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Intensive Glycaemic Control and Glucose-related Safety Signals in Older Adults Across Primary Care and Hospital Settings

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Abstract

Older adults with type 2 diabetes treated with medications associated with higher hypoglycaemia risk may be vulnerable to glucose-related adverse events, yet Asian real-world glycaemic patterns remain poorly characterised. This parallel cross-sectional study analysed routine electronic health data from a primary care network (n = 38,957) and a tertiary hospital (n = 6,855) in Singapore. We included adults receiving insulin, sulfonylureas, or meglitinides with ≥ 1 HbA1c record.

The proportion of patients achieving HbA1c thresholds < 7.0%, < 6.5%, and < 6.0% increased with age in both settings, reaching 31.9% and 36.3% among those aged ≥ 85 years in primary care and hospital cohorts, respectively. In primary care, lower HbA1c categories were associated with higher odds of hypoglycaemia (glucose < 3.9mmol/L) and borderline low glucose events (glucose ≤ 4.5mmol/L). Compared with HbA1c 7.0–<8.0%, HbA1c < 6.0% increased odds of hypoglycaemia (adjusted OR 1.90, 95% CI 1.15–3.15) and borderline events (adjusted OR 2.36, 95% CI 1.77–3.15). In the hospital cohort, HbA1c < 6.0% similarly increased odds of hypoglycaemia (adjusted OR 2.36, 95% CI 1.65–3.38), although risk remained elevated across multiple HbA1c categories.

These findings suggest that intensive glycaemic control was more prevalent with advancing age and HbA1c alone may not adequately reflect hypoglycaemia susceptibility in selected older adults.

Introduction

Type 2 diabetes mellitus (T2DM) is prevalent in Singapore's ageing population. Local surveillance indicates 22% of adults aged 70–74 years have diabetes [1], highlighting the importance for age- and risk-aligned care as the balance between benefits and risks of glycaemic management becomes increasingly delicate with advancing age, multimorbidity, and frailty. While intensive glycaemic control has been shown to reduce microvascular complications in younger adults with newly diagnosed T2DM [2, 3], subsequent trials in adults with more advanced T2DM and established cardiovascular disease/multiple cardiovascular risk factors suggest possibility of harm, including increased hypoglycaemia events and mortality, particularly when insulin or sulfonylureas were used [4–6]. In addition, older adults may be more susceptible to hypoglycaemic episodes – in the ACCORD study, older adults ≥ 65 years were at approximately three-fold higher risk of hypoglycaemia than younger adults (< 65 years) [7].

Recognizing this, authoritative guidance such as the American Diabetes Association and the Choosing Wisely initiative cautions against intensifying or maintaining pharmacotherapy to achieve tight HbA1c targets in most older adults, particularly those with significant comorbidity or frailty [3, 8]. However, real-world studies suggest that treatment de-intensification remains uncommon, even among multimorbid, frail older adults with low HbA1c [9].

Estimates of overtreatment prevalence in older adults vary across studies due to differing definitions in age thresholds, HbA1c cut-offs, and health status constructs. For example, Tseng et al. reported that

50% of adults aged ≥ 75 years with chronic kidney disease (CKD) or cognitive impairment/dementia receiving insulin and/or sulfonylureas fulfilled criteria for potential glycaemic overtreatment, defined as HbA1c < 7% [10]. In a separate cohort, Lipska et al. observed that among adults ≥ 65 years with diabetes and complex/intermediate health status, defined by significant comorbidities and functional impairment, 58.7% of those with HbA1c < 7% received insulin or sulfonylurea [11].

The prevalence of intensive glycaemic control in Singapore's older adult population remains poorly characterized. While the National Population Health Survey (NPHS) 2024 reported that 33.5% of adults with known diabetes achieved the recommended HbA1c target of ≤ 7.0% [1], the intensity of glycaemic control specifically among older adults receiving medications with higher hypoglycaemia risk requires further investigation. Characterizing HbA1c distributions in this population is essential to understand current prescribing patterns and identify where reassessment of glycaemic targets may be warranted, particularly given Singapore's super-aged status.

NHG Health is one of the 3 main public healthcare providers in Singapore, providing care for approximately 1.5 million residents in Central and North Singapore [12]. In this study, we analysed real-world data in a primary care and tertiary hospital cohort within the NHG Health cluster to (I) describe the prevalence of intensive glycaemic control in older adults receiving medications with higher hypoglycaemia risk, and (II) examine the association between age, HbA1c categories and glucose-related safety signals as defined within each care setting.

Methods

Study design and data sources

This study comprised two parallel, cross-sectional analyses over a one-year period from September 1, 2022 to August 31, 2023 using routinely collected electronic health data from a regional primary care network and a tertiary hospital within NHG Health. Although both institutions operate within the same healthcare cluster, cross-setting patient-level data linkage across settings was not available due to data governance and infrastructure constraints. Data extraction and analysis were therefore performed separately within each setting and findings represent parallel analyses rather than a unified longitudinal cohort. Data extracted from electronic medical records included patient age, the most recent HbA1c measurement within the study period, relevant diagnostic information, and glucose-related safety signals as defined for each care setting. Only anonymized datasets were provided to study investigators.

Study population

Adults with a diagnosis of T2DM (ICD-10 code E11) were included if they were prescribed ≥ 1 medication(s) with higher hypoglycaemic risk (sulfonylureas, insulin, or meglitinides) [13] and had ≥ 1 HbA1c measurement recorded within the study period. Eligibility criteria were applied independently within each care setting. A summary of inclusion criteria, data sources, and outcome definitions across both cohorts is presented in Supplementary Figure S1.

Operational definitions

High-risk older adults were pre-specified as individuals aged ≥ 75 years with Stage 4–5 CKD and/or cognitive vulnerability. Cognitive vulnerability was defined as cognitive impairment and/or dementia in the hospital cohort, identified using ICD-10 codes, and dementia only in the primary care cohort due to constraints in the primary care registry. CKD stage was determined using diagnosis codes corresponding to estimated glomerular filtration rate-based staging. This definition of high-risk older adults was adapted from prior work by Tseng et al., which evaluated potential glycaemic overtreatment risk in vulnerable populations [10].

Glucose-related safety signals were defined according to data availability and clinical context within each care setting. In the primary care cohort, the primary outcome was hypoglycaemia, defined as any recorded blood glucose value < 3.9mmol/L [70mg/dL], consistent with guideline-based biochemical thresholds [14]. A sensitivity analysis using borderline low/low glucose event (BLGE), defined as any recorded blood glucose ≤ 4.5 mmol/L [81mg/dL], was performed to capture early risk signals given the opportunistic nature of glucose measurements in routine outpatient care. In the hospital cohort, hypoglycaemia was defined as a hospital encounter with hypoglycaemia recorded as the primary diagnosis using ICD-10 codes, representing clinically recognized hypoglycaemia requiring acute medical care. Different glucose-related safety signals were therefore used across settings to reflect clinically meaningful outcomes within the respective care contexts.

Outcomes

The primary outcome was to characterize the proportion of older adults and high-risk older adults treated with medications with higher hypoglycaemia risk who had HbA1c < 7%, < 6.5%, < 6%. Secondary outcomes included associations between age, HbA1c categories and glucose-related safety signals within each setting.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and HbA1c distributions. To illustrate the prevalence of HbA1c distributions in different age or risk groups, we utilized nested HbA1c thresholds (i.e. <7.0%, < 6.5%, < 6.0%).

Inferential analyses included independent t-tests for continuous variables, Chi-square tests for categorical variables, and multivariate logistic regression analyses that included age (continuous) and HbA1c category to evaluate their independent association with glucose-related safety signals (i.e. hypoglycaemia and BLGE in primary care cohort, and hypoglycaemia admissions in hospital cohort). HbA1c was analysed as a categorical variable to reflect clinically meaningful glycaemic targets and to allow for non-linear associations with glucose-related safety signals. In multivariate analysis, HbA1c 7.0–<8.0% was used as the reference group, as this range reflects guideline-concordant moderate

glycaemic control for most older adults [3, 8]. Because exposure and outcome measures were ascertained within the same time frame, temporal directionality could not be established, and findings represent associations rather than risks. Analyses were performed using SPSS version 21. A two-sided p-value < 0.05 was considered statistically significant. All analyses were conducted separately within each cohort and no direct statistical comparisons between settings were performed.

Ethics

This study used anonymized routinely collected data and was conducted in accordance with relevant institutional guidelines. Ethical approval and waiver of informed consent was deemed not required according to NHG Domain Specific Review Board.

Results

Because this study comprised parallel cross-sectional analyses conducted separately in primary care and tertiary hospital settings, figures and tables are presented as composite panels to facilitate visual comparison of trends across care settings. These support descriptive comparison of trends but were not intended for direct statistical comparisons between cohorts.

Primary Care Cohort

In the primary care cohort, 38,957 adults receiving medications with higher hypoglycaemia risk who had ≥ 1 HbA1c reading during the study window were included. The mean [SD] age was 65.9 [11.1] years, and median HbA1c was 7.5% (IQR 6.9–8.4). High-risk older adults (≥ 75 years with stage 4–5 CKD and/or dementia) comprised 3.7% of the cohort.

The prevalence of intensive glycaemic control increased with advancing age. HbA1c < 7% was observed in 23.3%, 28.6%, 30.1% and 31.9% among adults aged < 65 years, 65-<75 years, 75-<85 years and ≥ 85 years, respectively (Fig. 1A). Similar age-associated increases were observed for HbA1c thresholds of < 6.5% and < 6%.

Among patients with ≥ 1 blood glucose measurement during the study period (19,711 [50.6%]), 278 (0.7%) experienced biochemical hypoglycaemia (< 3.9mmol/L or 70 mg/dL) and 826 (2.1%) patients had BLGE (≤ 4.5 mmol/L or 81 mg/dL). Patients with hypoglycaemia were older than those without (mean [SD] age 71.3 [6.5] vs 65.8 [11.1] years, p < 0.001). On univariate analysis, lower HbA1c categories were associated with progressively higher hypoglycaemia rates (p < 0.001), from 1.6% to 0.4% at HbA1c < 6% to ≥ 8.5%, respectively (Fig. 2A).

In multivariable logistic regression model including age and HbA1c categories, older age was independently associated with higher odds of hypoglycaemia (adjusted OR 1.05 per year, 95% CI 1.03–1.06). Compared with HbA1c 7–<8%, HbA1c < 6% was associated with higher odds of hypoglycaemia (adjusted OR 1.90, 95% CI 1.15–3.15), and HbA1c ≥ 8% categories were associated with lower odds (Table 1). Similar trends were observed for BGLE (Fig. 2B, Table 1).

Table 1
Association of age and HbA1c category with glucose-related safety outcomes across primary care and hospital settings

Variable	Primary care cohort (N_p = 38, 957)				Hospital cohort (N_H = 6,855)	
	Hypoglycaemia (< 3.9mmol/L or 70mg/dL)		**Borderline low/low glucose event (≤ 4.5mmoll/L or 81mg/dL)**		**Hypoglycaemia identified based on ICD-10 code as primary diagnosis**	
	Adjusted OR	**95% CI**	**Adjusted OR**	**95% CI**	**Adjusted OR**	**95% CI**
Age	1.05	1.03–1.06	1.04	1.04–1.05	1.04	1.03–1.05
HbA1c category						
< 6.0%	1.90	1.15–3.15	2.36	1.77–3.15	2.36	1.65–3.38
6.0–<6.5%	1.31	0.88–1.95	1.79	1.44–2.22	1.14	0.78–1.65
6.5–<7.0%	1.11	0.80–1.53	1.19	0.98–1.44	0.73	0.51–1.05
7.0–<8.0% (reference)	1.00	-	1.00	-	1.00	-
8.0–<8.5%	0.59	0.37–0.96	0.70	0.54–0.92	1.08	0.77–1.53
≥ 8.5%	0.63	0.44–0.91	0.65	0.53–0.81	0.76	0.57-1.00

Odds ratio (OR) were estimated using multivariable logistic regression models including age (continuous) and HbA1c category. In the primary care cohort, hypoglycaemia was defined as blood glucose measurement < 3.9 mmol/L [70mg/dL] and borderline low/low glucose event was defined as blood glucose measurement ≤ 4.5mmol/L [81mg/dL]. In the hospital cohort, hypoglycaemia was defined using ICD-10 codes recorded as primary diagnosis.

Age stratified plots showed highest hypoglycaemia rates at HbA1c < 6% across most age strata (Fig. 2A). Adults aged 65-<75 years and 75-<85 years and high-risk older adults exhibited higher hypoglycaemia and BLGE rates across most HbA1c categories compared with both younger adults (< 65 years) and the oldest-old (≥ 85 years) (Fig. 2A-B, **Supplementary Tables S2-3**).

Hospital Cohort

In the hospital cohort, 6,855 adults receiving medications with higher hypoglycaemia risk who had ≥ 1 HbA1c reading during the study window were included. The mean [SD] age was 67.2 [13.9] years, and median HbA1c was 7.8% (IQR 6.9-9.0). High-risk older adults (≥ 75 years with stage 4–5 CKD and/or cognitive impairment/dementia) comprised 14.1% of the cohort.

Similar to the primary care cohort, the prevalence of intensive glycaemic control increased with age. HbA1c < 7% was observed in 20.1%, 27.6%, 30.1% and 36.3% among adults aged < 65 years, 65-<75 years, 75-<85 years and ≥ 85 years, respectively (Fig. 1B).

Overall, 398 (5.8%) patients experienced at least one hospital encounter with hypoglycaemia recorded as the primary diagnosis recorded during the study window. Patients with hypoglycaemia were older than those without hypoglycaemia (mean [SD] age 74.1 [10.8] vs 66.8 [14.0] years, p < 0.001). On univariate analysis, HbA1c category was significantly associated with hypoglycaemia (p < 0.001), with the highest hypoglycaemia prevalence among those with HbA1c < 6% (13.9%). In contrast to that observed in the primary care cohort, hypoglycaemia rate across HbA1c categories was non-monotonic (Fig. 2C).

In multivariable logistic regression adjusting for age and HbA1c category, older age was independently associated with higher odds of hypoglycaemia (adjusted OR 1.04 per year, 95% CI 1.03–1.05). Compared with HbA1c 7–<8%, HbA1c < 6% was associated with higher odds of hypoglycaemia (adjusted OR 2.36, 95% CI 1.65–3.38) (Table 1). Among adults aged ≥ 65 years and high-risk older adults, hypoglycaemia rates remained elevated across most HbA1c categories, with less distinction between intensive and less intensive glycaemic control (Fig. 2C, **Supplementary Table S4**).

Comparison across care settings

Across both care settings, intensive glycaemic control was more prevalent with advancing age. Patterns of glucose-related safety signals differed by setting: in primary care, hypoglycaemia risk increased progressively with lower HbA1c, whereas in the hospital cohort, hypoglycaemia risk among older adults remained elevated across a broader range of HbA1c categories.

Discussion

In this parallel, cross-sectional study of older adults with type 2 diabetes receiving medications with higher hypoglycaemia risk across primary care and tertiary hospital settings in Singapore, intensive glycaemic control was common and increased with advancing age. Lower HbA1c levels and older age were both associated with a higher burden of glucose-related safety signals. Collectively, these findings suggest that hypoglycaemia vulnerability among older adults extends beyond glycaemic intensity alone.

Within primary care, lower HbA1c categories were consistently associated with higher odds of biochemical hypoglycaemia and BLGE. After adjusting for age, HbA1c < 6.0% was associated with higher odds of glucose-related safety signals compared with moderate glycaemic control. These findings are consistent with evidence from randomized trials demonstrating increased hypoglycaemia risk with intensive glycaemic control when medications with higher hypoglycaemia risk are used [4–6], and extends these observations to a large, real-world population of older adults managed in primary care.

In the hospital cohort, intensive glycaemic control was also associated with higher odds of hypoglycaemia, particularly among those with HbA1c < 6.0%. The persistence of hypoglycaemia risk

across a broad range of HbA1c categories in the hospital cohort suggests that hypoglycaemia susceptibility among older adults managed in tertiary care may not be fully explained by glycaemic intensity alone. While clinical complexity and dynamic health status may contribute to hypoglycaemia risk in this setting [15, 16], these factors were not directly measured in the present analysis. Nonetheless, these patterns are directionally consistent with findings from the Diabetes and Aging Study by Lipska et al, which reported higher rates of severe hypoglycaemia at both lower (< 6%) and higher (≥ 9%) HbA1c levels [17].

Notably, age-stratified analyses revealed differing patterns of glucose-related safety signals across care settings. In the primary care cohort, youngest-old (65–<75 years) and middle-old (75–<85 years) adults experienced higher rates of hypoglycaemia and BLGE across multiple HbA1c categories compared with both younger adults (< 65 years) and the oldest-old (≥ 85 years). In contrast, within the hospital cohort, the highest hypoglycaemia rates were observed predominantly among the oldest-old and high-risk older adults, with elevated risk persisting across most HbA1c levels. This observation highlights heterogeneity in hypoglycaemia susceptibility among older adults and suggests that risk may not increase uniformly with advancing chronological age.

Several factors may contribute to these observations. Youngest-old and middle-old adults represent a clinically diverse population transitioning into older adulthood, with variable comorbidity burden and tolerance to glucose-lowering therapy. In contrast, lower observed hypoglycaemia rates among the oldest-old in primary care may reflect selection bias towards healthier individuals maintaining primary care follow-up, more conservative treatment approaches, or reduced detection of biochemical hypoglycaemia in routine outpatient care. Conversely, in the hospital setting, the concentration of hypoglycaemia events among the oldest-old and high-risk older adults likely reflects a population with greater clinical complexity requiring acute care, although such factors were not directly measured in this study.

Contemporary guidance for diabetes management in older adults emphasizes individualized glycaemic targets, regular assessment of geriatric syndromes, and hypoglycaemia prevention, recognizing heterogeneity in comorbidity, functional status and time to benefit [3, 18, 19]. The therapeutic landscape of T2DM has evolved substantially since landmark trials which primarily employed insulin and sulfonylureas to achieve tight glycaemic targets [4–6]. Newer agents such as SGLT-2 inhibitors and GLP-1 receptor agonists offer glucose-lowering with cardiovascular and renal benefits whilst minimizing hypoglycaemia risk [13, 18], though these could be unavailable during the time when hypoglycaemic agents were initiated in our study cohort. With the switch to these newer agents, treatment intensification may not carry similar historical harm profiles when high-risk agents are avoided and individualized targets are maintained. Thoughtful switching to regimens with lower hypoglycaemia propensity should be considered for suitable patients during routine review.

However, the use of medications with higher hypoglycaemia remains clinically relevant in selected patients. Lean, frail older adults are common in the Asian population [20, 21] and are often characterized

by greater insulinopenia [22], and hence may benefit from carefully titrated insulin. Genitourinary adverse effects of SGLT-2 inhibitors may be of a concern in some older adults [23], and weight loss effects of both GLP-1 receptor agonists and SGLT-2 inhibitors may be undesirable in those with low body mass index (BMI), poor nutritional reserve, or sarcopenic [3].

This study has several strengths. First, it leveraged large, real-world datasets from complementary primary care and tertiary hospital settings within a single healthcare cluster, enabling characterization of intensive glycaemic control and glucose-related safety signals across distinct care contexts. Second, clinically meaningful HbA1c categories aligned with guideline thresholds were used, facilitating interpretation of glycaemic intensity in relation to hypoglycaemia risk. Third, the study focused on older adults treated with medications with higher hypoglycaemia risk, a population in whom the balance between glycaemic benefit and harm is particularly relevant. The use of parallel analyses across care settings also allowed for descriptive comparison of patterns, highlighting potential context-specific differences in hypoglycaemia vulnerability.

Several limitations should be considered. The cross-sectional design precludes assessment of temporal relationships between HbA1c levels, medication exposure, and glucose-related safety signals, and findings represent associations rather than causal effects. Data linkage across care settings was not available due to governance and infrastructure constraints, limiting longitudinal follow-up across the full care continuum. Definitions of glucose-related safety signals differed by setting, reflecting data availability and clinical context; biochemical hypoglycaemia in primary care and hypoglycaemia-related hospital encounters capture different but clinically meaningful safety signals, and rates should not be directly compared quantitatively across settings.

Medication-level details, including specific agents, doses, and changes over time, were not available, and other determinants of hypoglycaemia risk such as frailty, comorbidity burden, anaemia, or glycaemic variability could not be fully accounted for. HbA1c may be a limited marker of hypoglycaemia susceptibility in older adults, particularly those with advanced chronic kidney disease or altered red blood cell turnover [24, 25], and hypoglycaemia events may have been under-ascertained if they occurred outside routine visits or hospital encounters. Finally, the operational definition of high-risk older adults was necessarily pragmatic and may not capture the full spectrum of clinical complexity relevant to individualized treatment decisions.

Findings from our study underscore the importance of routine and systematic reassessment of glycaemic targets in older adults treated with medications with higher hypoglycaemia risk. HbA1c thresholds alone may not fully capture vulnerability to hypoglycaemia, particularly in more clinically complex populations. In practice, this supports proactive screening for hypoglycaemia vulnerability, regular medication review, and consideration of treatment de-intensification or regimen simplification where the potential harms of tight glycaemic control may outweigh benefits.

Our study could inform development and implementation of risk stratification tools locally. Future studies are needed to examine longitudinal relationships between medication intensification and

hypoglycaemia outcomes, including the role of newer glucose-lowering agents in diverse populations with different phenotypic characteristics. Such initiatives could bridge the gap between research findings and clinical practice, ultimately improving patient safety whilst maintaining effective glycaemic control in those who would benefit most.

Conclusion

This study demonstrates that intensive glycaemic control remains prevalent among older adults receiving medications with higher hypoglycaemia risk across hospital and primary care settings in Singapore, with rates paradoxically increasing with advancing age despite heightened vulnerability to hypoglycaemia. The complex, non-linear relationship between age, HbA1c, and hypoglycaemia risk observed across care settings challenges the utility of HbA1c thresholds as sole indicators of appropriate glycaemic management in older populations, highlighting the need for individualized risk and treatment assessment to mitigate preventable harm while supporting safer, patient-centred diabetes care in ageing population.

Declarations

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Author Contributions

Christina Tan and Hui Shan Chia contributed to the concept and design of the study; submitted requests for data extraction; performed data analysis and interpretation; and drafted the manuscript. Christina Tan also conducted the statistical analysis. Tat Ming Ng contributed to the concept and design, interpretation of data, critical revision of the manuscript, and provided supervision and advisory input. Timothy Quek, Daniel Chew, and Darren Seah contributed to interpretation of data, critical revision of the manuscript for important intellectual content, and provided supervision and advisory input. All authors approved the final manuscript.

Competing Interest

Conflict of Interest Disclosures:

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Use of Artificial Intelligence

An artificial intelligence–based language model (M365 Copilot, Microsoft) was used to assist with language editing and manuscript revision. The authors take full responsibility for the accuracy, integrity, and originality of the content.

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Figures

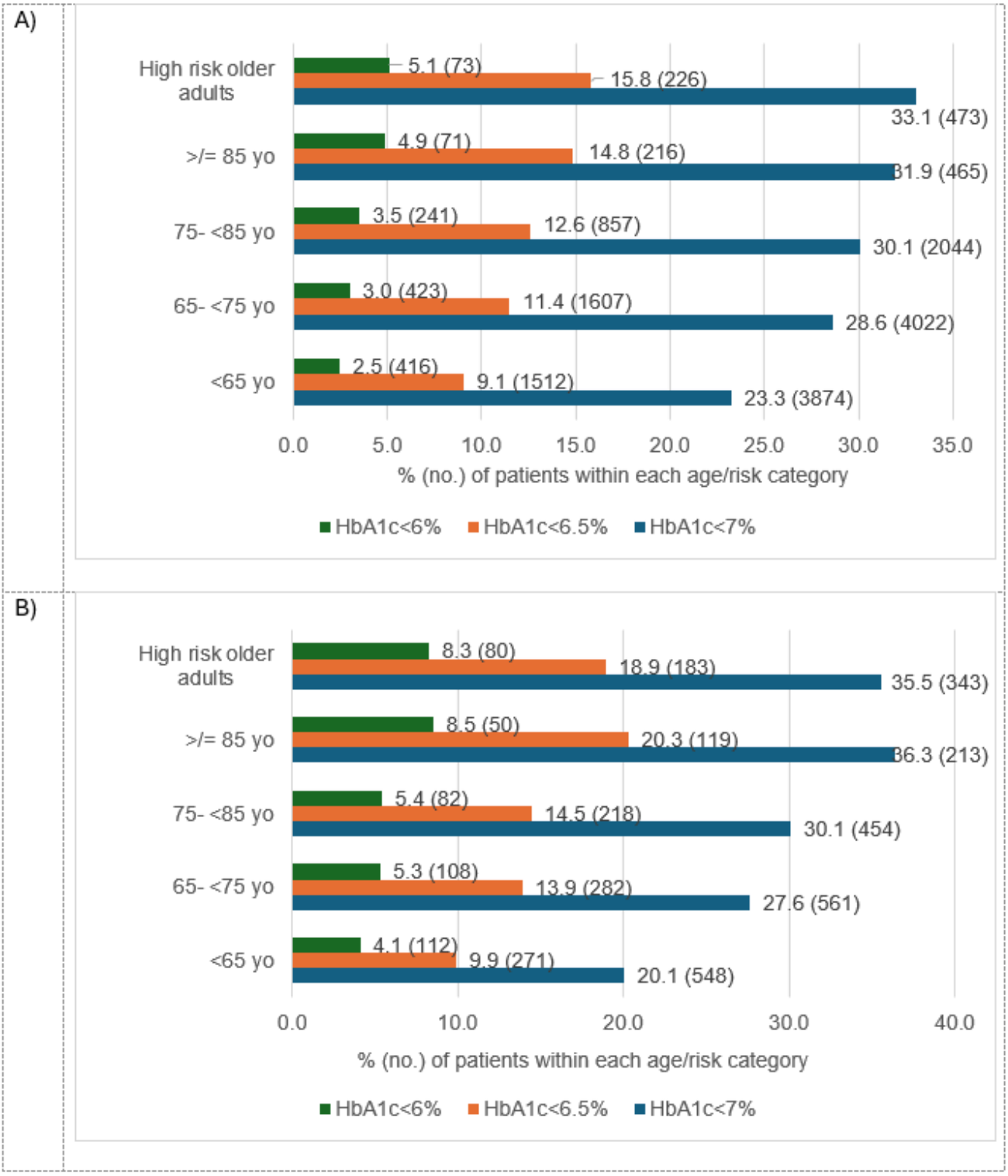


Figure 1

Distribution of HbA1c thresholds by age group in (A) Primary care and (B) Hospital cohort.

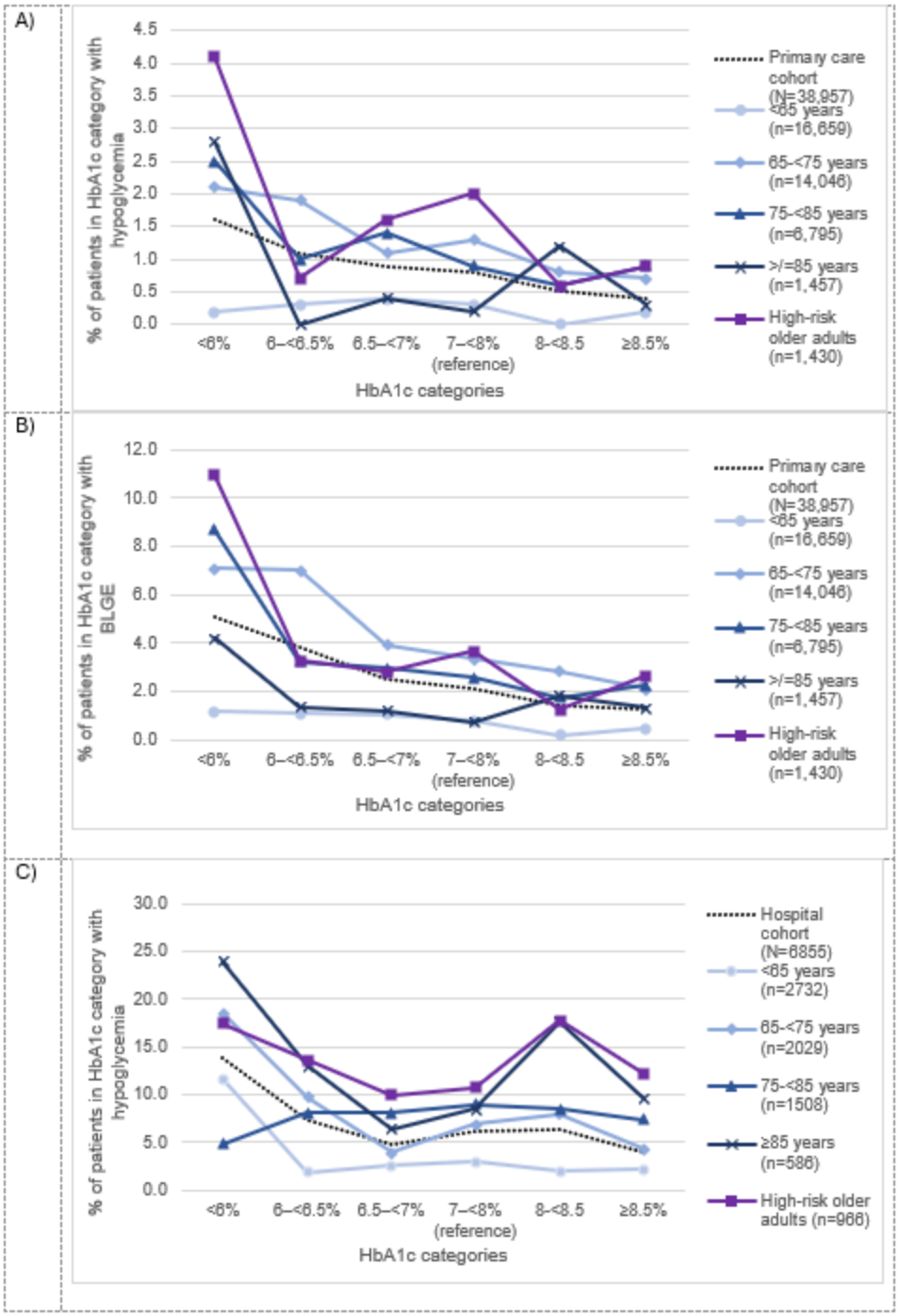


Figure 2

Glucose-related safety signal rates across HbA1c categories stratified by age and risk groups.

(A) Hypoglycaemia (<3.9mmol/L) rates in primary care cohort (N_p = 38, 957)

(B) Borderline low/low glucose event (BLGE, ≤4.5mmol/L) in primary care cohort (N_p = 38, 957)

(C) Hypoglycaemia rates identified from hospital encounters with a primary ICD-10 diagnosis of hypoglycaemia in the hospital cohort (N_H = 6,855)

Panels represent parallel analyses across care settings and outcome definitions and are not intended for direct comparison.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfiguretables.docx