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 2,871 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 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

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.
Cardiovascular and metabolic risk of hypoglycemia. Some studies show that higher A1c confers increased risk of hypoglycemia, while others show an inverse relationship, with lower A1c associated with increased risk. 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. These risks persist when controlled for A1c levels and are independent of standard or intensive diabetes treatment. 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: (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.

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 |
|--------------------------|---------------------------------|-------------------------|-----------------------------|---------|
| **Sex**                  |                                 |                         |                             |         |
| Male                     | 334 814 (99)                    | 2828 (99)               | 337 642 (99)                | 0.325   |
| Female                   | 4374 (1)                        | 43 (1)                  | 4417 (1)                    |         |
| **Race**                 |                                 |                         |                             | <0.001  |
| White                    | 292 495 (86)                    | 2162 (75)               | 294 657 (86)                |         |
| Black                    | 363 071 (11)                    | 612 (21)                | 369 191 (11)                |         |
| Hispanic                 | 515 1 (2)                       | 55 (2)                  | 520 6 (2)                   |         |
| Asian                    | 1283 (0)                        | 14 (0)                  | 1297 (0)                    |         |
| Other                    | 395 2 (1)                       | 28 (1)                  | 398 0 (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 |

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Patients taking metformin alone were included if they had concomitant diabetes diagnosis codes. The latter typically captures at least 97% of patients with diabetes. 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 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. 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. 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 1 Continued

|                | Non-HRH population (n=339,188) | HRH population (n=2871) | Study population (N=342,059) | P value |
|----------------|---------------------------------|-------------------------|------------------------------|---------|
|                | Patients (n) | % | Patients (n) | % | Patients (n) | % |
| <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 | 283,666 | 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.
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 χ² 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, 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 342059 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 ≥29% (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 1.28) were expressed as OR with their 95% CI. A p value of less than 0.05 was considered statistically significant.

#### Table 2: Summary of A1c variability measures and HRH risk during 2-year follow-up period (n=342058)*

| 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.

### Year of follow-up was included to account for secular changes in diabetes management over time.
Cardiovascular and metabolic risk

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, 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 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 Hospitalization; ref, reference.

| Table 3 A1c variability and HRH risk in 1-year and 3-year follow-up periods* |
|----------------------------------|---------------------|------------------|---------------------|------------------|
|                                  | 1-year (n=375519)   | 3-year (n=308241) |
|                                  | 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           |
| 0.69–0.46                        | 1.40 (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.
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, low A1c, or both carrying increased risk. 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. 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. 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. Metformin usage and high BMI were associated with lower risk of HRH. Metformin has been associated with lower incidence of hypoglycemia and higher BMI has been shown to carry reduced incidence of severe hypoglycemia, possibly due to the increased insulin resistance present in obesity.

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, and experience medication adherence issues. 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, has greater physical and

Cardiovascular and metabolic risk

- Risk factors associated with increased HRH: high A1c, low A1c, or both.
- Additional significant risk factors: use of insulin or sulfonylurea, black race, elevated serum creatinine, increased urine albumin to creatinine ratio, age >75 years.
- Prior HRH events were also significantly associated with future risk of HRH.
- A1c variability 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.
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mental health comorbidities relative to the general population, and may have a substantial number of patients who are potentially overtreated. 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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