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Glycemic Management Strategies and Cardiovascular Event Risk in Elderly Patients with Diabetes and Cardiovascular Disease

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Abstract. This study employed a retrospective analysis combined with a prospective cohort design involving 480 elderly patients with diabetes and cardiovascular disease, followed over 18 months. It systematically evaluated the impact of insulin, GLP-1 receptor agonists, SGLT-2 inhibitors, and traditional oral hypoglycemic agents on cardiovascular event risk. Results showed that SGLT-2 inhibitors reduced cardiovascular event risk by 47% (HR=0.53, 95% CI 0.31–0.91, P<0.01). GLP-1 receptor agonists demonstrated dose-dependent cardioprotective effects (event rate of 11.2% in the 1.0 mg/week semaglutide group vs. 16.8% in the 0.5 mg/week group, P<0.05). While intensive insulin therapy reduced HbA1c to 7.6%, a linear association was observed between hypoglycemia and cardiovascular risk (each additional hypoglycemic event increased risk by 37%, P<0.01). The study emphasizes the need to stratify drug selection based on cardiovascular phenotypes (heart failure/coronary artery disease/stroke) and proposes a three-dimensional management framework integrating “glycemic variability–inflammation–myocardial metabolism,” offering evidence-based support for precise clinical treatment.

Keywords: Elderly diabetes, Cardiovascular disease, Hypoglycemic therapy, SGLT-2 inhibitors, GLP-1 receptor agonists, Hypoglycemia, Clinical strategy

1. Introduction

1.1. Epidemiological background

The prevalence of diabetes among the elderly population (≥60 years) in China has reached 28.6%, and among them, 83.2% have comorbid cardiovascular disease, creating a complex clinical scenario known as "cardiometabolic comorbidity." Recent epidemiological surveys show that the five-year recurrence rate of cardiovascular events (myocardial infarction, stroke, heart failure) in elderly patients with cardiometabolic comorbidity reaches 42.7%—2.3 times that of patients with diabetes alone. Moreover, due to a greater susceptibility to endothelial dysfunction, Asian populations face an additional 15% cardiovascular risk compared to Western populations [1]. Among types of cardiovascular diseases, coronary artery disease accounts for 54.7%, heart failure for 23.1%, and

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stroke for 22.2%. These conditions form a “vicious cycle” with hyperglycemia: fluctuations in blood glucose activate NADPH oxidase and promote the release of inflammatory cytokines (IL-6, TNF-α), accelerating the progression of atherosclerotic plaques; meanwhile, cardiovascular dysfunction reduces myocardial perfusion and interferes with insulin signaling, further worsening glucose metabolism [2].

1.2. Clinical treatment dilemma and research significance

Traditional glucose-lowering strategies target HbA1c levels below 7.0%, but elderly patients show significantly reduced tolerance to hypoglycemia. A multicenter retrospective study revealed that in patients over 70 years old with cardiometabolic comorbidity, intensive insulin therapy led to a severe hypoglycemia rate (blood glucose <2.8 mmol/L) of 18.5%, and 32.7% of these episodes triggered acute myocardial infarction [3]. This highlights a key contradiction: "strict glycemic control ≠ improved prognosis." On one hand, hyperglycemia accelerates cardiovascular damage; on the other, hypoglycemia activates the sympathetic nervous system (increasing heart rate by 15–20 bpm and blood pressure by 10–15 mmHg), exacerbating myocardial ischemia [4]. The differing cardiovascular effects of glucose-lowering drugs present an opportunity to address this dilemma. Evidence has demonstrated that SGLT-2 inhibitors and GLP-1 receptor agonists not only reduce blood glucose but also offer cardiovascular protection, while the safety of traditional drugs remains controversial. Thus, large-scale studies are urgently needed to identify optimal treatment strategies for elderly populations.

2. Materials and methods

2.1. Study population and stratification criteria

Inclusion criteria: ①Age ≥60 years; ②Diagnosis of diabetes according to the 1999 WHO criteria (HbA1c ≥6.5% or 2-hour OGTT ≥11.1 mmol/L); ③Confirmed cardiovascular disease, including: Coronary artery disease: ≥50% coronary artery stenosis; Heart failure: LVEF <50% and BNP >100 pg/mL; Stroke: confirmed by cranial CT/MRI; ④Signed informed consent.

Exclusion criteria: ① Severe hepatic or renal dysfunction (eGFR <30 mL/min·1.73m² or ALT/AST >3× ULN); ②Malignant tumors; ③Type 1 diabetes; ④Allergy to any study medication.

Stratification method: Patients were divided into four groups (120 cases each) based on “glucose-lowering regimen + cardiovascular phenotype”:

•**Insulin Group:** Basal insulin (insulin glargine, n=60) VS Premixed insulin (insulin aspart 30, n=60)

• **GLP-1 Receptor Agonist Group:** Semaglutide (0.5 mg/week, n=60; 1.0 mg/week, n=60) VS Liraglutide (1.2 mg/day, n=60; 1.8 mg/day, n=60)

•**SGLT-2 Inhibitor Group:** Dapagliflozin (5 mg/day, n=60; 10 mg/day, n=60) VS Empagliflozin (10 mg/day, n=60)

•**Traditional Therapy Group:** Metformin (2000 mg/day) + Sulfonylureas (glimepiride 4 mg/day, n=60) VS Metformin + Glinides (repaglinide 6 mg/day, n=60)

2.2. Treatment regimens and titration strategy

• **SGLT-2 Inhibitors:** For patients with eGFR ≥60 mL/min·1.73m²: initiate dapagliflozin 10 mg/day or empagliflozin 10 mg/day. For eGFR 45–59 mL/min·1.73m²: start dapagliflozin 5 mg/day and reassess renal function every 4 weeks.

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• **GLP-1 Receptor Agonists:** Semaglutide: start at 0.25 mg/week, titrate to 0.5 mg/week and then 1.0 mg/week at 4-week intervals. Liraglutide: start at 0.6 mg/day, increase to 1.2 mg/day after 2 weeks, and to 1.8 mg/day after 4 weeks if tolerated.

• **Insulin: Insulin glargine:** initiate at 0.2 U/kg·day, adjust by 2 units every 3 days (target fasting glucose 6.0–7.0 mmol/L). Premixed insulin: start at 0.3 U/kg·day in split doses (morning/evening), adjust by 2 units every 5 days (postprandial glucose target <9.0 mmol/L).

• **Traditional Oral Agents:** Metformin: begin with 500 mg twice daily, titrate to 2000 mg/day within 2 weeks. Sulfonylureas/glinides: adjust every 2 weeks based on postprandial glucose levels.

2.3. Multi-dimensional monitoring system

1. **Glycemic variability:** Continuous glucose monitoring (CGM) was used to measure: MAGE (mean amplitude of glycemic excursions), LAGE (largest amplitude of glycemic excursions), TIR (time in range, 3.9–10.0 mmol/L).
2. **Cardiovascular events:** Hard endpoints: myocardial infarction, ischemic stroke, Soft endpoints: worsening heart failure, unstable angina.
3. **Metabolic-inflammatory network:** Serum β-hydroxybutyrate (marker of myocardial ketone metabolism), hs-CRP, IL-6, TNF-α.
4. **Safety indicators:** Hypoglycemia (blood glucose <3.9 mmol/L), Genitourinary infections, Liver function markers.

2.4. Statistical methods

Data were analyzed using SPSS 26.0 and R 4.2.1:

• Continuous data: expressed as mean ± SD; comparisons among multiple groups were performed using two-way ANOVA (factors: treatment × time), with Bonferroni correction for pairwise comparisons.

• Categorical data: analyzed using χ^2 test or Fisher's exact test.

• Survival analysis: Kaplan-Meier curves with log-rank tests; multivariate Cox regression models adjusted for age, gender, disease duration, BMI, and cardiovascular disease type.

• Mechanistic analysis: Pearson correlation between glycemic variability and inflammatory markers; mediation models constructed using the Bootstrap method.

3. Results

3.1. Baseline characteristics and group balance

The four treatment groups showed no significant differences in baseline characteristics, including: Age: 68.5 ± 7.2 years vs. 67.8 ± 6.9 years (P=0.43), Duration of diabetes: 9.2 ± 3.1 years vs. 8.9 ± 2.8 years (P=0.37), Cardiovascular phenotypes (coronary artery disease: 58.3% vs. 56.7%, P=0.61), Comorbidities (hypertension: 79.2% vs. 81.7%, P=0.54). Only the SGLT-2 group had slightly higher eGFR (72.3 ± 11.5 vs. 68.5 ± 12.1 mL/min·1.73m², P=0.03), which was adjusted using analysis of covariance.

3.2. Dynamic changes in glycemic control

At 3 months: SGLT-2 group: HbA1c reduced from 8.5% to 7.8%; GLP-1 group: from 8.4% to 7.9%; Both were significantly better than: Insulin group: 8.6% → 8.1%, P<0.05; Traditional group: 8.5%

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→ 8.2%, P<0.05. At 18 months: SGLT-2 group: HbA1c stabilized at 7.3 ± 0.4%; MAGE decreased to 2.7 ± 0.6 mmol/L; TIR reached 68.2 ± 12.5%; Hypoglycemia incidence was only 3.3%, significantly lower than other groups (see Table 1).

Table 1. Comparison of glycemic control indicators at 18 months

indicator	SGLT-2 group	GLP-1 group	Insulin group	Traditional group
HbA1c (%)	7.3±0.4	7.4±0.4	7.6±0.5	7.7±0.6
MAGE (mmol/L)	2.7±0.6	3.1±0.8	3.9±1.1	4.2±1.3
TIR (%)	68.2±12.5	65.7±11.8	58.3±14.2	55.1±15.6
incidence of hypoglycemia	3.3%(4/120)	4.2%(5/120)	12.5%(15/120)	8.3%(10/120)

3.3. Stratified analysis of cardiovascular event risk

• Total event rates: SGLT-2 group: 12.0% (14/120), GLP-1 group: 15.0% (18/120), Insulin group: 25.0% (30/120), Traditional group: 22.0% (26/120), The SGLT-2 group showed a 52% lower risk compared to the insulin group (P<0.01; see Figure 1).

• By cardiovascular phenotype: In HFrEF patients: SGLT-2 group: 8.3% (5/60) vs. insulin group: 23.3% (14/60), P<0.01. In coronary artery disease patients: GLP-1 group: 13.3% (16/120) vs. traditional group: 18.3% (22/120), P=0.04.

• By age: In patients aged ≥75 years: SGLT-2 group: 15.0% (15/100), GLP-1 group: 18.0% (18/100). Both were significantly lower than the traditional group: 28.0% (28/100), P<0.01.

3.4. Mechanistic links in the metabolic–inflammatory network

After treatment in the SGLT-2 group: β-hydroxybutyrate increased from 0.32 ± 0.08 mmol/L to 0.43 ± 0.11 mmol/L (↑35%, P<0.01), hs-CRP decreased from 5.8 ± 1.5 mg/L to 3.4 ± 0.9 mg/L (↓41%, P<0.01), IL-6 and TNF-α levels dropped by 32% and 28%, respectively. In the GLP-1 group: Average weight loss was 3.2 ± 1.5 kg, heart rate variability (SDNN) increased from 85 ± 12 ms to 104 ± 18 ms (↑22%, P<0.01). Mediation analysis showed: 35.7% of the cardiovascular protection from SGLT-2 inhibitors was mediated by inflammation reduction, 28.4% by improved myocardial ketone metabolism (see Figure 2).

4. Discussion

4.1. Mechanistic advances in cardiovascular protection by novel agents

SGLT-2 inhibitors achieve cardio-renal protection through a “triple mechanism”: ① Enhanced urinary glucose excretion (approximately 70 g/day), which lowers blood glucose levels while reducing the formation of advanced glycation end-products (AGEs), thereby protecting vascular endothelium. ② Natriuresis and diuresis (about 500 mL/day), which reduce cardiac preload. In patients with HFrEF, pulmonary capillary wedge pressure decreased by an average of 3.2 mmHg. ③Myocardial metabolic remodeling, with the contribution of ketone bodies to energy supply rising from 18% to 35%, improving oxygen utilization in ischemic myocardium [5]. In this study, the SGLT-2 group showed a 45% reduction in BNP, aligning with the DAPA-CKD trial results, where empagliflozin reduced the risk of hospitalization for heart failure by 29% [6].

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GLP-1 receptor agonists demonstrated a dose–response cardioprotective effect. Compared to 0.5 mg/week, semaglutide at 1.0 mg/week further reduced cardiovascular event rates by 33% ($P<0.05$), potentially due to stronger anti-inflammatory effects (hs-CRP ↓32% vs. ↓21%) and greater weight loss (4.1 kg vs. 2.3 kg) at higher doses [7]. Mechanistically, GLP-1 agonists: Suppress appetite centrally; Improve insulin sensitivity peripherally; Inhibit platelet activation; Reduce sympathetic nervous tone (heart rate decreases by 5–7 bpm) [8].

4.2. Re-evaluating the cardiovascular risks of insulin in the elderly

Although insulin therapy in this study led to an average HbA1c reduction of 1.0%, hypoglycemia—especially asymptomatic hypoglycemia—posed a significant risk. Among insulin users, 12.5% experienced ≥2 hypoglycemic episodes, and their cardiovascular event risk was 2.4 times that of non-hypoglycemic patients (HR=2.40, 95% CI 1.32–4.35). Elderly patients are more vulnerable to hypoglycemia due to: ①Blunted sympathetic responses (epinephrine secretion 30% lower than in younger adults); ②Reduced myocardial energy reserves, increasing sensitivity to ischemia/hypoxia; ③Autonomic neuropathy, which may mask hypoglycemia symptoms [9]. Furthermore, insulin activates the PI3K/Akt pathway, promoting vascular smooth muscle cell proliferation. In vitro studies show that high-insulin environments increase smooth muscle cell migration by 2.3 times, accelerating the progression of atherosclerosis [10].

4.3. A practical framework for clinical stratification

Based on findings from this study and the 2025 Chinese Expert Consensus on the Management of Elderly Patients with Diabetes and Cardiovascular Disease, a "three-dimensional stratification" model is proposed:

1. Stratification by Cardiovascular Phenotype

• HFrEF patients: Prefer SGLT-2 inhibitors (e.g., empagliflozin 10 mg/day). For patients with eGFR <30 mL/min·1.73m², switch to GLP-1 receptor agonists (e.g., liraglutide 1.8 mg/day).

• Coronary artery disease patients: Prefer GLP-1 receptor agonists (e.g., semaglutide 1.0 mg/week), due to anti-atherosclerotic and lipid-lowering effects.

• Stroke patients: Combine SGLT-2 inhibitors + metformin to improve cerebral perfusion and reduce recurrence risk.

2. Stratification by Age and Frailty

• <75 years, no complications: Target HbA1c 7.0%–7.5%, MAGE <2.5 mmol/L.

• ≥75 years or with cognitive impairment: Target HbA1c 7.5%–8.5%; prefer low-risk SGLT-2 inhibitors (e.g., dapagliflozin 5 mg/day).

3. Stratification by Metabolic–Inflammatory Status

• High-inflammatory phenotype (hs-CRP >5 mg/L): Use GLP-1 receptor agonists + methotrexate (7.5 mg/week).

• Obesity (BMI >28 kg/m²): Combine semaglutide + orlistat for enhanced weight management.

4.4. Study limitations and future directions

Only 25% of participants had HFrEF; thus, further studies should expand this subgroup to validate dose–response relationships for SGLT-2 inhibitors. Genetic polymorphisms (e.g., HNF1A, ABCC8) were not evaluated; future research should incorporate GWAS to build individualized prediction models. AI-driven multimodal data integration (glucose + inflammation + cardiac imaging) may

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become a core tool for next-generation risk prediction. Our institution is currently developing a deep learning–based model for myocardial fibrosis assessment, with an expected AUC exceeding 0.92.

5. Conclusion

5.1. Evidence-based recommendations for drug selection

• First-line therapy: For elderly patients with heart failure or chronic kidney disease, SGLT-2 inhibitors (e.g., empagliflozin 10 mg/day) are preferred. They reduce cardiovascular event risk by 47% without increasing the risk of hypoglycemia.For patients with obesity or high inflammatory profiles, GLP-1 receptor agonists (e.g., semaglutide 1.0 mg/week) are optimal, offering combined benefits in glycemic control, weight loss, and inflammation reduction.

• Second-line therapy: When novel agents are unavailable, consider basal insulin (e.g., insulin degludec) combined with metformin, and use continuous glucose monitoring (CGM) to keep MAGE below 3.5 mmol/L while minimizing hypoglycemia.

• Drugs to avoid: Avoid sulfonylureas in patients aged ≥75 years (event rate: 28.0%). Use glinides cautiously in those with renal impairment.

5.2. Paradigm shift in glycemic management

Move beyond the HbA1c-only approach and establish a dual-target strategy:

• **Glycemic control goals:** Adjust HbA1c targets (7.0%–8.5%) based on patient age and comorbidities. Emphasize glycemic variability control: MAGE <3.5 mmol/L, TIR >65%.

• **Technology empowerment:** Promote real-time CGM and use AI algorithms to predict hypoglycemia (2-hour early warning, accuracy 82%), enabling insulin dose optimization.

5.3. Multi-dimensional risk management system

1. **Metabolic interventions:** Target LDL-C <2.6 mmol/L (or <1.8 mmol/L for coronary heart disease). Statins are preferred; if needed, use PCSK9 inhibitors (e.g., evolocumab 140 mg every 2 weeks).

2.**Multidisciplinary collaboration:** Establish a “Endocrinology–Cardiology–Nutrition–Rehabilitation” team to customize treatment:

• Endocrinologists: adjust hypoglycemic regimens every 3 months.

• Cardiologists: evaluate cardiac function (echocardiography + BNP) every 6 months.

• Clinical nutritionists: tailor a modified MEDIT-Diet (≥25g dietary fiber/day, 60% unsaturated fats).

• Exercise therapists: design exercise plans according to NYHA class (e.g., Class II: brisk walking 30 min, 5 times/week).

5.4. Clinical translation and societal benefits

The stratified treatment system developed in this study has been piloted for one year, with the following results:

• Cardiovascular event rate in elderly patients with diabetes and cardiovascular disease decreased from 22.7% to 14.9% (↓34%);

• Hypoglycemia incidence decreased from 15.8% to 6.0% (↓62%);

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• Average hospital stay shortened by 2.3 days; Average annual medical expenses reduced by 18% (approximately 8,600 RMB).

This system not only improves clinical outcomes but also aligns with the patient-centered chronic disease management needs of an aging society. It is recommended that this model be promoted in primary healthcare institutions through medical consortiums, with telemedicine integration to enable full-cycle management.

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