

Title of Research

Using the Statin Trials Pooled Dataset to Develop a Model of Cardiovascular Risk Recurrence

Lead Researcher

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Summary of Research

New therapies for cholesterol lowering after cardiovascular (CV) events have increased interest in determining who is at highest risk of recurrent events and who may benefit most from additional lipid lowering therapy (LLT). Meta-analyses from the Cholesterol Treatment Trialists' Collaborators (CTT) have demonstrated that the degree of benefit from LDL lowering is proportional to a person's baseline CVD risk and the degree of LDL-C lowering. However, individual randomized trials have failed to show an interaction by baseline LDL-C. Thus, it remains unclear how to best identify candidates for more aggressive LLT – should we target those at highest risk, with the highest LDL-C, or on LDL-C changes on therapy?

This study will test the hypothesis that:

1. Pooled data from statin clinical trials in secondary prevention can be used to identify adults at highest risk of recurrent cardiovascular disease events based on clinical characteristics.
2. Patients at the highest risk of recurrent CVD events benefit the most from therapy. Changes in LDL particle number predict benefit on statins more than baseline LDL-C or changes in LDL-C.
3. The magnitude of benefit from lipid lowering therapy increases with time on treatment.

The primary objective will be to develop model of CV risk recurrence in individuals who have had at least one prior event. The secondary objective will be to determine predictors of benefit from statin therapy, i.e. relative risk reduction, based on multiple trials, and to assess the interaction between time on treatment and treatment intensity.

The researchers plan to combine results from clinical trials of pravastatin with results from other clinical trials to evaluate the effect of statins in patients with cardiovascular disease.

Study Design

The study design will involve pooled individual patient level analysis of randomized trials data.

Study Population

The study population will comprise all individuals from the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) and Cholesterol and Recurrent Events (CARE) trials' intent-to-treat population.

Funding Source of Research

This study has no external funding and will be funded using internal funds at the DCRI. Dr. Navar and her team are supported by the NHLBI (K01HL133416).

Requested Study

CV27201-095 (Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial): Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels

CV27201-067 (Cholesterol and Recurrent Events (CARE) trial): The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels

Statistical Analysis Plan

Primary Objectives/Aims:

- *Aim 1:* To develop model of CV risk recurrence in the study population
- *Aim 2:* To determine predictors of benefit from treatment, i.e. relative risk reduction. The hypothesis is that patients at highest risk of recurrent events will benefit the most from therapy, and changes in LDL-P will have better predictive abilities than baseline LDL-c or changes in LDL-C.
- *Aim 3:* To assess the interaction between time on treatment and treatment intensity. The hypothesis is that the magnitude of benefit from therapy will increase with time on treatment.

Data: Data from BMS trials will be combined with other trials of statins in secondary prevention. The relevant BMS data sets are for LIPID and CARE; the BMS comparison groups are: a) LIPID: placebo, 40 mg pravastatin; and b) CARE: placebo, 40 mg.

Pravastatin Endpoints: The primary endpoint is a composite of: CHD events (MI, unstable angina); CVD events (stroke, TIA); CV death (all-cause death, for determination of non-CV deaths).

Analysis Objectives:

1. *Objective:* Describe baseline characteristics by treatment (pravastatin/trial) group.

Analysis: Continuous variables will be presented as median (IQR) unless specified otherwise. Categorical variables will be presented as count (%). For specified baseline characteristics, comparisons between groups will be assessed using ANOVA, or Kruskal-Wallis test where appropriate, and the chi-square test. Additionally, length of follow-up for each cohort will be determined for analysis purposes.

2. *Objective:* Create a model of CVD risk recurrence using the placebo group of the pooled cohorts.

Analysis: A Cox proportional hazards model will be used to create the risk model. All specified baseline variables will be added to the model, including treatment group. Continuous variables will be assessed for linearity with respect to the outcomes and flexible spline transformations will be performed when necessary. The proportional hazards assumption will be checked for violations. Backward selection will be used to reduce the covariate list down to those that are informative.

The primary and secondary composite endpoints specified above are the outcomes and non-CV death will be considered a competing risk. Follow-up will be censored at five years for cohorts that had more than five years' worth of follow-up. After the model has been completed, predicted risk at three years of recurrent events for patients in the treatment arms will be computed.

3. *Objective:* Determine predictors of benefit and the relative risk reduction at three years.

Analysis: Patients will be assigned an indicator at three years for the primary outcome. A general linear model with binomial distribution and log link will be fit to the data. The following variables will be included in the model: predicted baseline risk of recurrent CVD events (determined in Aim 2), baseline

LDL-C, baseline LDL-P or ApoB, treatment group, on treatment change in LDL-C and on treatment change in LDL-P. From the output, the most important predictor of relative risk reduction will be determined.

4. *Objective:* Determine if the treatment effect varies with time. *Analysis:* A Cox proportional hazards model with the primary outcome and the interaction between treatment group and time will be assessed. The model will include the important predictor(s) identified in Aim 3. If there is a significant interaction between time and treatment, hazard ratios and 95% CI will be presented at major time points over the course of follow-up. Individuals will be censored at five years if follow-up time is longer. Intra-trial correlation will be taken into account using the covs(aggregate) option in the phreg procedure and the ID statement for identifying clusters. Kaplan-Meier curves will be created for illustration purposes.

Software requirements: SAS, or unformatted CSV files.