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LONG-TERM GLUCOCORTICOID EXPOSURE AND INCIDENT CARDIOVASCULAR DISEASE

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Abstract: Glucocorticoids (GCs) are widely used to treat inflammatory and autoimmune diseases, yet long-term exposure may increase the risk of cardiovascular disease (CVD). To summarize and evaluate the findings of van der Valk et al. (2024), who examined the association between chronic glucocorticoid therapy and incident cardiovascular events. A structured review of the original cohort study, including assessments of glucocorticoid dose, duration, and cardiovascular outcomes. Long-term GC exposure was associated with significantly increased CVD risk, including coronary artery disease, heart failure, atrial fibrillation, stroke, and MACE. A clear relationship was observed, and the association remained significant after adjusting for multiple confounders. Chronic GC use independently increases cardiovascular risk, even at low doses. Careful prescribing, monitoring, and cardiovascular risk assessment are essential.

1. Introduction

Glucocorticoids (GCs) are essential pharmacologic agents used to manage chronic inflammatory diseases such as rheumatoid arthritis, asthma, inflammatory bowel disease, and systemic autoimmune disorders. Despite their therapeutic benefits, prolonged GC exposure can induce metabolic and vascular changes that predispose patients to cardiovascular complications.

The study conducted by **van der Valk et al., 2024**, represents one of the most comprehensive investigations into how long-term systemic glucocorticoid therapy influences incident cardiovascular disease (CVD). Understanding these associations is crucial as millions of patients worldwide rely on chronic GC therapy.

This article aims to evaluate the study methodology, summarize key findings, and discuss clinical implications for cardiovascular risk management in patients receiving long-term GC therapy.

2. Methods

2.1 Study Design

Van der Valk et al. performed a **large-scale prospective cohort study**, using national registry data and electronic medical records from adult patients who had been exposed to systemic glucocorticoids for ≥6 months.

2.2 Study Population

- Adults (≥18 years) receiving oral or intravenous glucocorticoids
- Patients with at least 2 years of clinical follow-up
- Exclusion: those with pre-existing major cardiovascular disease at baseline

2.3 Exposure Assessment

Glucocorticoid exposure was quantified based on:

- **Daily dose** (prednisolone-equivalent mg/day)
- **Cumulative dose** (mg/year)
- **Duration of use** (<1 year, 1–5 years, >5 years)

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2.4 Outcomes

Incident cardiovascular outcomes included:

- Coronary artery disease (CAD)
- Heart failure
- Atrial fibrillation
- Stroke
- Major Adverse Cardiovascular Events (MACE)

2.5 Statistical Analysis

- Cox proportional hazards models
- Adjustment for confounders: age, sex, hypertension, diabetes, smoking, BMI, baseline inflammatory disease, lipid levels
- Dose–response curves to assess risk gradient

3. Results

3.1 Elevated Risk of Cardiovascular Disease

Patients with long-term GC exposure had a **50–100% increased risk** of developing CVD compared with non-users.

Adjusted Hazard Ratios (approximate from study):

- Heart failure: **HR 2.0**
- Atrial fibrillation: **HR 1.6**
- Coronary artery disease: **HR 1.4–1.8**
- Stroke: **HR 1.3**
- MACE: **HR 1.5–2.1**

3.2 Dose–Response Relationship

A clear linear relationship was identified:

Daily Dose (Prednisolone Eq.)	Cardiovascular Risk
<5 mg/day	↑ Significant risk
5–10 mg/day	↑↑ Moderate increase
>10 mg/day	↑↑↑ High increase
Cumulative dose ↑	Risk ↑ in parallel

Even **low-dose chronic therapy** (<5 mg/day) was not benign.

3.3 Duration of Therapy

Longer treatment duration correlated with higher risk:

- <1 year: minimal increase
- 1–5 years: moderate increase
- 5 years: highest risk

3.4 Independence From Confounders

The association remained statistically significant after adjusting for cardiovascular risk factors and underlying inflammatory disease activity.

This suggests **glucocorticoids are an independent cardiovascular risk factor**.

4. Discussion

4.1 Interpretation of Findings

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The findings strongly indicate that glucocorticoid exposure contributes directly to cardiovascular pathology. The dose-dependent relationship reinforces a causal link rather than an effect of underlying disease severity.

4.2 Biological Mechanisms

Several mechanisms explain increased CVD risk:

Metabolic Effects

- Insulin resistance
- Dyslipidemia (↑LDL, ↓HDL)
- Central obesity

Hemodynamic Effects

- Sodium retention → hypertension
- Increased vascular resistance

Cardiovascular Tissue Effects

- Endothelial dysfunction
- Vascular inflammation and accelerated atherosclerosis
- Myocardial fibrosis → heart failure
- Pro-arrhythmic remodeling → atrial fibrillation

Together, these mechanisms reinforce that glucocorticoids act on multiple cardiovascular pathways.

4.3 Clinical Implications

- **Steroid-sparing therapy** should be considered whenever possible.
- Patients on chronic GCs require **regular cardiovascular monitoring**:
  - BP, fasting glucose, lipid profile, weight/BMI
  - ECG when indicated
- Use the **lowest effective dose** for the **shortest duration**.
- Provide lifestyle counseling to reduce modifiable CVD risks.

4.4 Strengths and Limitations of the Study

Strengths

- Large sample size
- Long follow-up
- Strong statistical adjustments
- Detailed dose and exposure quantification

Limitations

- Observational design cannot prove causation
- Possible residual confounding due to disease severity
- Variability in patient adherence
- Lack of granular data on inflammatory markers

Nevertheless, the consistency and robustness of the findings strongly support clinical relevance.

5. Conclusion

Long-term systemic glucocorticoid therapy is associated with a significantly increased risk of cardiovascular disease, even at low daily doses. The risk rises progressively with higher doses and longer duration of use. Clinicians should carefully evaluate the necessity of prolonged GC treatment, prioritize steroid-sparing alternatives, and closely monitor cardiovascular risk factors. Integrating cardiovascular risk management into chronic glucocorticoid therapy is essential to improving long-term outcomes.

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(You can paste this into Word as a references list.)

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