healthy subjects and patients with diabetes [25,26]. Daily glucose fluctuations are associated with oxidative stress, carotid intimal thickness and increased left ventricular mass [26,27]. Among hospitalized patients, greater day-to-day glucose variability is associated with adverse outcomes, including longer length of stay, infections and in-hospital mortality [4–6] as well as risk of asymptomatic hypoglycaemia [7,8]. Nonetheless, there remain substantial gaps in our understanding of the links between diabetes treatment, glucose variability, HbA_{1c} variability and complications.

A direct relationship between HbA_{1c} variability and micro- and macrovascular complications and mortality has important clinical implications. Clinical measures that prospectively identify individuals who are at higher risk of complications will have great relevance to patients, clinicians and policy-makers. For example, potential overtreatment in current Type 2 diabetes management sits at the intersection of overuse of low value practices and medication safety. Several diabetes clinical practice guidelines now recommend that HbA_{1c} levels be targeted to a range that balances benefits and harms for a given patient [28,29]; however, many older patients are potentially overtreated to near-normal HbA_{1c} levels [30], with the likelihood of also amplifying HbA_{1c} variability and exposing them to risks of macrovascular complications, hospitalization and decreased life expectancy.

In summary, patients with Type 2 diabetes and higher HbA_{1c} variability are at increased risk of mortality, ACSC hospitalization and MI or stroke. Limiting the range of HbA_{1c} fluctuations over time and adhering to guideline-directed HbA_{1c} target levels may reduce the risk of diabetes complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

- Glucose variability over time may contribute to microvascular and macrovascular complications. This retrospective cohort study uses data on US military veterans diagnosed with Type 2 diabetes (n = 50 861) to examine the relationship between HbA_{1c} variability and health outcomes.
- Greater HbA_{1c} variability is associated with increased risk of mortality, hospitalization for ambulatory care-sensitive conditions and myocardial infarction or stroke.
- The models controlled for mean HbA_{1c} levels and the direction of change in HbA_{1c} levels, emphasizing the independent effect HbA_{1c} variability has on outcomes.
- Limiting the range of HbA_{1c} fluctuations over time may reduce adverse complications in patients with Type 2 diabetes.

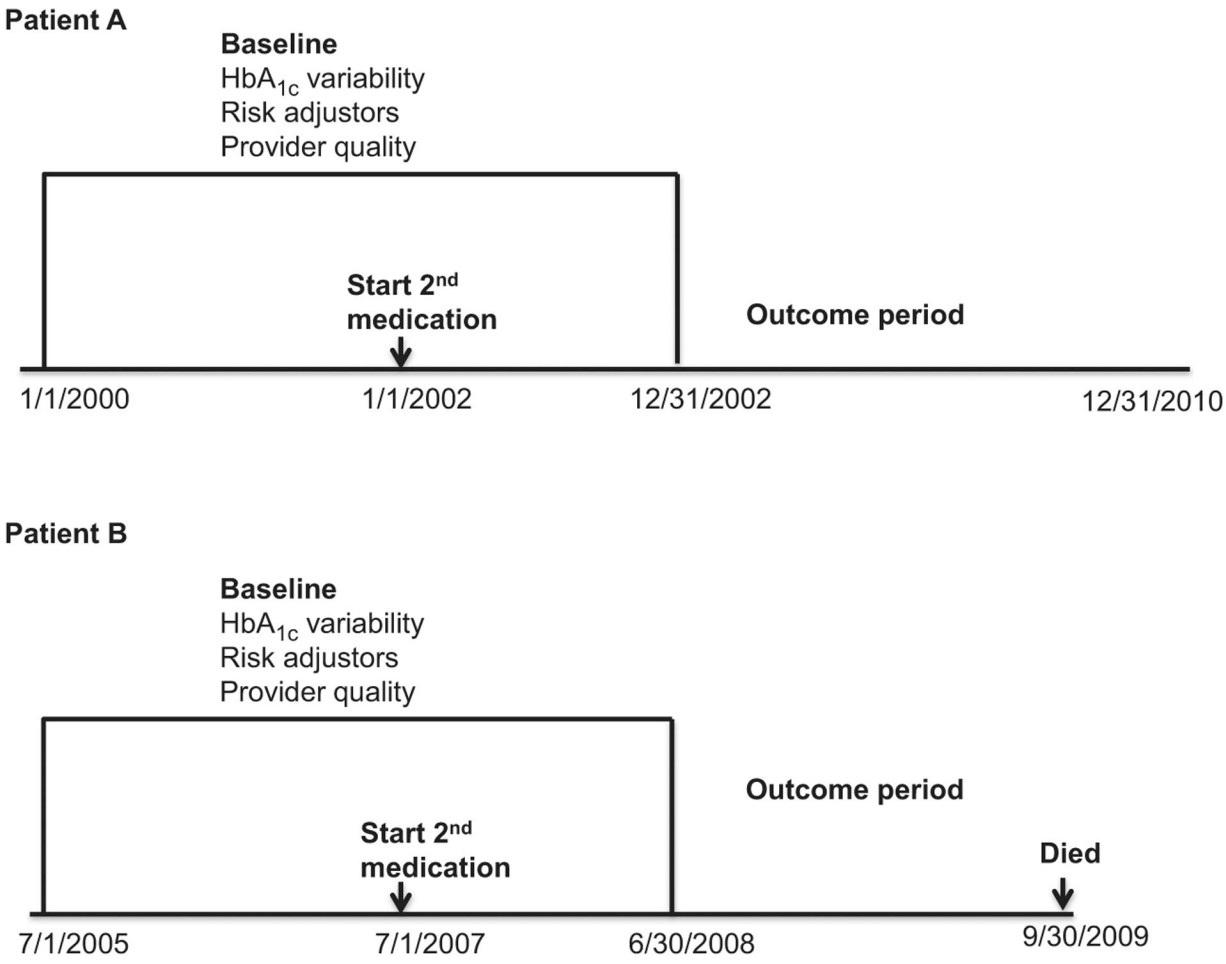

FIGURE 1.
Examples of study design and timing.

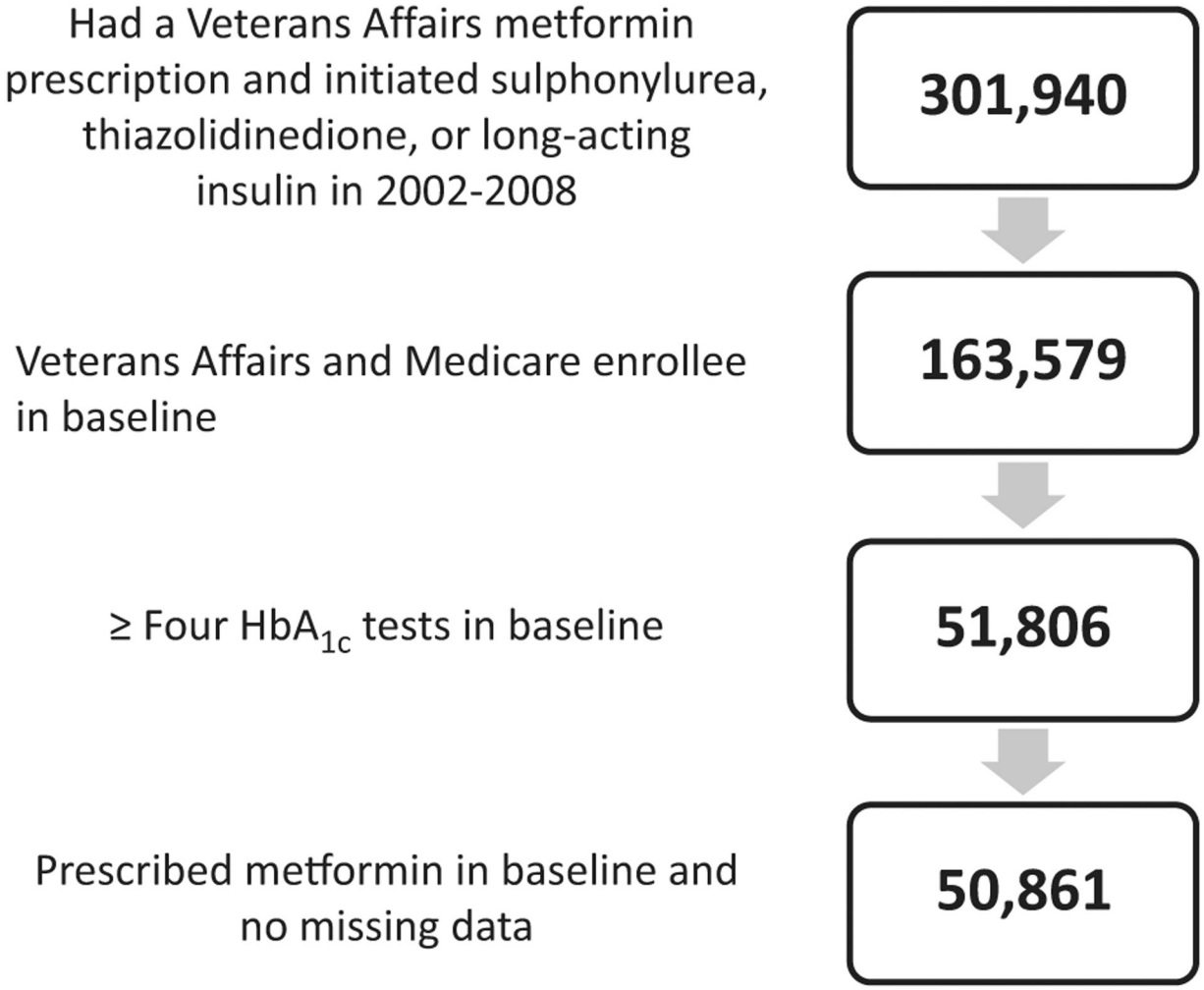

FIGURE 2.

Sample selection.

[a]Models include baseline change in HbA_{1c} slope, demographics, Elixhauser comorbidities, Young severity index, BMI, microalbumin, serum creatinine, blood pressure, LDL, starting a thiazolidinedione or insulin compared to sulphonylurea, provider quality controls, year fixed effects and Veterans Affairs Medical Center random effects.

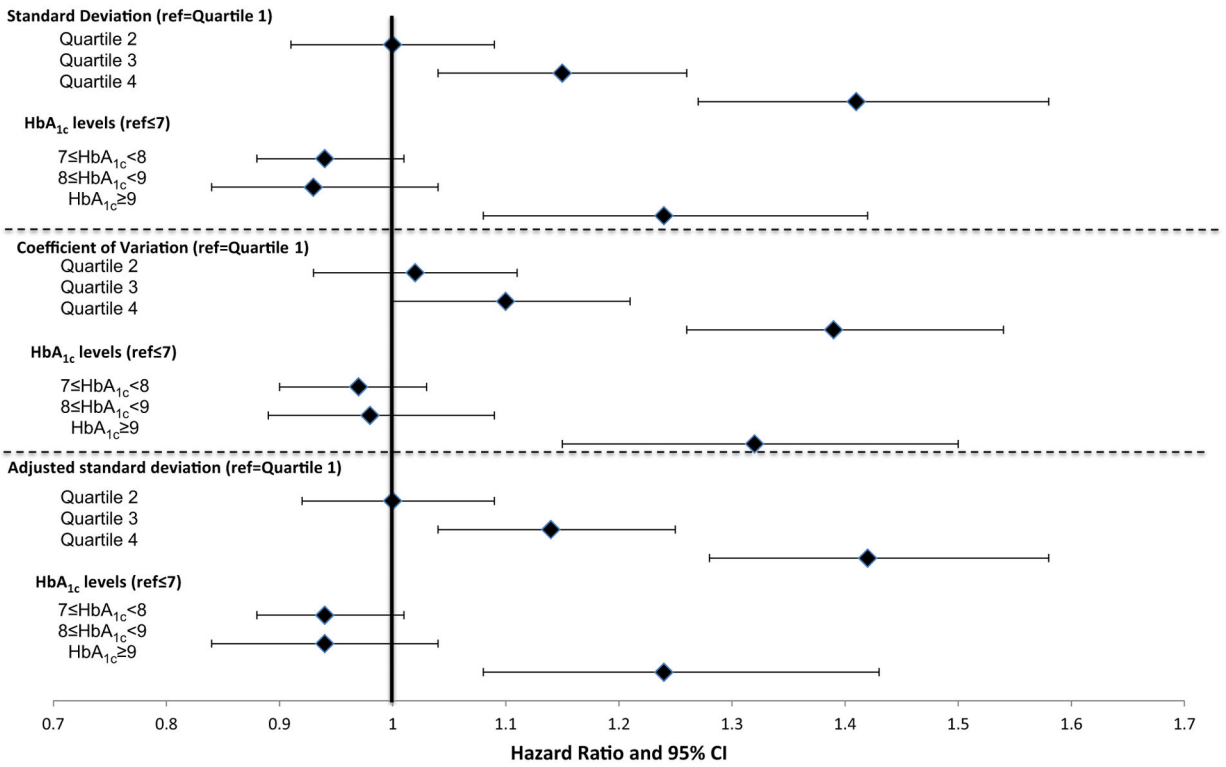

FIGURE 3.

Effect of HbA_{1c} variability and levels on mortality (n = 50 861).

[a]Models include baseline change in HbA_{1c} slope, demographics, Elixhauser comorbidities, Young severity index, BMI, microalbumin, serum creatinine, blood pressure, LDL, starting a thiazolidinedione or insulin compared to sulphonylurea, provider quality controls, year fixed effects and Veterans Affairs Medical Center random effects

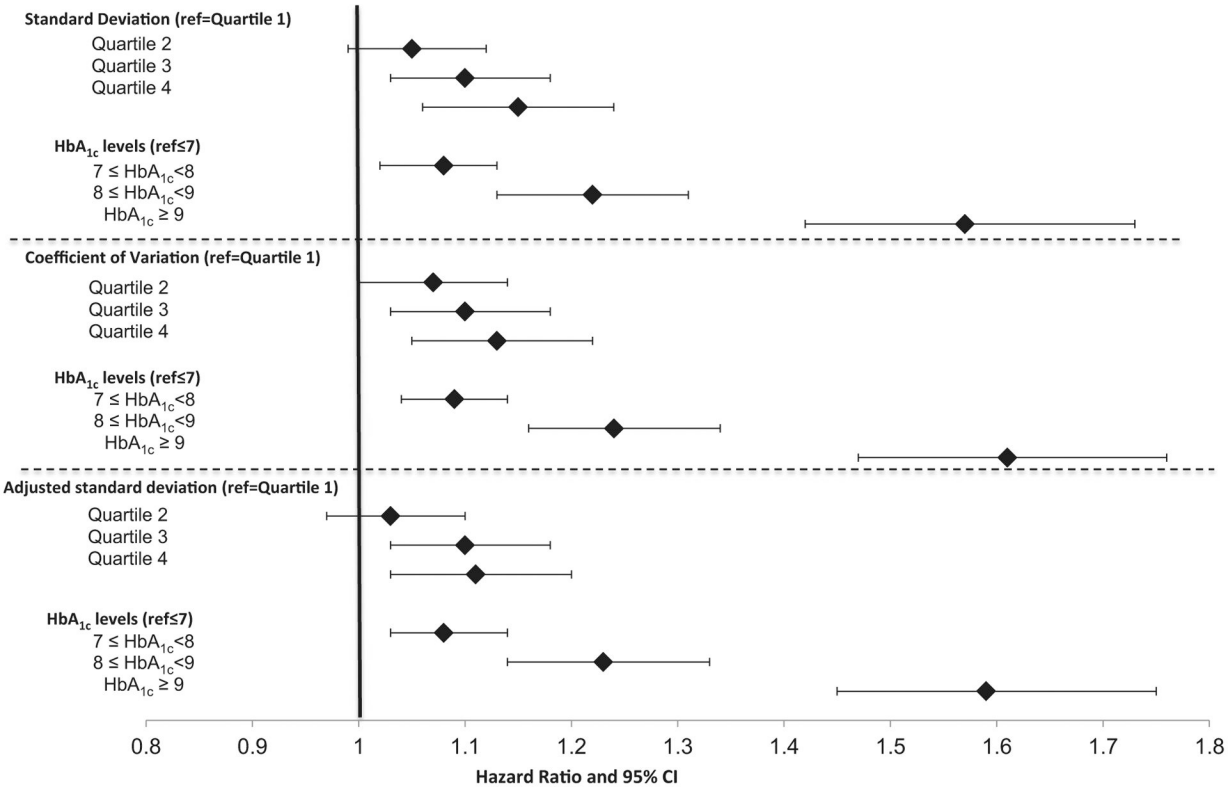

FIGURE 4.

Effect of HbA_{1c} variability and levels on hospitalization for ambulatory care-sensitive conditions (n = 50 861).

[a]Models include baseline change in HbA_{1c} slope, demographics, Elixhauser comorbidities, Young severity index, BMI, microalbumin, serum crea nine, blood pressure, LDL, starting a thiazolidinedione or insulin compared to sulphonylurea, provider quality controls, year fixed effects and Veterans Affairs Medical Center random effects.

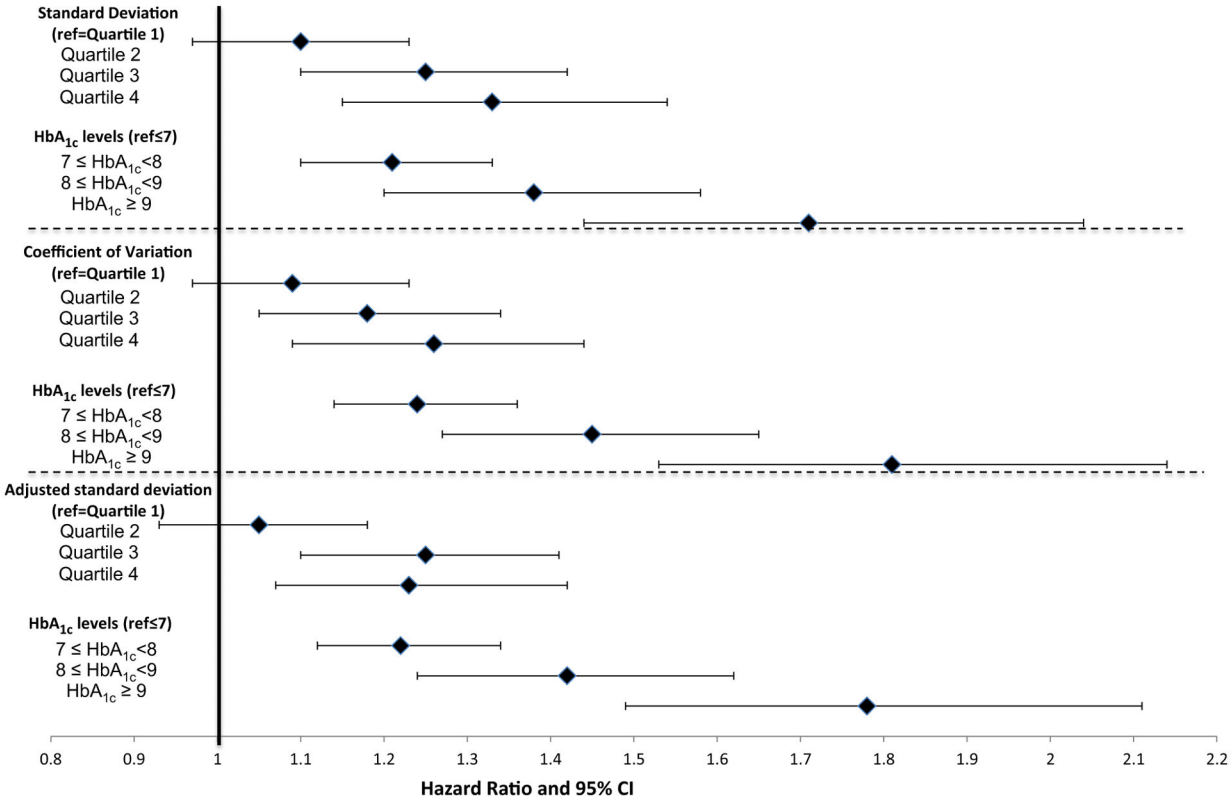

FIGURE 5.

Effect of HbA_{1c} variability and levels on myocardial infarction or stroke (n = 50 861).

Table 1

Selected descriptive demographic, comorbidity and outcome statistics (n = 50 861)*

Demographics	
Mean ± SD age, years	65.64 ± 9.42†
Male, *n* (%)	49 629 (98)
White, *n* (%)	43 730 (86)
HbA_{1c} measures	
Mean ± SD HbA_{1c} variability measures, mmol/mol (%)	
SD	0.81 ± 0.67
Coefficient of variation	10.78 ± 7.67
Adjusted standard deviation	1.29 ± 1.04
Mean HbA_{1c} levels, *n* (%)	
< 53 mmol/mol (< 7%)	22 834 (45)
≥ 53 mmol/mol (≥ 7%) and < 64 mmol/mol (< 8%)	19 214 (38)
≥ 64 mmol/mol (≥ 8%) and < 75 mmol/mol (< 9%)	6031 (12)
≥ 75 mmol/mol (≥ 9%)	2782 (5)
Mean ± SD HbA_{1c} overall trends, mmol/mol (%)	
Slope coefficient	−0.0005 ± 0.003
Diabetes complications, *n* (%)	
Retinopathy‡	12 312 (24)
Nephropathy‡	9500 (19)
Neuropathy‡	17 749 (35)
Cerebrovascular‡	9568 (19)
Cardiovascular (some)‡	12 568 (25)
Cardiovascular (severe)‡	16 262 (32)
Peripheral vascular complications‡	10 566 (21)
Metabolic complications‡	792 (2)
Cardiovascular comorbidities, *n* (%)	
BMI defined as overweight	16 080 (32)
BMI defined as obese	28 372 (56)
High blood pressure	17 933 (35)
Mean LDL > 100 mg/dl	19 074 (38)
Congestive heart failure§	9045 (18)
Cardiac arrhythmias§	15 046 (30)
Valvular disease§	7287 (14)
Pulmonary circulatory disorder§	1430 (3)
Chronic pulmonary disease§	17 276 (34)

Demographics	
Outcomes, *n* (%)	
All-cause mortality	4759 (9)
ACSC hospitalization	9261 (18)
MI or stroke	2676 (5)

ACSC, ambulatory care-sensitive conditions; MI, myocardial infarction.

[*] For complete descriptive statistics refer to Table S1.

[†] Values are *n* (%) unless indicated otherwise.

[‡] Young severity index

[§] Elixhauser comorbidity