CNODES

Scientific Protocol

The Effect of High Potency Statins on the Risk of Incident Diabetes in Patients with Occlusive Vascular Disease

Version 2.0

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BACKGROUND:

 Statins are a class of lipid lowering drugs commonly prescribed for the primary and secondary prevention of cardiovascular disease. With over 30 million prescriptions filled annually (IMS 2010), statins are the most commonly prescribed class of medications in Canada. Historically, statins have been considered to have a favorable safety profile, although they have long been considered in rare instances to cause rhabdomyolysis. Recent evidence also suggests the presence of important adverse drug effects. The Canadian Network of Observational Drug Effect Studies (CNODES) recently demonstrated that high-dose statins are associated with an increased risk of acute kidney injury (AKI) compared with low-dose statins. In addition, statins have been linked to changes in cognitive function, which prompted the U.S. Food and Drug Administration (FDA) to revise the mandatory labeling for statins in February 2012.[[1]](#endnote-1)

 Labeling changes in February 2012 also reflected recent evidence that statins increase the risk of incident type 2 diabetes mellitus. Sattar et al. (2010) examined the effect of statins on the risk of incident diabetes in a meta-analysis of randomized controlled trials (RCTs).[[2]](#endnote-2) Inclusion was restricted to RCTs of at least 1,000 patients treated for a minimum duration of 1 year. Using data from 13 RCTs (n=91,140 patients), the investigators reported that statins were associated with a 9% increased risk of incident diabetes (odds ratio [OR] = 1.09, 95% confidence interval [CI] = 1.02, 1.17). Using similar inclusion criteria, the same research group then compared the risk of incident diabetes in high-dose statin patients to that of low-dose statin patients in a meta-analysis of 32,752 patients in 5 RCTs. When these data were pooled across studies, high-dose statins were associated with a 12% increased risk of incident diabetes relative to low-dose statins (OR = 1.12, 95% CI = 1.04, 1.22). The generalizability of these results to a real-world population is unclear.

# **JUSTIFICATION FOR A CNODES STUDY**

 Meta-analyses of randomized controlled trials of statins have reported an association between treatment with statins and incident diabetes.,[[3]](#endnote-3) Although those meta-analyses were based on RCT data and appear to be suitably executed, more research is needed for the following reasons:

1. Diabetes can lead to serious morbidity and early death, and it is a major driver of health care expenditure in Canada.

1. The statin RCTs included in the meta-analyses of diabetes were not specifically designed to assess the outcome of diabetes. Furthermore, a common definition of diabetes was not used across RCTs, with some trials having used physician reports while others used laboratory test results.
2. Better precision would increase confidence in the validity of a statin-diabetes association. While the above mentioned meta-analyses used RCT data, the diabetes event counts and the number of patients included in those RCTs was relatively small, and 95% CIs nearly included 1.00 on a relative scale
3. The physicians who participated in statin RCTs were likely aware of subsequent laboratory test values in their patients, which in turn could have influenced their treatment choices, potentially biasing treatment effect estimates.
4. It remains to be shown whether any incremental increase in diabetes with high potency statins compared to low potency statins is offset by additional protective benefits such as reduced myocardial infarction (MI), stroke, and total mortality.

# PROPOSED STUDY QUESTIONS

The proposed CNODES study will be specifically designed to examine diabetes as an outcome of statin use. The proposed study will compare several outcomes in patients after an occlusive vascular disease (OVD) event and/or OVD procedure, who received either high potency or low potency statins after discharge from hospital. The study will be restricted to post-OVD patients for the following reasons:

1. RCT data have demonstrated a total mortality benefit of statins in secondary prevention of occlusive vascular disease. Unfortunately, the above-mentioned meta-analyses provide no guidance for treatment potency in these patients in light of a possible elevated risk for diabetes; a risk that could conceivably be greater at higher statin potencies.

1. While it would be extremely valuable to examine diabetes risk in primary prevention patients (those without a history of occlusive vascular disease or at relatively lower risk of cardiovascular disease), this type of analysis would be difficult in claims data because it would be impossible to determine whether statin treatment was a cause of diabetes or a possible consequence of it. More specifically, metabolic syndrome could be a reason for starting a statin in many primary prevention patients. However, metabolic syndrome and the timing of its onset (rather than its diagnosis, which could be years later) would be poorly captured in claims data. In post-OVD event patients, the OVD event or procedure can be assumed to be the most compelling reason for proximally starting a statin, so long as treatment starts soon after the post-OVD event occurs.

**Questions**:

In patients without diabetes mellitus admitted to hospital for an

1. MI, or
2. stroke, or
3. coronary artery bypass graft (CABG) or
4. Percutaneous transluminal coronary angioplasty (PTCA)

and then discharged alive and dispensed a statin:

Primary question:

1. Does exposure to higher-potency statins (rosuvastatin ≥ 10mg, atorvastatin ≥ 20mg, simvastatin ≥40mg) convey a different risk of incident diabetes compared with exposure to lower-potency statins (all doses of fluvastatin, all doses of pravastatin, all doses of lovastatin, rosuvastatin <10mg,atorvastatin <20mg, simvastatin <40mg)?

Secondary research question(s):

1. Does exposure to higher-potency statins convey a different risk of all-cause mortality compared with exposure to lower-potency statin?
2. Does exposure to higher-potency statins convey a different risk of MI compared with exposure to lower-potency statins?
3. Does exposure to higher-potency statins convey a different risk of stroke compared with exposure to lower-potency statins?
4. Does exposure to higher-potency statins convey a different risk of serious adverse events (SAE) (composite endpoint of all-cause mortality or any emergency admission to hospital) compared with exposure to lower-potency statins? Although statins are meant to lower some of these outcomes, they are still properly referred to as SAEs.[[4]](#endnote-4) The word ‘Adverse’ refers to the event not the drug.

# STUDY DESIGN

CNODES will investigate a possible association between statins and diabetes by conducting retrospective observational cohort studies in 8 administrative health care databases (Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia, U.S. MarketScan and the United Kingdom General Practice Research Database [GPRD]). Specifically, CNODES will assess whether post-OVD patients who take statins have a greater risk of acquiring diabetes while on treatment for up to 2 years. We will conduct As-Treated analyses using case-control methodology on a nested cohort of post-OVD event statin patients. Accordingly, rate ratios for different lengths of current and past exposure to high potency or low potency statins will be estimated using conditional logistic regression. Study patients will be those post-OVD patients who start either a low potency or high potency statin, with low potency statin patients serving as the reference group. Although these reference patients will also have used statins, this design feature may not eliminate all confounding. Therefore, control for any residual confounding will be achieved using high-dimensional propensity scores (hdPS). The results of these database-specific analyses will then be pooled via meta-analysis to obtain overall treatment effects. Results of the study will be reported to Health Canada and CIHR prior to publication in a peer-reviewed medical journal.

## Data Sources

All participating jurisdictions will contribute data from their respective administrative health care databases. Prescription data will include patient-level prescriptions that specify the drug dispensed, the quantity or days supply of medication dispensed, and the date of dispensing. The databases for ambulatory medical encounters and hospitalizations will include the date of the service encounter or hospital admission, up to 25 International Classification of Disease (ICD)-9 or ICD-10 diagnosis codes, and procedure and billing codes. The Saskatchewan and GPRD databases will include laboratory test data, and the GPRD database will include body mass index and smoking status.

## Settings and Source Populations

A common analytical protocol will be used to conduct separate Statin-Diabetes studies in each of the six Canadian provinces (Alberta, Manitoba, Nova Scotia, Ontario, Quebec and Saskatchewan; source population 33 million in 2011), as well as in two international databases: the UK GPRD, population 11.6 million, and the U.S. MarketScan database, population 4 million. The source populations will be patients 40 years of age or older, without previous diabetes mellitus, treated with statins after experiencing an OVD event or procedure between January 1, 1998 (or 2 years after site-specific data is available, whichever is later) and November 30, 2010 (or 4 months before site-specifc data ends, whichever is later). In three participating provinces (Alberta, Ontario and Nova Scotia), only patients 65 years of age and older will be available for analysis.

## Cohort Inclusion Criteria

 In each jurisdiction, patients will be included in a nested cohort if they were a member of the source population. Specifically, a patient will be included in the nested cohort if, between January 01, 1998 (or two years after the beginning of data availability) and November 30, 2010 (or 4 months before the end of data in each jurisdiction): (1) the patient was admitted to hospital where (a) an MI or stroke diagnosis was recorded in the admission record, and/or (b) underwent a CABG or PTCA procedure, and (2) the patient was discharged home alive, and (3) the patient was dispensed or prescribed a statin medication within 90 days of discharge from hospital. The date of the first statin in the 90-day window will be defined as the cohort entry date. Daily statin doses will be categorized as high potency statins (rosuvastatin ≥10mg, atorvastatin ≥20mg, and simvastatin ≥40mg) or low potency statins (all other statins). This categorization was derived from a meta-analysis of RCTs which quantified the effects of statins on LDL cholesterol concentration.[[5]](#endnote-5) In this categorization, statins were divided into three groups based on LDL reductions: one group which produced an approximately 35% reduction, one which reduced LDL by about 45%, and rosuvastatin 80mg, which lowered LDL by approximately 60%. This classification has been used by others.[[6]](#endnote-6),[[7]](#endnote-7),[[8]](#endnote-8) We will group rosuvastatin 80mg with the other higher potency statins because the number of such prescriptions is known to be very small. Patients will only be allowed to enter the nested cohort once.

## Cohort Exclusion Criteria

Patients will be excluded from the nested cohorts if they were less than 40 years of age at the time of cohort entry (66 years of age in jurisdictions that only had drug data on those aged > 65 years), had less than 1 year of enrollment in their medical system, or, in the 1 year prior to their OVD event or procedure, received any cholesterol lowering drug, or any diabetes diagnosis or drug.

## Event Definitions

Event definitions will be precisely more defined in the technical analytical protocol.

Diabetes: One hospitalization with a diabetes diagnosis [The ICD code can be in any of the up to 25 diag fields but the diagnosis type must be (a) most responsible (type M), or (b) preadmission (type 1) where the same diagnosis does not appear in another field as ‘arose in hospital’ (type 2)], or a prescription for insulin or an oral diabetes medication.

All-cause mortality: Date of death.

MI: an ICD code for MI in the first diagnostic position of the discharge abstract (Dx1 = ICD-9: 410 or ICD-10 I21), where the diagnosis type is the most responsible diagnosis (DxType = ‘M’), and other Dxcode Dxtype NOT = 2 (post-admit), and the total length of stay ≥3 days.

Stroke: an ICD code for stroke in the first diagnostic position of the discharge abstract (Dx1 = ICD-9: 433.x, 434.x, 431, 436 ; or ICD-10 I63.x, I65.x, I66.3, I61.x, I64), where the diagnosis type is the most responsible diagnosis (DxType = ‘M’), and other Dxcode Dxtype NOT = 2 (post-admit), and the total length of stay ≥3 days.

SAE: The earliest occurrence of death from any cause or emergency admission (admission category = “urgent/emergent”) to hospital for any reason.

## High-Dimensional Propensity Scores

 hd-PS will be estimated for all patients in the nested cohorts.[[9]](#endnote-9) hd-PS is an empirically driven, multistep process to adjust for confounding bias in observational studies. The hd-PS algorithm prioritizes thousands of drug, diagnostic, procedure and demographic variables according to their potential to cause bias in the estimate of a multiplicative estimate of an exposure-outcome association (e.g. rate ratio). Typically, the 200 to 500 variables most likely to cause bias are included in a propensity score model. Logistic regression will used to estimate the predicted probability (propensity score) of exposure to high potency statins versus low potency statins, conditional on all of the included covariates. Theoretically, balancing or adjusting a study dataset for treatment propensity score should remove confounding from any confounders that were included.

##  As-treated analysis

In each nested cohort, and separately for each primary and secondary outcome, a follow-up end date will be defined for each patient as the earliest occurrence of the outcome, date of death, date of emigration, 24 months after initiation on statin treatment, a dispensing for cerivastatin, or the end of data availability. We will identify all outcomes occurring within patients’ follow-up windows and define the case index date as the date of the outcome-specific hospital admission (death of death for all-cause mortality). For each case, we will randomly select ten controls from a matched risk set comprised of all of the patients of the same sex and age within one year (within five years if no controls were available), but who also entered the cohort within +/-90 days of the cohort entry date of the case.

 We will use conditional logistic regression to estimate matched ORs for three durations of current exposure (<120 days, 120 to <365 days, and 365 to 730 days) and past exposure (no exposure within 120 days of the index date). Adjusted matched ORs will be estimated by including decile of propensity score (nine binary indicator variables).

## Meta-Analysis

Fixed effect or random effects models estimates will be pooled according to results of χ2 tests for heterogeneity.[[10]](#endnote-10) Matched ORs will be reported as rate ratios. Inverse variance weighted ORs and 95% CIs will be calculated to estimate the total effect across all study populations.

## Sensitivity Analyses

We so far propose that post-OVD event patients start a statin within 90 days of being discharged from in order to enter the cohort. In one database, we will examine different lengths for this statin starting window. Those other lengths will be 30 and 60 days. A shorter window will permit fewer patients to enter the cohort because some patients will be dispensed statins later. However, the closer the date of starting a statin is it to the date of the event or procedure, the more likely the event or procedure is to be the reason for starting the statin. Ultimately, a window length 30, 60 or 90 days will be chosen that provides adequate power to detect a relative increase of at least 15% in the primary outcome.

# POWER

In the previous CNODES study on statins and acute kidney injury, 32% of statin patients started on a high dose statin. The remainder started on a low dose statin. In our nested cohort we will assume that 20%[[11]](#footnote-1) of post-OVD event patients took a statin for the first time (no cholesterol lowering medication in the previous 2 years) and that among those statin patients, 32% took a high potency statin (i.e. exposure prevalence of 0.32 in the nested cohort, possibly an underestimate in an OVD population). We will match up to 10 controls per case. Extrapolating from the Canadian Institute of Health Information’s 2011 Health Indicators Report[[12]](#endnote-11), there should be approximately 500,000 MI’s and 260,000 ischemic strokes in the Canadian databases during our proposed study period. If it is assumed that 30% of those will be lost to cohort exclusion criteria, the number of patients with an eligible cohort-defining event will number approximately 540,000. If it is further assumed that 20% of those took a statin within 30 days of being discharged from hospital, then the nested cohort of post-OVD event statin patients should number approximately 108,000. Extrapolating the incident diabetes data from the Sattar meta-analysis to the Canadian databases suggests that approximately 1,950 incident diabetes cases will be found.

The table below show that, given the above assumptions and a predicted number of diabetes events of 1,950, there will be 80% power to detect an odds ratio for incident diabetes of 1.15 or greater for HPS compared to LPS in post-OVD event patients. These calculations do not include British or American data, and do not include additional patients entering the cohort due to CABG and PTCA procedures not associated with an MI.

 

# POTENTIAL LIMITATIONS

Confounding by indication will be a possible threat to validity of our study. To minimize this bias, the reference exposure will also consist of patients who take statins (i.e. lower potency statins). Still, confounding by indication could bias our results if patients at higher risk of the study outcomes tended to disproportionately take higher dose statins, and if some of those predictors of risk go uncaptured by the hdPS. Therefore, extra caution will be exercised in making inferences from small odds ratios. There will likely be a trend over time towards use of higher-potency statins and fewer MIs. To account for this trend we will also match controls to cases on day of cohort entry ±90 days, in addition to sex and age (±2 years). Unlike MI, the primary outcome of diabetes is not necessarily an accurately timed event. It is hoped that by following post-MI patients for up to 2 years, a difference in diabetes risk between higher potency and lower potency statins will be detectible. The fact that diabetes onset is not easily timed will mean that comparing odds ratios from different durations of cumulative exposure might not necessarily be informative.

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