

Intolerance and Adverse Events With High-Intensity Statin Therapy in Real-World Practice

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Background

- Statins are the standard of care for hypercholesterolemia and are guideline-recommended for patients requiring lipid-lowering therapy (LLT)¹
- Many patients on statin therapy remain above low-density lipoprotein cholesterol (LDL-C) goals, leaving them at increased risk¹⁻³
- Statin intolerance and adverse events (AEs) contribute to low adherence, dosing limitations, and statin discontinuation⁴
- High-intensity statins (HIS) provide greater reductions in LDL-C levels compared with moderate-to-low-intensity statins (MLIS) but are associated with higher rates of AEs and increased discontinuation¹
- Retrospective identification of intolerance often relies on narrow definitions

Objective

- To identify real-world rates of statin intolerance or AEs among individuals treated with HIS vs MLIS

Methods

- Using Komodo Claims and Research Dataset, a data schema designed for real-world evidence (RWE) and health economics and outreach research (HEOR) studies enriched with Komodo-populated imputed allowed amounts and derived from Komodo's HealthcareMap[®], statin intolerance and prespecified AEs were compared between age/gender/payer-matched patients (N=1,555,978 sets) newly started on HIS and MLIS in 2022 (index event) and who had ≥60 days of statin persistence
- Rates of statin intolerance and AEs were compared using claims-based approaches and included
 - Diabetes-/glycemic-, liver-, and muscle-related AEs
 - Proportion of patients achieving or maintaining LDL-C <70 or <55 (individualized to atherosclerotic cardiovascular disease [ASCVD] history), ≥50% LDL-C reduction, or <25% reduction
- Both assessment windows—pre- and post-index—were 2 years
- Goal attainment required ≥1 pre- and ≥1 post-index LDL-C result; maintenance was defined as either 2 of 2 post-statin results at goal, or 66% of post-statin results at goal in patients who had ≥3 post-statin results

Results

- Cardiovascular (CV) risk baseline characteristics were generally worse in HIS vs MLIS groups (**Table 1**)
 - Mean LDL-C was 83 mg/dL for patients receiving HIS and 90 mg/dL for patients receiving MLIS
 - Patients receiving HIS had a higher burden of comorbidities compared with MLIS, including greater prevalence of diabetes (43% vs 35%), ASCVD (33% vs 12%), myocardial infarction (10% vs 2%), ischemic stroke (12% vs 6%), and peripheral arterial disease (10% vs 6%)
 - Among the 1,555,978 matched sets, patients receiving HIS showed higher intolerance rates compared with patients receiving MLIS based on 2 algorithms (Administrative Claims Data [ACD] method: 8% vs 3%; Multidisciplinary Panel [MP] method: 21% vs 15%) (**Table 2**)
- Compared with patients receiving MLIS, patients receiving HIS had significantly higher rates of AEs (**Table 3**) and increased risk for new-onset diabetes, prediabetes, worsening glycemic control, and an increased risk for muscle injury, rhabdomyolysis, and elevated liver tests (**Table 3, Figure 1**)
- LDL-C goal attainment and maintenance were suboptimal in both the HIS group and the MLIS group and significantly lower in HIS vs MLIS groups (**Figure 2**)
 - 61% in the HIS group and 59% in the MLIS group achieved LDL-C goals, with only 52% and 54% maintaining goals, respectively
 - 37% in the HIS group and 23% in the MLIS group achieved ≥50% LDL-C reduction, while 38% and 40% achieved <25% LDL-C reduction
 - Time to goal exceeded 1 year in both groups

Figure 1. Odds of Select AEs for HIS vs MLIS Patients

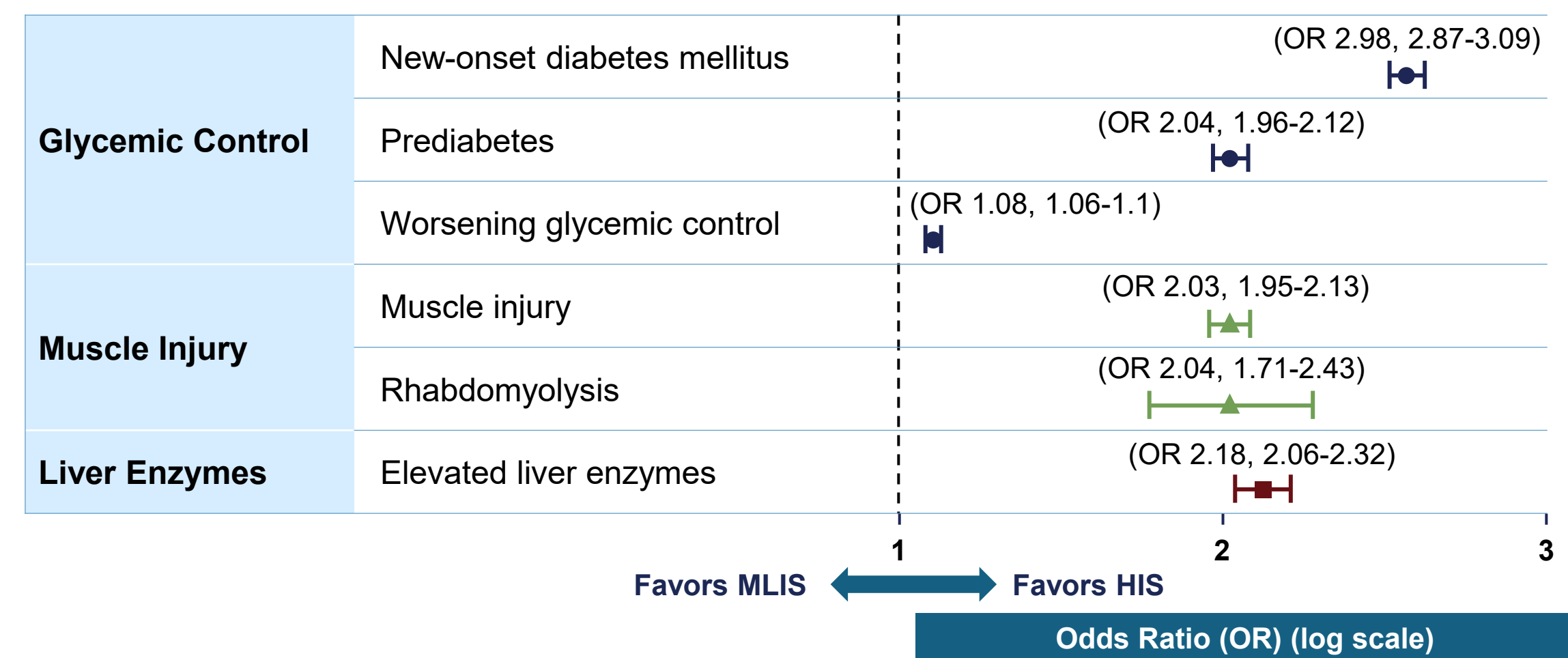


Table 1. Cardiovascular Risk Baseline Characteristics (Cohort With LDL-C Results)

	HIS (n=247,432)	MLIS (n=241,373)
Diabetes (%)	43	35
ASCVD (%)	33	12
Myocardial Infarction (%)	10	2
Ischemic Stroke (%)	12	6
Peripheral Arterial Disease (%)	10	6
CCI	Mean ± SD: 1.62±1.61 Median: 1.00 (IQR: 2.00)	Mean ± SD: 1.14±1.33 Median: 1.00 (IQR: 2.00)

CCI, Charlson Comorbidity Index; IQR, interquartile range; SD, standard deviation.

Table 3. AE Rates

Metric	Metric Description	HIS (%)	MLIS (%)	Significance (Chi Square test or t-test)
New-onset diabetes mellitus	≥1 post-index diabetes diagnosis OR new antidiabetic RX OR new HbA1C≥6.5%	14	5	P<0.05
Prediabetes	1+ post-index prediabetes diagnosis claim OR new HbA1C≥5.7-6.4%	8	4	P<0.05
Worsening glycemic control	≥0.5% increase between baseline and post-index HbA1C	23	21	P<0.05
Muscle injury	1+ post-index muscle injury diagnosis	5.7	2.9	P<0.05
Rhabdomyolysis	1+ post-index rhabdomyolysis diagnosis	0.3	0.2	P<0.05
LFT Elevations	>1 diagnosis OR any post-index ALT ≥3 x upper limit of normal	1.1	0.8	P<0.05

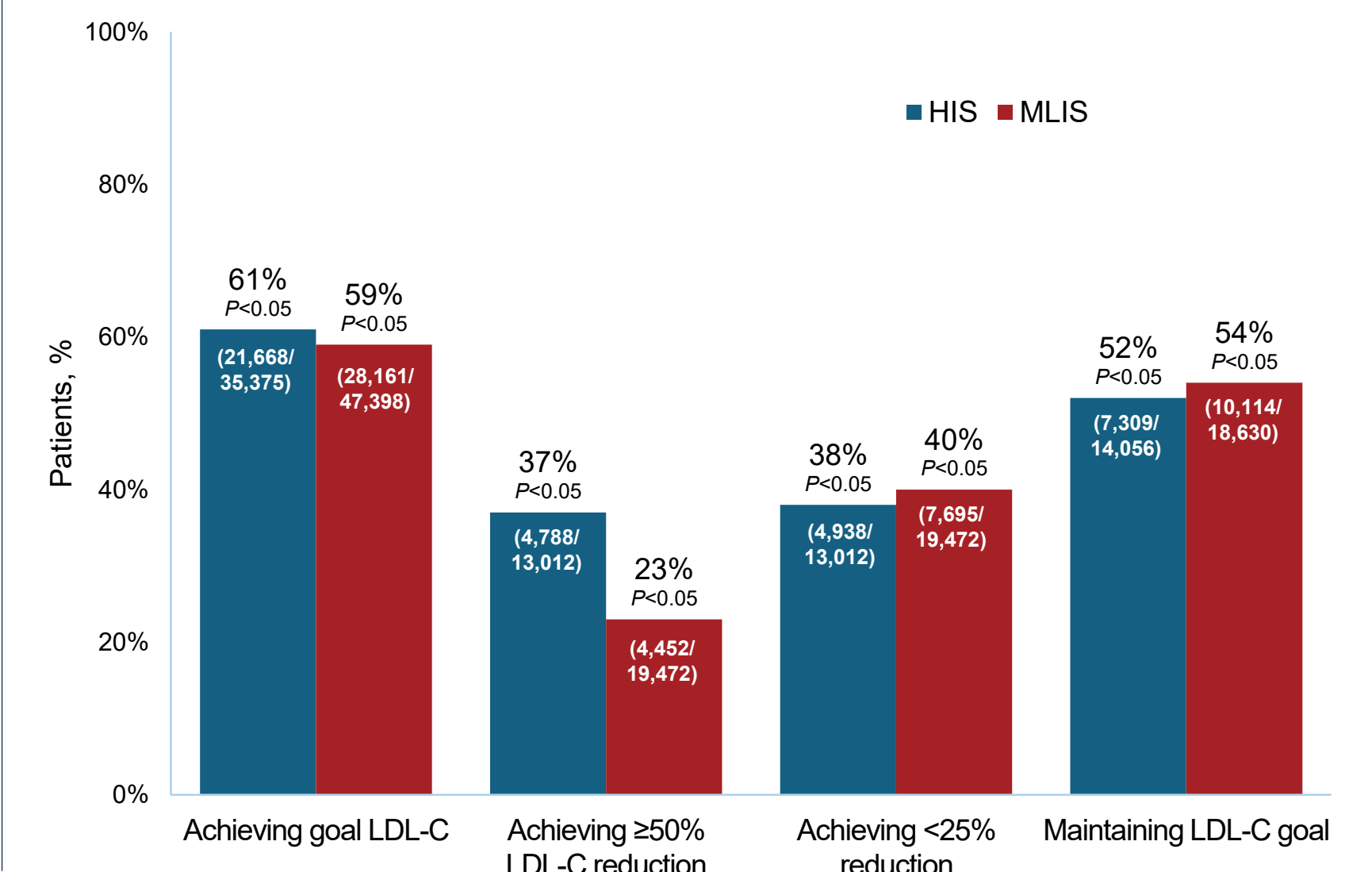
ALT, alanine aminotransferase; HbA1C, hemoglobin A1C; LFT, liver function test; RX, prescription.

Table 2. Statin Intolerance Prevalence Across Definitions

Definition	HIS (%)	MLIS (%)	Significance
MP-adapted algorithm:			
1+ claim muscle injury OR rhabdomyolysis			
OR OP claim CK test	21	15	P<0.05
OR 2 different statin claims, OR statin dose lowering, OR statin discontinuation AND non-statin LLT start			
ACD-adapted algorithm:			
2 different statin claims OR statin dose lowering	8	3	P<0.05
OR statin discontinuation AND non-statin LLT start			

CK, creatine kinase; OP, outpatient.

Figure 2. Goal Attainment, All Patients With Sufficient LDL-C Results



Conclusions

- Intolerance and AEs occurred in significantly greater proportions of HIS vs MLIS patients, including ~3-fold odds of new-onset diabetes (OR 2.98) and ~2-fold odds of muscle injury, rhabdomyolysis, and elevated liver enzymes
- LDL-C goal attainment and maintenance were suboptimal in both groups (~40% of HIS patients failed to reach goal; median time to goal was 396 days). Only a small proportion of individuals in both groups achieved a >50% reduction, while a large proportion experienced <25% LDL-C reduction. These findings highlight an unmet need for non-statin therapies that achieve LDL-C reduction without the AE burden of high-intensity statins

Limitations

- Limitations included focusing only on new statin users, incomplete laboratory data, and a follow-up period potentially insufficient to capture routine monitoring or disease progression. Cohorts also excluded patients with high LDL-C who did not initiate statins and did not adjust for certain patient characteristics that could increase the risk of AEs. Statins do not meaningfully address atherogenic factors beyond LDL-C — including Lp(a) and LDL particle composition — which contribute to residual CV risk



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Affiliations and Disclosures:

JK, NO: Employees and shareholders of NewAmsterdam Pharma; AA, DD, NH: Employees of Trinity Life Sciences. Trinity Life Sciences funded by NewAmsterdam Pharma for conduct and completion of analyses; ND: Nothing to disclose.