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Validation of Electronic Health Records for the Assessment of Statin Dosing In Research

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remnant risk. PCSK9 inhibitors represent a new class of antilipemics that provide additional LDL-C lowering. While there are no cardiovascular outcomes data for this class of medications, surrogate markers for cardiovascular risk (i.e., reduction in LDL-C and atheroma volume) show remarkable results. Limited long-term data currently exist with PCSK9 inhibitor use in real-world practice and concerns regarding attenuation of effect have come to fruition. Furthermore, managed care continues to be a barrier to patient access with an estimated approval rate of 16%.

Objective/Purpose: The goal of this research is to report long-term, follow-up safety and efficacy data of alirocumab and evolocumab in a pharmacist-run PCSK9 inhibitor clinic.

Methods: This is a prospective, observational, institutional review board-approved study from an endocrinology practice involving patients referred to a pharmacist-managed PCSK9 inhibitor clinic. This study is a follow-up to a previously presented abstract evaluating 4-week data; here we further assess the efficacy [percent change in LDL-C, total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) from baseline] and tolerability [via collection of reported adverse events] of alirocumab and evolocumab. Collected data include: patient demographic information, duration of use, history of prior antilipemic therapy, adverse medication events and managed care approval rate.

Results: Forty-nine patients (61% alirocumab, 39% evolocumab) had follow-up lipid data beyond four weeks with a mean treatment duration of 45 weeks. The mean baseline LDL-C of the entire cohort (N = 66) was 135 mg/dL \pm 58. Long-term results are as follows in comparison to baseline [mean percent change \pm standard deviation]: -50.7% \pm 29.8 in LDL-C; -30.6% \pm 19.7 in TC; -42.7% \pm 24.9 in non-HDL-C; -7.4% \pm 38.4 in TG, and +10.4% \pm 22.2 in HDL-C. Twenty-six patients have received therapy for at least one year and demonstrated sustained efficacy. No additional adverse effects were reported beyond the initial 4 weeks. The managed care approval rate was 76%.

Conclusions: PCSK9 inhibitors demonstrate durable lipid-lowering effects and are well tolerated. Pharmacist incorporation into the healthcare team improves patient access to these novel therapies.

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Background/Synopsis: Accurate assessment of medication use is a key component of quality pharmacoepidemiologic and pharmacogenetic research; however, few studies rigorously evaluate the accuracy of drug dosing data in prescription databases.

Objective/Purpose: To evaluate the validity of statin prescription dosing data recorded in the electronic health records (EHRs) of a large health plan cohort using lipids outcome data.

Methods: We analyzed a large EHR-derived dataset of dispensed statin prescriptions and serum lipid measurements based on the Kaiser Permanente Northern California Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort of 110,000 individuals. We determined the accuracy of the first statin prescription dispensed for each patient by assessing the concordance of two sets of variables, each of which calculates a daily dose: (1) days' supply and amount supplied and (2) dose/day and tablets/dose. To account for differences in potency among statin types, we derived a defined daily dose (DDD) such that 1.0 DDDs is equipotent to 10 mg atorvastatin daily. To assess the validity of the DDD, we analyzed dose response utilizing LDL-C measurements from the EHRs that were linked to the prescription data. In particular, dose response was calculated from LDL-C measurements before and after statin initiation and then analyzed using linear regression. For prescriptions for which the two estimates of DDD differed, or for which some information was missing, we developed a novel imputation scheme. This algorithm was based on the dispensing characteristics of the concordant dataset.

Results: Data from 40,493 patients were included in the analysis. Patients had a median (IQR) age of 64.8 (13.8) years, were 50.6% female, had a median BMI of 27.8 (6), and had a median LDL-C of 152 (48) mg/dL before receiving statin treatment. Among all included patients, 39,604 (97.8%) had a first statin prescription that was concordant and 889 (2.2%) had a prescription that was imputed. A clear dose response existed (Beta = -5.9 ± 0.09 , $P < 1.0 \times 10^{-15}$) among patients with concordant prescriptions that was consistent with the well-established rule of 6%, which describes the additional reduction of LDL-C upon statin dose-doubling. We observed a similar dose response among patients within the imputed set (Beta = -3.9 ± 0.63 , $P = 1.4 \times 10^{-9}$).

Conclusions: This EHR-based prescription and clinical laboratory dataset demonstrated a predicted LDL-C dose response and thereby is a reliable source for future

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Validation of Electronic Health Records for the Assessment of Statin Dosing In Research



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pharmacoepidemiologic and genetic research. We also successfully implemented a novel approach to predict the DDD of dispensed prescriptions with missing or contradictory data.

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Efficacy of Alirocumab Treatment on Lipoproteins At Week 12: Pooled Analyses of 10 ODYSSEY Phase 3 Trials



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Study Funding: This analysis was funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Background/Synopsis: ODYSSEY Phase 3 alirocumab trials have been reported at their primary endpoint of 24 weeks (W), which for eight of the ten trials meant that a percentage of patients had their alirocumab 75 mg every 2 weeks (Q2W) dose increased to 150 mg Q2W at W12 because of not meeting pre-specified low density lipoprotein cholesterol (LDL-C) goals. Here we report the effects of alirocumab on lipid parameters at W12 prior to potential dose change.

Objective/Purpose: To assess alirocumab effects on LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein(a) [Lp(a)] and apolipoprotein (Apo) B at W12.

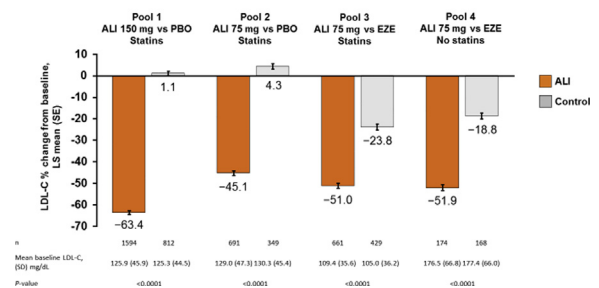
Methods: Data were pooled from ten double-blind Phase 3 trials involving 4974 patients. Patients were randomized (1:1 in OPTIONS I and OPTIONS II; 2:1 in others) to alirocumab or control (placebo or ezetimibe), mostly added to background maximal tolerated statin therapy or as monotherapy in MONO. In eight trials, all patients allocated to alirocumab received 75 mg Q2W up to W12; in two trials the dose was 150 mg Q2W throughout the study. On treatment changes in lipids at W12 were analyzed in four pools defined by alirocumab dose, control and background statin use (Figure 1).

Results: Mean age was 55.5–63.1 years and mean baseline LDL-C was 105.0–177.4 mg/dL across the pools. Alirocumab at 75 mg Q2W reduced LDL-C by 45.1–51.9% across Pools 2–4 and at 150 mg Q2W by 63.4% in Pool 1 at W12 (Figure 1). LDL C reductions with 75 mg or 150 mg Q2W were consistent across the pools and were independent of variations in baseline LDL-C levels or use of background statins. Proportions of patients reaching LDL-C goals were 52.0–78.9% with 75 mg Q2W and 82.2% with 150 mg Q2W. Alirocumab at 75 mg Q2W reduced non-HDL-C by 38.5–45.7% (53.8 % at 150 mg Q2W), Apo B by 35.1–39.9% (55.4%) and Lp(a) by 21.5–22.2% (28.3%)

across the pools ($P < 0.001$ vs placebo or ezetimibe). Alirocumab was generally well tolerated in patients pooled across all trials compared with control.

Conclusions: Alirocumab 75 mg and 150 mg Q2W resulted in significant and consistent on treatment reductions in lipid levels at W12 prior to potential dose change (in three pools on 75 mg Q2W) in this analysis from 10 Phase 3 trials.

Figure 1. Percentage change from baseline in calculated LDL-C at Week 12: MMRM (on-treatment analysis)



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Safety and Efficacy of Evinacumab, A Monoclonal Antibody to ANGPTL3, in Homozygous Familial Hypercholesterolemia



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Study Funding: This study was funded by Regeneron Pharmaceuticals, Inc.

Background/Synopsis: Patients with homozygous familial hypercholesterolemia (HoFH) have very severe elevations in LDL-cholesterol (LDL-C), resulting in coronary heart disease as early as teenage years. Almost all HoFH patients have attenuated responses to currently available lipid lowering therapies (LLTs). By nature, HoFH patients with LDL-receptor (LDLR) null/null mutations are refractory to