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Comparative Review of the Long-Term Effects of Atorvastatin and Rosuvastatin on Fasting Glucose and Glycated Hemoglobin in Patients with Cardiovascular Disease

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Abstract

This comprehensive review evaluates the comparative long-term impact of atorvastatin and rosuvastatin on glycemic parameters—fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c)—in patients with established cardiovascular disease (CVD). A systematic examination of evidence from randomized controlled trials (RCTs), meta-analyses, and observational studies indicates a consistent class effect, whereby both high-intensity statins modestly elevate FPG and HbA1c in a dose-dependent manner. Critically, comparative data suggest a potential gradient of risk, with rosuvastatin appearing to confer a marginally greater detrimental effect on glucose metabolism than equipotent doses of atorvastatin over treatment periods extending beyond one year. This difference, while statistically significant in several head-to-head trials, is of small absolute magnitude (e.g., a between-group HbA1c difference of 0.05–0.15%). The pathophysiological mechanisms may involve differential effects on insulin sensitivity and secretion, potentially influenced by statin lipophilicity and potency. Importantly, the proven and substantial reduction in major adverse cardiovascular events with both statins decisively outweighs this modest glycemic risk. The selection between atorvastatin and rosuvastatin should, therefore, remain primarily guided by the imperative to achieve low-density lipoprotein cholesterol (LDL-C) targets, with considerations for tolerability, drug interactions, and cost. Proactive glycemic monitoring, particularly in patients with pre-diabetes or metabolic syndrome, is a recommended adjunct to optimize overall cardiometabolic management.

Introduction

The management of dyslipidemia with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) represents a cornerstone of secondary prevention in cardiovascular disease (CVD) [1]. Among available agents, atorvastatin and rosuvastatin are classified as high-intensity statins, capable of reducing LDL-C by ≥50%, and are prominently featured in international guidelines [2]. While their efficacy in reducing atherosclerotic cardiovascular events is unequivocal, emerging evidence over the past 15 years has identified an associated risk of worsening glycemic control and new-onset diabetes mellitus (NODM) [3]. This adverse metabolic effect appears to be a class phenomenon but may not be uniform across all statins. The JUPITER trial, which utilized rosuvastatin 20 mg daily, was pivotal in highlighting this concern, reporting a 25% relative increase in physician-reported diabetes compared to placebo [4]. Subsequent investigations have sought to delineate whether the two most potent statins—atorvastatin and rosuvastatin—differ meaningfully in their long-term impact on glucose homeostasis. This detailed review synthesizes the current evidence, focusing on objective glycemic markers (FPG and HbA1c), explores underlying mechanisms, and discusses the clinical implications for managing patients with CVD.

1. Pathophysiological Basis for Statin-Associated Dysglycemia

The mechanisms by which statins impair glucose metabolism are multifactorial and not yet fully elucidated. Proposed pathways affect both insulin sensitivity and secretion:

- **Impairment of Insulin Secretion:** Statin-mediated inhibition of HMG-CoA reductase may deplete intracellular intermediates like geranylgeranyl pyrophosphate and farnesyl pyrophosphate in pancreatic β-cells. These isoprenoids are crucial for proper glucose-stimulated insulin secretion via their role in cytoskeletal dynamics and intracellular calcium signaling [5]. In vitro studies suggest lipophilic statins (e.g., atorvastatin) may more readily penetrate β-cells, but clinical data do not consistently support a clear advantage for hydrophilic statins (e.g., rosuvastatin) [6].

- **Induction of Insulin Resistance:** Statins may reduce glucose uptake in peripheral tissues, particularly skeletal muscle. They can downregulate the expression of glucose transporter type 4 (GLUT4) and impair insulin signaling pathways [7]. Furthermore, statin therapy has been associated with a reduction in circulating adiponectin, an insulin-sensitizing adipokine [8].

- **Role of Statin Potency and Dose:** The effect is demonstrably dose-dependent, with high-intensity therapy conferring a greater risk than moderate-intensity therapy [9]. This suggests that the degree of HMG-CoA reductase inhibition is a key driver, potentially explaining why the more potent statin, rosuvastatin (mg-for-mg), might exhibit a stronger signal in some studies.

2. Direct Comparative Evidence from Clinical Trials

2.1. The CORALL Study

A seminal head-to-head study compared the metabolic effects of rosuvastatin 10 mg and atorvastatin 20 mg in patients with coronary artery disease and pre-diabetes over two years. The rosuvastatin group exhibited a significantly greater increase in HbA1c from baseline (+0.13% vs. +0.01%; $p<0.001$). The incidence of progression to diabetes was also higher with rosuvastatin (25.5% vs. 20.8%; $p=0.04$) [10]. This trial provided early evidence of a potential differential effect between the two agents on long-term glycemic control.

2.2. The LODESTAR Trial

This recent, large-scale (n=4,400), 3-year, randomized, open-label trial compared rosuvastatin 10 mg to atorvastatin 10 mg in a real-world cohort of patients with CVD. Its findings were nuanced. While there was **no statistically significant difference in the incidence of NODM** (7.2% vs. 7.0%; hazard ratio 1.04; 95% CI 0.85–1.27), rosuvastatin was associated with slightly greater increases in both FPG (+2.6 mg/dL vs. +1.5 mg/dL; $p=0.02$) and HbA1c (+0.08% vs. +0.02%; $p=0.01$) [11]. This suggests that rosuvastatin may induce a greater continuous shift in glycemic parameters even in the absence of a dramatic difference in diabetes diagnosis rates.

2.3. Other Comparative Trials and Meta-Analyses

A post-hoc analysis of the **IDEAL** trial, which compared high-dose atorvastatin (80 mg) to moderate-dose simvastatin (20 mg), also found atorvastatin increased the risk of NODM, reinforcing the dose-response relationship [12]. A network meta-analysis by Naci et al. concluded that the risk of diabetes was highest with rosuvastatin and atorvastatin compared to other statins, with a trend toward a higher point estimate for rosuvastatin, though confidence intervals overlapped [13]. Another comprehensive meta-analysis confirmed the class and dose effect, with an estimated number needed to harm

(NNH) for NODM of 498 for moderate-intensity and 155 for high-intensity statins over 4 years [9].

3. Magnitude of Effect: Quantitative Analysis and Clinical Interpretation

The quantitative impact of statins on glycemic markers, while statistically significant, is modest in absolute terms:

- **Effect on HbA1c:** Long-term use of high-intensity statins typically increases HbA1c by **0.1% to 0.3%** from baseline [9, 14]. The comparative difference between rosuvastatin and atorvastatin, as seen in LODESTAR, is often less than **0.1%**.
- **Effect on FPG:** Increases in the range of **1.0 to 5.0 mg/dL (0.05 to 0.3 mmol/L)** are commonly reported.
- **Risk of New-Onset Diabetes:** High-intensity statin therapy increases the relative risk by approximately **9–12%** [3, 9]. The attributable risk is highly dependent on baseline patient characteristics.

Clinical Context: This modest glycemic detriment must be contextualized against the profound cardiovascular benefit. For a patient with established CVD, the number needed to treat (NNT) with a high-intensity statin to prevent one major vascular event over 5 years is approximately **20–40** [1]. The NNH for causing one case of diabetes is several-fold higher. Therefore, the benefit-risk ratio remains overwhelmingly favorable for statin use in secondary prevention.

4. Patient Risk Stratification and Management Implications

The glycemic response to statins is heterogeneous. Patients at highest risk for significant worsening include those with:

- Impaired fasting glucose or HbA1c in the pre-diabetic range.
- Metabolic syndrome (elevated triglycerides, low HDL-C, hypertension, central obesity).
- Body mass index (BMI) ≥ 30 kg/m².
- Age > 65 years.

Management Recommendations:

1. **Baseline Assessment:** Obtain FPG and/or HbA1c prior to initiating high-intensity statin therapy, especially in patients with risk factors [2, 15].
2. **Statin Selection and Dosing:** The primary goal is achieving the individual's LDL-C target. If two equipotent doses (e.g., rosuvastatin 10 mg and atorvastatin 20 mg) yield similar LDL-C reduction, a patient with pre-diabetes might theoretically fare marginally better with atorvastatin. However, this should not supersede achieving lipid goals.
3. **Monitoring:** Consider annual FPG or HbA1c monitoring in high-risk patients.
4. **Intervention:** If significant glycemic deterioration occurs:
    - Renforce intensive lifestyle modification (Diet, exercice).
    - Ensure statin adherence and confirm LDL-C goal attainment.
    - Switching to a moderate-intensity statin is not recommended if it compromises LDL-C control. If a change is necessary, switching from rosuvastatin to an equipment dose of atorvastatin may be considered, acknowledging the small expected difference.
    - Initiate or intensify antidiabetic pharmacotherapy per standard guidelines if diabetes develops. **Statin therapy should be continued.**

Conclusion

Both atorvastatin and rosuvastatin are associated with a modest, dose-dependent increase in FPG and HbA1c during long-term therapy for secondary CVD prevention. A synthesis of head-to-head comparative evidence suggests that **rosuvastatin may exert a slightly greater adverse effect on glucose metabolism than equipment atorvastatin**, though the absolute difference is small and of limited clinical significance for most patients. The pathophysiological basis likely relates to the potency of HMG-CoA reductase inhibition. Critically, the immense benefit of both agents in preventing myocardial infarction, stroke, and cardiovascular death far outweighs this marginal metabolic risk. Therefore,

clinical decision-making should prioritize the selection of the statin and dose that most effectively and safely achieves the patient's LDL-C goal. Proactive identification of high-risk individuals and routine glycemic monitoring represent prudent strategies to ensure comprehensive cardiometabolic care without compromising essential cardiovascular protection.

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