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Association between hemoglobin A1c variability and hypoglycemia-related hospitalizations in veterans with diabetes mellitus

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ABSTRACT

Introduction To study the impact of hemoglobin A1c (A1c) variability on the risk of hypoglycemia-related hospitalization (HRH) in veterans with diabetes mellitus.
Research design and methods 342 059 veterans with diabetes aged 65 years or older were identified for a retrospective cohort study. All participants had a 3-year baseline period from January 1, 2005 to December 31, 2016, during which they had at least four A1c tests. A1c variability measures included coefficient of variation (A1c CV), A1c SD, and adjusted A1c SD. HRH was identified during a 2-year follow-up period from Medicare and the Veterans Health Administration through validated algorithms of International Classification of Diseases (ICD)-9 and ICD-10 codes. Logistic regression modeling was used to evaluate the relationship between A1c variability and HRH risk while controlling for relevant clinical covariates.
Results 2871 patients had one or more HRH in the 2-year follow-up period. HRH risk increased with greater A1c variability, and this was consistent across A1c CV, A1c SD, and adjusted A1c SD. Average A1c levels were also independently associated with HRH, with levels <7.0% (53 mmol/mol) having lower risk and >9% (75 mmol/mol) with greater risk. The relationships between A1c variability remained significant after controlling for average A1c levels and prior HRH during the baseline period.
Conclusion Increasing A1c variability and elevated A1c levels are associated with a greater risk of HRH in older adults with diabetes. Clinicians should consider A1c variability when assessing patients for risk of severe hypoglycemia.

INTRODUCTION

Severe hypoglycemia resulting in hospitalization leads to poor health outcomes and mortality in older adults with diabetes mellitus.[1–5] Concerns about treatment-associated hypoglycemia have assumed greater importance as rates of hypoglycemia-related hospitalization (HRH) increased between 1999 and 2011 and surpassed hyperglycemia-related hospitalization rates between 1999 and 2011.[6]

Several patient-level risk factors independently predict severe hypoglycemia

Significance of this study

What is already known about this subject?
► Hypoglycemia-related hospitalization (HRH) increases the risk of mortality in older adults with diabetes.
► Several patient-level factors predict the risk of severe hypoglycemia, but hemoglobin A1c (A1c) levels have an uncertain relationship to HRH, which highlights that A1c levels alone may be insufficient to understand risk.
► Variability in A1c levels is associated with increased risk of diabetes complications and mortality.

What are the new findings?
► Increasing A1c variability was associated with greater risk of HRH over a 2-year follow-up period, after controlling for A1c levels and several clinical and sociodemographic covariates.
► Higher A1c levels >9% (75 mmol/mol) conferred greater risk of HRH after controlling for A1c variability.
► The relationship between A1c variability and HRH risk remained significant after controlling for prior HRH events.

How might these results change the focus of research or clinical practice?
► A1c variability over time should be considered when assessing risk of severe hypoglycemia in older adults with diabetes.

events, such as older age, diabetes treatment that includes insulin or sulfonylureas, black race, lower body mass index (BMI), renal disease, cognitive impairment, and history of hypoglycemic events.[2 7–10] Additional concerns exist for older adults who are potentially overtreated in the setting of comorbid conditions.[11] Thus, many diabetes treatment guidelines favor individualized and higher hemoglobin A1c (A1c) targets for at-risk older adults to balance long-term glycemic benefits and short-term hypoglycemia risk.[12–15] Maintaining patients in an appropriate glycemic range is also complicated by uncertainty about the relationship between A1c and risk

of hypoglycemia. Some studies show that higher A1c confers increased risk of hypoglycemia,[16] while others show an inverse relationship, with lower A1c associated with increased risk.[17] This suggests that A1c levels alone may not define risk but are part of a dynamic relationship with patient-level factors and medications that result in greater glucose variability over time.

A1c variability is associated with increased hospitalizations, diabetes complications, and mortality.[18–23] These risks persist when controlled for A1c levels[18 19 21] and are independent of standard or intensive diabetes treatment.[24 25] Therefore, more indepth study of the relationship between A1c variability and HRH is warranted.

This study was designed to validate the clinical implications of A1c variability and substantiate its effects on HRH in older adults with diabetes. We used a large nationwide sample of veterans with diabetes to study the association between measures of A1c variability and risk of HRH while controlling for several relevant sociodemographic and clinical factors.

METHODS

Study population

We combined administrative data sets from the Veterans Health Administration (VA) and Medicare to gather sociodemographic and clinical measures and outpatient and inpatient utilization. Visit dates and diagnosis codes necessary for identifying HRH were obtained from inpatient discharge records in VA and Medicare inpatient databases. Medications, laboratory tests, financial means tests, and percentage of service-connected disability were extracted from the VA's administrative claims.

We identified veterans diagnosed with diabetes who were aged 65 years or older, enrolled in VA care and dually eligible for Medicare during the period of January 1, 2005 through December 31, 2014 (figure 1). A diabetes diagnosis was determined using published criteria[26]: (1) two or more diabetes diagnosis codes from outpatient visits or (2) one inpatient hospitalization for diabetes over a 2-year period or (3) a prescription for diabetes medication (excluding metformin alone) in the current year.

Patients meeting the following criteria:

a) VA- Medicare eligible patients
b) Two outpatient visits or one inpatient visit with an ICD-9 code for diabetes (362.0X, 357.2, 250.X, 366.41), or prescription for a diabetes medication (excluding metformin-only)
c) ≥ 4 A1c tests in a 3-year baseline period between 2005 and 2013

Excluded patients younger than 65 in the year prior to baseline date

Excluded patients without a full 3-year baseline period
Excluded patients with missing comorbidities

Excluded patients whose 3-year baseline period ended after 2014

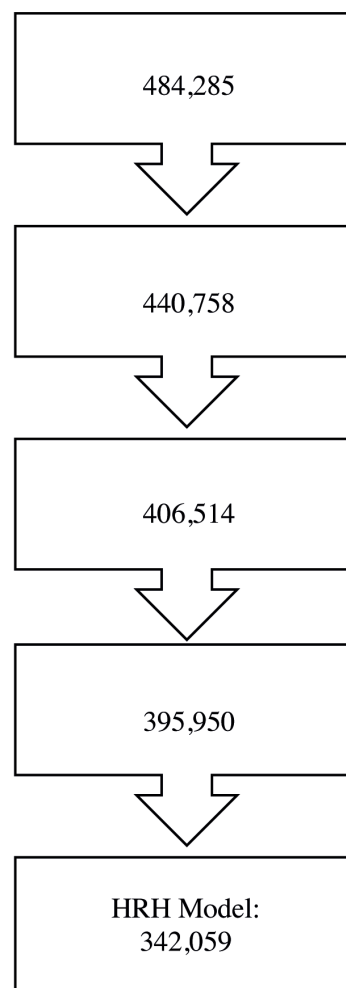Excluded patients who died anytime in the two-year follow up period

484,285

440,758

406,514

395,950

HRH Model:
342,059

Figure 1 Flow chart of the selective criteria used to create the final study sample (N=342 059). HRH, hypoglycemia-related hospitalization; ICD, International Classification of Diseases; VA, Veterans Health Administration.

Table 1 Sociodemographic and clinical characteristics

	Non-HRH population (n=339 188)		HRH population (n=2871)		Study population (N=342 059)		P value
	Patients (n)	%	Patients (n)	%	Patients (n)	%	
Sex							0.325
Male	334 814	99	2828	99	337 642	99	
Female	4374	1	43	1	4417	1	
Race							<0.001
White	292 495	86	2162	75	294 657	86	
Black	36 307	11	612	21	36 919	11	
Hispanic	5151	2	55	2	5206	2	
Asian	1283	0	14	0	1297	0	
Other	3952	1	28	1	3980	1	
Age (years)							<0.001
64–74	203 585	60	1332	46	204 917	60	
75+	135 603	40	1539	54	137 142	40	
Diabetes medication use							
Insulin							<0.001
No	262 008	77	1445	50	263 453	77	
Yes	77 180	23	1426	50	78 606	23	
Metformin							<0.001
No	165 771	49	1685	59	167 456	49	
Yes	173 417	51	1186	41	174 603	51	
Sulfonylurea							<0.001
No	157 968	47	1007	35	158 975	47	
Yes	181 220	53	1864	65	183 084	54	
Alpha-glucosidase inhibitors							0.013
No	332 630	98	2797	97	335 427	98	
Yes	6558	2	74	3	6632	2	
Thiazolidinedione							<0.001
No	283 997	84	2258	79	286 255	84	
Yes	55 191	16	613	21	55 804	16	
Other medications*							0.512
No	333 948	98	2831	99	336 779	98	
Yes	5240	2	40	1	5280	2	
Average A1c (%)							<0.001
<6	38 233	11	175	6	38 408	11	
6–6.9	157 548	46	878	31	158 426	46	
7–7.9	97 676	29	1015	35	98 691	29	
8–8.9	32 664	10	496	17	33 160	10	
≥9	13 067	4	307	11	13 374	4	
Serum creatinine (mg/dL)							<0.001
<0.6	298	0	3	0	301	0	
0.6–1.2	188 122	55	1027	36	189 149	55	
>1.2	141 253	42	1780	62	143 033	42	
Missing†	9515	3	61	2	9576	3	
Urine albumin to creatinine ratio (mg/g)							<0.001

Continued

	Non-HRH population (n=339 188)		HRH population (n=2871)		Study population (N=342 059)		
	Patients (n)	%	Patients (n)	%	Patients (n)	%	P value
<30	93 900	28	530	18	94 430	28	
30–300	43 612	13	494	17	44 106	13	
>300	6607	2	114	4	6721	2	
Missing†	195 069	58	1733	60	196 802	58	
Serum albumin (g/dL)							<0.001
<3.5	20 665	6	366	13	21 031	6	
≥3.5	282 093	83	2273	79	284 366	83	
Missing†	36 430	11	232	8	36 662	11	
Body mass index (kg/m²)							<0.001
<18.5	413	0	9	0	422	0	
18.5–24.9	40 730	12	422	15	41 152	12	
25–29	129 697	38	1078	38	130 775	38	
30–39	138 732	41	1139	40	139 871	41	
≥40	14 854	4	117	4	14 971	4	
Missing†	14 762	4	106	4	14 868	4	
Service-connected disability† (%)							0.898
<50	292 564	86	2474	86	295 038	86	
≥50	46 623	14	397	14	47 020	14	
Missing†	1	0	0	0	1	0	
Financial means test							<0.001
Exempt	104 110	31	1039	36	105 149	31	
Copayment required	98 130	29	717	25	98 847	29	
Missing†	136 948	40	1115	39	138 063	40	

*Other medications: amylin analog, bile acid sequestrants, dipeptidyl peptidase inhibitors, dopamine receptor agonist, glucagon-like peptide, meglitinides, and sodium-glucose cotransporter inhibitor.
†Values missing from source database.
HRH, hypoglycemia-related hospitalization.

Patients taking metformin alone were included if they had concomitant diabetes diagnosis codes. The latter typically captures at least 97% of patients with diabetes.[26] A small number of patients may take metformin for non-diabetes diagnoses, so this criterion was used to increase specificity. Patients were required to have four or more A1c measurements over a consecutive 3-year baseline period, with sequential A1c tests ≤365 days apart. A total of 395 950 patients met these criteria. We excluded 53 891 patients who died in the follow-up period. Thus, 342 059 patients remained in the study sample for statistical analyses.

Outcomes, exposures and covariates

HRH was defined as hospital admissions with a principal discharge diagnosis of hypoglycemia based on validated algorithms of International Classification of Diseases (ICD)-9 and ICD-10 codes[27 28] occurring prior to December 31, 2016. The outcome did not include transfers and secondary diagnoses of hypoglycemia

because these may have occurred during hospitalization or secondary to another acute event.[6]

A1c variability was described by A1c coefficient of variation (A1c CV), A1c SD, and adjusted A1c SD. A1c CV was calculated by dividing A1c SD by the average A1c value and expressed as per cent. Adjusted A1c SD accounted for the number of A1c measurements and the days between each measurement using a linear regression formula.[21] Finally, the three measures of A1c variability were transformed into quartiles for analysis. We also included mean A1c categories (<6% (42 mmol/mol), 6%–6.9% (42–52 mmol/mol), 7%–7.9% (53–63 mmol/mol), 8%–8.9% (64–74 mmol/mol), ≥9% (75 mmol/mol)) as a covariate to assess the independent effect of A1c variability on HRH.

Sociodemographic factors included age at the start of the baseline period (categorized as 65–74 and ≥75 years), sex, race, financial means test (which assesses financial resources and determines a requirement for

Table 2 Summary of A1c variability measures and HRH risk during 2-year follow-up period (n=342 058)*

Model†	OR (95% CI)	P value
Model 1		
A1c coefficient of variation (%) (ref <4)		
4–5.9	1.19 (1.04 to 1.36)	0.011
6–9.4	1.28 (1.13 to 1.47)	<0.001
9.5–66	1.44 (1.26 to 1.65)	<0.001
A1c mean (%) (ref=7–7.9)		
<6	0.66 (0.56 to 0.78)	<0.001
6–6.9	0.78 (0.71 to 0.86)	<0.001
8–8.9	1.11 (1.00 to 1.24)	0.060
≥9	1.53 (1.33 to 1.75)	<0.001
Model 2		
A1c SD (ref <0.25)		
0.25–0.40	1.26 (1.10 to 1.45)	0.001
0.41–0.68	1.36 (1.18 to 1.56)	<0.001
0.69–6.46	1.56 (1.35 to 1.81)	<0.001
A1c mean (%) (ref=7–7.9)		
<6	0.71 (0.59 to 0.84)	<0.001
6–6.9	0.81 (0.73 to 0.89)	<0.001
8–8.9	1.09 (0.98 to 1.22)	0.125
≥9	1.49 (1.30 to 1.72)	<0.001
Model 3		
Adjusted A1c SD (ref <0.62)		
0.62–0.97	1.08 (0.95 to 1.24)	0.239
0.98–1.56	1.12 (0.98 to 1.27)	0.103
1.57–17.40	1.37 (1.20 to 1.57)	<0.001
A1c mean (%) (ref=7–7.9)		
<6	0.67 (0.56 to 0.79)	<0.001
6–6.9	0.79 (0.71 to 0.87)	<0.001
8–8.9	1.09 (0.98 to 1.22)	0.115
≥9	1.48 (1.29 to 1.70)	<0.001

*One patient was dropped from logistic regression due to missing service-connected disability.
†Each model was run with a measure of A1c variability in quartiles, A1c mean, and the covariates listed in the Methods section.
HRH, hypoglycemia-related hospitalization; ref, reference.

copayments for VA services), and percentage of service-connected disability (as a marker of disability status, where >50% exempts patients from copayments). Other clinical covariates from the baseline period included glucose-lowering medications (eg, insulin, sulfonylurea, metformin, alpha-glucosidase inhibitor, thiazolidinedione, and less commonly used medications), serum creatinine, urine albumin to creatinine ratio, serum albumin, and BMI. All biological measures were averaged over the baseline period. We calculated the logarithmic number of outpatient and inpatient visits from the baseline period to account for utilization of clinical services.

Year of follow-up was included to account for secular changes in diabetes management over time.

Statistical analysis

Statistical analyses were performed using STATA MP V.15.1. Patient characteristics in the HRH and non-HRH populations were assessed for significance with the χ^2 test for binary attributes, the Wilcoxon rank-sum test for intervals of clinical characteristics, and the two-sample t-test for continuous measures. We performed a logistic regression for each A1c variability measure to evaluate the relationship between A1c variability and the risk of HRH in the 2-year follow-up period, controlling for relevant clinical and sociodemographic covariates. Results were expressed as OR with their 95% CI. A p value of less than 0.05 was considered statistically significant.

Sensitivity analyses

To test the robustness of our results, we evaluated statistical models with 1-year and 3-year follow-up periods. Because prior HRH may confer higher risk for new HRH events,[8] we evaluated the association between A1c variability and HRH risk with an additional covariate that identified patients with any HRH during the baseline period. We also determined if the number of A1c tests during the baseline period impacted the study results.

RESULTS
Study cohort

The study sample of 342 059 had 2871 patients with one or more HRH in the 2-year follow-up period. The baseline sociodemographic and clinical characteristics of patients with no HRH and those who developed HRH in the 2-year follow-up period are presented in table 1. Both groups were predominantly male and white, but the HRH group had twice the percentage of black patients than the non-HRH group. The average (SD) age of patients in the HRH and non-HRH groups was 75.8 (5.5) and 74.1 (5.5) years, respectively, and the average (SD) A1c level was 7.5% (1.2%) (58 mmol/mol) and 7.0% (1.0%) (53 mmol/mol), respectively. Insulin, sulfonylurea, and thiazolidinedione use was higher and metformin use was lower in the HRH group. There were more patients with A1c ≥9% (75 mmol/mol) in the HRH population, whereas in the non-HRH population there were more patients with A1c ≤7% (53 mmol/mol). The mean values of A1c CV, A1c SD, and adjusted A1c SD (10%, 0.76, and 1.72, respectively) were significantly higher (p<0.001) among patients with HRH than those without HRH (7%, 0.54, and 1.28).

There was a consistent and positive relationship between A1c variability and HRH in models that controlled for mean A1c levels and sociodemographic and clinical covariates (table 2). A1c CV, A1c SD, and adjusted A1c SD showed increasing risk of HRH throughout quartiles 2–4 in comparison with quartile 1. The adjusted A1c SD had significantly increased odds of HRH in the highest quartile. Higher mean A1c levels were also associated with

Table 3 A1c variability and HRH risk in 1-year and 3-year follow-up periods*

Model†	1-year (n=375 519)		3-year (n=308 241)	
	OR (95% CI)	P value	OR (95% CI)	P value
Model 1				
A1c coefficient of variation (%) (ref <4)				
4–5.9	1.10 (0.92 to 1.31)	0.286	1.20 (1.06 to 1.35)	0.003
6–9.4	1.12 (0.94 to 1.33)	0.201	1.35 (1.20 to 1.52)	<0.001
9.5–66	1.33 (1.12 to 1.58)	0.001	1.48 (1.31 to 1.67)	<0.001
Model 2				
A1c SD (ref <0.25)				
0.25–0.40	1.18 (0.98 to 1.41)	0.075	1.26 (1.11 to 1.43)	<0.001
0.41–0.68	1.15 (0.96 to 1.38)	0.138	1.42 (1.25 to 1.60)	<0.001
0.69–6.46	1.4 0 (1.16 to 1.69)	0.001	1.58 (1.39 to 1.80)	<0.001
Model 3				
Adjusted A1c SD (ref <0.62)				
0.62–0.97	1.02 (0.86 to 1.21)	0.812	1.17 (1.04 to 1.32)	0.008
0.98–1.56	1.03 (0.87 to 1.22)	0.731	1.23 (1.10 to 1.38)	0.001
1.57–17.40	1.29 (1.09 to 1.54)	0.004	1.48 (1.31 to 1.67)	<0.001

*The risk of HRH in 1-year and 3-year follow-up periods was assessed separately using the logistic regression model indicated in the Methods section.

†Each model was run with a measure of A1c variability in quartiles, A1c mean, and the covariates listed in the Methods section.

HRH, hypoglycemia-related hospitalization; ref, reference.

greater HRH risk after controlling for each of the A1c variability measures. Compared with patients with mean baseline A1c 7%–7.9% (53–63 mmol/mol), patients with A1c <7% (53 mmol/mol) had a significantly lower risk of HRH and A1c >9% (75 mmol/mol) had a significantly higher risk. Other factors carrying increased HRH risk included insulin and sulfonylurea use, increased urine albumin to creatinine excretion (>30 mg/g), higher serum creatinine (>1.2 mg/dL), black race, and age ≥75 years. These associations remained consistent across all three measures of A1c variability (online supplemental appendix tables 1–3).

Sensitivity analyses

The same models of A1c CV, A1c SD and adjusted A1c SD were used to study 1-year and 3-year follow-up periods (table 3; online supplemental appendix tables 4 and 5). During the 1-year of follow-up, relationships between A1c variability measures and HRH risk were significant in the highest quartile. The 3-year follow-up model generated ORs very similar to the 2-year model, showing increased HRH risk associated with all A1c variability measures.

Additional analysis that assessed the impact of prior HRH events did not modify the association between A1c variability and increased HRH risk (table 4). Prior HRH conferred a threefold higher risk of future HRH,[8] but higher A1c variability and mean A1c continued to be significantly associated with HRH (table 4; online supplemental appendix tables 6–8).

To determine if more frequent A1c testing during baseline impacted the study results, we included the number of A1c tests in the analysis model of A1c CV. This did not change the study results (data not shown).

DISCUSSION

We found a significant and positive relationship between higher A1c variability and HRH over a 2-year follow-up period among veterans with diabetes who were 65 years or older. A1c levels and variability were measured over a 3-year baseline period and patients were then followed to assess HRH events. Significance of the associations and the level of risk varied somewhat across the different A1c variability measures, but all showed consistent and graded relationships with HRH. Average A1c levels were also significantly and independently associated with HRH, with levels <7.0% (53 mmol/mol) associated with lower risk and levels >9% (75 mmol/mol) conferring greater risk. In sensitivity analyses, prior HRH carried higher HRH risk, but when prior HRH was included as a covariate, A1c variability measures remained strong predictors of HRH. High A1c variability was significantly and independently associated with risk of HRH for up to 3 years following the baseline period.

Clinical practice guidelines[13–15] have emphasized the need for individualized and higher A1c targets in older adults with diabetes to balance risks and benefits. Our results also suggest that A1c variability has an independent and significant effect on HRH risk, and tracking A1c levels alone may be insufficient to mitigate risk. We confirmed that guideline-directed A1c targets for many older adults with diabetes are reasonable for minimizing

Table 4 Sensitivity analysis of prior HRH's impact on HRH risk* (n=342 058)†

Model‡	OR (95% CI)	P value
Model 1		
A1c coefficient of variation (%) (ref <4)		
4–5.9	1.19 (1.04 to 1.37)	0.010
6–9.4	1.28 (1.12 to 1.46)	<0.001
9.5–66	1.42 (1.24 to 1.63)	<0.001
Prior HRH (ref=no)		
Yes	3.12 (2.65 to 3.67)	<0.001
A1c mean (%) (ref=7–7.9)		
<6	0.67 (0.56 to 0.79)	<0.001
6–6.9	0.78 (0.71 to 0.86)	<0.001
8–8.9	1.11 (1.00 to 1.25)	0.057
≥9	1.53 (1.33 to 1.75)	<0.001
Model 2		
A1c SD (ref <0.25)		
0.25–0.40	1.26 (1.10 to 1.45)	0.001
0.41–0.68	1.35 (1.17 to 1.55)	<0.001
0.69–6.46	1.54 (1.33 to 1.79)	<0.001
Prior HRH (ref=no)		
Yes	3.12 (2.65 to 3.67)	<0.001
A1c mean (%) (ref=7–7.9)		
<6	0.71 (0.60 to 0.85)	<0.001
6–6.9	0.81 (0.73 to 0.89)	<0.001
8–8.9	1.09 (0.98 to 1.23)	0.117
≥9	1.49 (1.30 to 1.72)	<0.001
Model 3		
Adjusted A1c SD (ref <0.62)		
0.62–0.97	1.08 (0.95 to 1.23)	0.253
0.98–1.56	1.11 (0.97 to 1.26)	0.127
1.57–17.40	1.36 (1.19 to 1.56)	<0.001
Prior HRH (ref=no)		
Yes	3.12 (2.65 to 3.68)	<0.001
A1c mean (%) (ref=7–7.9)		
<6	0.67 (0.57 to 0.80)	<0.001
6–6.9	0.79 (0.71 to 0.87)	<0.001
8–8.9	1.10 (0.98 to 1.23)	0.113
≥9	1.48 (1.29 to 1.70)	<0.001

*The sensitivity analysis was executed by adding prior HRH from the baseline period as a binary covariate to the logistic regression indicated in the Methods section.
†One patient was dropped from logistic regression due to missing service-connected disability.
‡Each model was run with a measure of A1c variability in quartiles, previous HRH event, A1c mean, and the covariates listed in the Methods section.
HRH, hypoglycemia-related hospitalization; ref, reference.

risk of HRH, since A1c levels between 7% and 8.9% (53–74 mmol/mol) carried similar risk. We also showed that A1c levels >9% (75 mmol/mol) are linked to increased risk of HRH and lower levels (<7%, 53 mmol/mol) are

associated with lower risk. Studies have shown differing relationships between A1c levels and severe hypoglycemia, with high A1c,[16 29] low A1c,[17] or both[30] carrying increased risk.[16 17 30] Unlike other studies, we included a large and broad sample of older adults with diabetes and captured outcomes from both VA and Medicare data. It is possible that differences across various studies may reflect variations in the patient population, diabetes treatment, definitions of hypoglycemia, and duration of follow-up. We acknowledge that several methods for calculating A1c variability have been proposed, including traditional variance measures such as CV and SD, as well as categorical measures that incorporate absolute change in A1c.[18 19 23 25 31] Since the majority of prior publications have used CV or SD to measure A1c variability we also opted for these methods.

Additional significant risk factors associated with HRH include use of insulin or sulfonylurea medications, black race, elevated serum creatinine, increased urine albumin to creatinine ratio, and age >75 years. Many of these same characteristics or conditions have been associated with risk of severe hypoglycemia.[7–10] It is most likely that these factors are linked to HRH through effects of treatment, including adverse effects, or are markers of disease burden. Prior HRH events were also significantly associated with future risk of HRH, as has been previously shown.[8 18] Metformin usage and high BMI were associated with lower risk of HRH. Metformin has been associated with lower incidence of hypoglycemia[32] and higher BMI has been shown to carry reduced incidence of severe hypoglycemia, possibly due to the increased insulin resistance present in obesity.[33–35]

Patients at highest risk for HRH are those with both high A1c levels and high A1c variability, and these clinical findings often reflect the complex interplay of disease severity, treatment, and sociodemographic factors. For example, patients with high A1c levels and A1c variability are more likely to be treated with insulin or multidrug regimens, have competing conditions or comorbidities that complicate diabetes treatment,[31 36] and experience medication adherence issues.[37] A1c variability is clearly influenced by these underlying factors that affect glucose control over time. The fact that increasing variability is independently associated with HRH should not be overlooked as a marker of increased risk. From an implementation standpoint, healthcare systems may choose to calculate A1c variability measures and identify patients at high risk for major hypoglycemia events. A1c CV ≥6%, A1c SD >0.4 and A1c >9% identify patients at increased HRH risk over a period of 2–3 years. The presence of these measures may alert physicians to individualize care and minimize such risks.

Our study has limitations that may affect its generalizability. The study sample represented an older and predominantly white male population and we included only patients with at least four A1c levels over 3 years. Further, the study sample included only veterans, which is a group that has a high prevalence of diabetes,[26] has greater physical and

mental health comorbidities relative to the general population,[38] and may have a substantial number of patients who are potentially overtreated.[11] Our results may not extend to younger patients or those with fewer comorbidities. Limited data were available on socioeconomic status and this may not fully account for the impact of social determinants of health on HRH outcomes. We assessed HRH as our outcome of interest, although this represents a more severe form of hypoglycemia. Administrative data do not reliably include milder forms of hypoglycemia such as those treated in the outpatient setting, so these more frequent events were not captured. In addition, our findings do not allow us to determine causality. Nonetheless, the study design has several strengths. We employed a large study sample encompassing a 12-year study period and employed various A1c variability measures. We applied a 3-year baseline period before determining HRH outcomes, which limits concerns about reverse causality. Statistical models included a number of relevant covariates, and we performed sensitivity analyses to assess the robustness of the findings.

In summary, older adults with diabetes with increasing A1c variability and elevated A1c levels (>9%, 75 mmol/mol) are at significantly greater risk of HRH over a 2-year period. Our results suggest that clinicians should consider A1c variability for its potential role in predicting risk of severe hypoglycemia.

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