CNODES

MODIFIED FOR TRAINING

Statistical Analysis Plan (SAP)

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

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A. Document Control

Version	Date	Author(s)	Type of Change
M0.1	02/07/2019	SJ	Initial draft of modified protocol (adapted from V2.5 of original protocol)
M1.0	23/09/2019	SJ	Changed dates referenced so in line with simulated data
M2.0	30/09/2021	TM	Modified dates in order to calculate propensity scores; removed some outcomes to reduce repetition
M3.0	08/06/2022	DS	Updated links, added notes for clarification

This Statistical Analysis Plan is from one of the first studies conducted by CNODES. This protocol has been modified for training use with the *CNODES Simulated Data Sets.* The modifications account for differences between the simulated data sets and actual administrative health data. It is important to note that adaptations made may not reflect the scientific intent of the original protocol, and may not be adaptations that would be appropriate in an actual study. We have kept as much of the original protocol wording as possible, to give an accurate sense of how CNODES protocols are written to account for differences in data across sites.

NOTE: any results obtained from following this protocol do not have any medical significance.

You can find a summary of the original study, along with a link to the publication here: https://www.cnodes.ca/project/statins-diabetes

B. Study Aim, Questions and Hypotheses

Aim: Determine if new use of a higher-dose statin (HPS) in post-event occlusive vascular disease (OVD) patients is associated with an elevated or reduced risk of incident diabetes compared to new use of a lower-dose statin (LPS).

Questions: Main analysis: Does exposure to HPS (rosuvastatin, atorvastatin, simvastatin) convey a different risk of incident diabetes compared with exposure to LPS (fluvastatin, pravastatin, lovastatin)?

Exploratory analysis: Does exposure to HPS convey a different risk of all-cause mortality compared with exposure to LPS?

Exploratory analysis: Does exposure to HPS convey a different risk of serious adverse events (SAE) (composite endpoint of all-cause mortality, MI, or stroke) compared with exposure to LPSs?

C. Study Design

This is a high-dimensional propensity score adjusted case-control study nested within a cohort (i.e., nested case-control). The cohort will be patients with a diagnosis of MI or stroke, followed by a statin prescription within 90 days after being discharged. Different outcome events in this cohort will be analyzed. The primary analysis will assess the relative risk for incident diabetes. Exploratory analyses will assess the relative risks for all-cause mortality, MI, stroke, and serious adverse events (SAE).

D. Study Population

1. **Source Population**

   All residents with an MI, stroke, who were registered for provincial medical services coverage at any time between:

   i. March 31, 2009, or 1 year after your data begins if later than March 31, 2009, whichever is later; and

   ii. 4 months before your data ends (e.g. if your data ends on March 31, 2017, diagnosis dates for OVD events used in defining cohort entry should occur on or before November 30, 2016).

Note: The first year in your database should only be used for determining cohort eligibility and providing baseline covariate information as necessary.

2. **Cohort Entry Criteria**

   Patients can only enter the cohort when they start a statin and have had a cohort defining event as follows:

   i. **New Statin Users**

   - Identify the first statin prescription for each patient, not including cerivastatin and combination statins
   - Verify the patient is new to cholesterol lowering pharmacotherapy by checking that no cholesterol lowering drug (World Health Organization Anatomical Therapeutic Class = C10) or prescription for niacin (including C10AD02 and C04AC01) was dispensed in the 1 year prior to starting the statin. Include cerivastatin and combination statins in this look back check.
   - Define the day of statin initiation as the **Cohort Entry Date**.

ii. **Cohort-Defining Event (CDE)**

In order to enter the cohort, a new statin patient must also have a diagnosis for MI or stroke within 90 days before their cohort entry date. MI and stroke for the CDE are defined as:

MI or Stroke (must meet all of (a) through (b)):

a) an ICD code for (note: a code ending in 'x' means any and all numbers after the decimal place)
   i. MI (Diagnosis = ICD-9: 410.x; or ICD-10 I21.x) or
   ii. stroke (Diagnosis = ICD-9: 433.x, 434.x, 431, 436; or ICD-10 I63.x, I65.x, I66.3, I61.x, I64)

b) The diagnosis date falls in the interval defined in *1. Source Population*

Important: if multiple diagnoses occur 90 days before Cohort Entry, assume the most recent one is the CDE.

3. **Cohort Exclusion Criteria**

i. Patients are not allowed to enter the cohort more than once. For patients who meet the entry criteria more than once, keep only the first instance of meeting the cohort entry criteria.

ii. Age < 40 on the cohort entry date; or age < 66 in databases with seniors only; or age < minimum age available in your jurisdiction plus 1 year

iii. Less than 1 year of provincial medicare enrollment preceding the Cohort Entry Date

iv. In the 1 year (365 days) prior to the Cohort Entry Date, occurrence of >= 1 of the following diagnosis or medicines:

v. Received more than one prescription for any cholesterol lowering drug on the cohort entry date (WHO ATC_3=C10, or niacin)

Exclusion Type	**Details**
Medicines	Lipid-modifying agents (WHO ATC C10), but also including niacin (including C10AD02 and C04AC01). See http://www.whocc.no/atc_ddd_index/.
Diagnoses (any field, any reason)	Diabetes: ICD-9: 250.x – Diabetes mellitus ICD-10: E10.x - Insulin-dependent diabetes mellitus E11.x - Non-insulin-dependent diabetes mellitus E12.x - Malnutrition-related diabetes mellitus E13.x - Other specified diabetes mellitus

	E14.x - Unspecified diabetes mellitus
Medicines	Drugs used in diabetes (WHO ATC A10)
Diagnoses / Medicines	Admitted to, or resided in a long-term care facility (Databases that are unable to make this exclusion should note is in Appendix IV)

*Note that CHF and loop diuretics have been dropped from this table.

4. End of Follow-up

Define the End of Follow Up Date for each patient and outcome as the earliest occurrence of:

i. The first occurrence of the outcome definition after cohort entry;

ii. Date of Death;

iii. Date of emigration from your province;

iv. Date of first loss of continuous health plan or drug plan enrolment;

v. 730 days after initiation of statin treatment

vi. Entry into a long-term care facility

vii. A dispensing for cerivastatin

viii. March 31, 2017, or when your data ends, as per the definition under *Source Population* above.

5. Cases and Controls

The outcomes of interest are defined below in Section F on Outcomes. The primary analysis will estimate incident diabetes in post-OVD event HPS patients compared to LPS patients. Secondary analyses will estimate all-cause mortality, MI, stroke, and SAEs. Because each patient can have one or more of these events, which can occur at different times, control selection will need to be redone for each of the five analyses. Controls will be at-risk patients who have the same sex, age within ±2 years, and day of cohort entry ±90 days. **A matching macro is provided in Appendix IV.** For further understanding of matching cases to controls, see *Section H Analytic Steps*.

6. Study Period

i. **Outcomes assessment period:** The following period will be examined for outcomes or reasons for censoring (death, leaving the jurisdiction, or entry into a long-term care facility).

a. March 31, 2008, or 1 year after your data begins if later than March 31, 2008, whichever is later; and

b. The end of your data.

ii. **Index date:** For cases, and separately for each outcome, the index date will be defined as the date during the outcomes assessment period when the study outcome endpoint

occurred. For controls, this date will be matched to the case's index date. Index dates will need to be created for each subject for the five different analyses.

iii. **High Dimensional Propensity Score (hd-PS) comorbidity adjustment:** Use the hd-PS SAS macro provided by the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital. It can be downloaded here, under Pharmacoepidemiology Toolbox including High-dimensional Propensity Score (hd-PS) Adjustment version 2. The methods are described in detail by Schneeweiss, 2009 available here. The hd-propensity scores are constructed for patients at cohort entry using data from the previous 365 days.

7. Accrual Start/End Dates

Accrual Start/End Dates

BC (MarketScan):	Start Date: January 01, 2009; End Date: August 31, 2017
Alberta:	Start Date: January 01, 2009; End Date: March 31, 2015
Saskatchewan:	Start Date: April 01, 2010; End Date: March 31, 2016
Manitoba:	Start Date: January 01, 2009; End Date: March 31, 2016
Ontario:	Start Date: April 1, 2009; End Date: November 30, 2016
Quebec:	Start Date: [Complete]; End Date: [Complete]
Maritimes:	Start Date: January 01, 2009; End Date: November 30, 2015
GPRD:	Start Date: [Complete]; End Date: [Complete]
CNODES Simulated data:	Start Date: March 31, 2009; End Date: November 30, 2016

E. Covariates

Note: Refining the hd-PS in each jurisdiction **should** be an iterative process. The selection of interaction terms and the functional form of covariates may vary from jurisdiction to jurisdiction. Each jurisdiction is responsible for generating an hd-PS model that achieves an acceptable level of fit and discrimination.

Note on missing data: Do not impute missing values for demographic data. Exclude patients missing sex or age.

***Include covariate data in the propensity score that occurred within 1 year before the Cohort-Entry Date**. For all dimensions, use the same granularity of coding as was used in the statin-AKI analysis, as follows. 4 digit ICD-9 diagnoses and ICD-10 diagnoses, generic name for drugs (non-strength specific, example WHO ATC 5).*

Predefined covariates to ALWAYS be INCLUDED in the propensity score model

1. Demographics (vars_demographic=):

i. Cohort entry year

2. Health care utilization (vars_predefined=):
   i. > 4 distinct drugs (generic chemical name; yes=1 or no=0)
   ii. > 4 diagnoses (yes=1 or no=0)
3. Disease Characteristics:
   i. Hypertensive Disease (ICD9 401.x - 405.x; ICD10 I10.x-I15.x)
   ii. Hypercholesterolemia (ICD9 272.x; ICD10 E78.x)
   iii. Peripheral Vascular Disease (ICD9 443.x; ICD10 I73.x)
   iv. CHF (ICD9 428.x; ICD10 I50.x)
   v. Loop diuretics (All WHO ATC C03CA)
   vi. BMI, if you have it (make note in protocol deviation form)
   vii. Smoking, if you have it (make note in protocol deviation form)

<u>Predefined covariates to ALWAYS be EXCLUDED in the propensity score model</u>

1. The statin on the cohort entry date
2. The Cohort Defining Event (CDE):
   i. MI (Diagnosis = ICD-9: 410.x; or ICD-10 I21.x)
   ii. Stroke (Diagnosis = ICD-9: 433.x, 434.x, 431, 436; or ICD-10 I63.x, I65.x, I66.3, I61.x, I64)

*Note: number 2 above will be included in the outcome models.

F. Outcomes

For all outcomes, the **Event Date** is the date of the outcome (i.e. diagnosis date, death date or drug dispensation date). This date will also be called the **Index Date** for the case and its matched controls.

1. Incident Diabetes:

In the interval defined in *Section D.6.i*:

- One diabetes diagnosis ***or***
- A prescription for insulin or an oral hypoglycemic drug

Diagnostic Codes for Diabetes:

ICD-9	250	Diabetes mellitus
ICD-10	E10	Insulin-dependent diabetes mellitus
	E11	Non-insulin-dependent diabetes mellitus
	E12	Malnutrition-related diabetes mellitus
	E13	Other specified diabetes mellitus
	E14	Unspecified diabetes mellitus

Anti-diabetic Agent ATC Classes:

ATC3	A10A	Insulins and Analogues
ATC_3	A10B	Blood Glucose Lowering Drugs, Excl. Insulins
ATC_3	A10X	Other Drugs Used in Diabetes

2. **Exploratory analysis of All-cause mortality:** Date of death in the interval defined in *Section D.6.i*.

3. **Exploratory analysis of SAE:** The earliest occurrence of death from any cause or MI or stroke, in the interval defined in *Section D.6.i*.

G. Exposures of Interest

The definition of higher dose statin in this protocol is based on summarized results of LDL reductions observed in 164 clinical trials (Law et al., BMJ, 2003). Accordingly, high dose statins will be defined as those which were estimated to reduce LDL cholesterol by >=2 mmol/l on average (≥40% LDL reduction). Those statins were rosuvastatin, atorvastatin, and simvastatin)

High dose statins (HPS): defined as those which were estimated to reduce LDL cholesterol by >=2 mmol/l on average (≥40% LDL reduction). Those statins were rosuvastatin, atorvastatin, and simvastatin)

Lower dose statins (LPS): defined as those which were estimated to reduce LDL cholesterol by <2 mmol/l on average (<40% LDL reduction). (Law et al., BMJ, 2003). Those statins were pravastatin, fluvastatin. We will modify the Law algorithm to also include lovastatin.

Note: make the following modification in your jurisdiction:

If your jurisdiction has days supply data available, for the index prescription, divide quantity dispensed by days supply. If the result is exactly equal to 0.5 then assume the patient is taking half a tablet per day. If the result is exactly 2.0 then assume the patient is taking 2 tablets per day. Categorize to HPS and LPS accordingly.

Eligible statin medications for exposure measurement are listed on the left-hand side of Appendix II. Beware that the list of statins in Appendix II differs from the list of statins used in the cohort entry criteria in that combination statins are allowed after cohort entry.

For HPS and LPS statins, ascertain exposure in 3 intervals as follows (MAKE SURE TO INCLUDE THE STATIN DISPENSED ON THE *COHORT_ENTRY_DATE*).

HD120 = 1 if ≥1 HPS prescriptions were dispensed before or on the Index_Date and after the Index_Date minus 120 days, =0 otherwise;

HD365 = 1 if ≥1 HPS prescriptions were dispensed before or on the Index_Date minus 120 days and after the Index_Date minus 365 days, =0 otherwise;

HD730 = 1 if ≥1 HPS prescriptions were dispensed before or on the Index_Date minus 365 days and after the Index_Date minus 730 days, =0 otherwise;

Note: HD*n* exposures above must be calculated before LD*n* exposures below.

LD120 = 1 if ≥1 LPS prescriptions were dispensed before or on the Index_Date and after the Index_Date minus 120 days, =0 otherwise

If HD120 = 1 then LD120 = 0;

LD365 = 1 if ≥1 LPS prescriptions were dispensed before or on the Index_Date minus 120 days and after the Index_Date minus 365 days, =0 otherwise

If HD365 = 1 then LD365 = 0;

LD730 = 1 if ≥1 LPS prescriptions were dispensed before or on the Index_Date minus 365 days and after the Index_Date minus 730 days, =0 otherwise

If HD730 = 1 then LD730 = 0.

Define exposure categories* (exposure categories are mutually exclusive):

a) ≤120 days current cumulative exposure to HPS* medication (***High_Dose_Statin_120***):
HIGH_DOSE_STATIN_120 = 0;
IF HD120=1 AND HD365=0 THEN HIGH_DOSE_STATIN_120 = 1;

b) ≤120 days current cumulative exposure to LPS* medication (***Low_Dose_Statin_120***):
LOW_DOSE_STATIN_120 = 0;
IF LD120=1 AND LD365=0 THEN LOW_DOSE_STATIN_120 = 1;

c) 121 to 365 days of current cumulative exposure to HPS* medication (***High_Dose_Statin_365***):
HIGH_DOSE_STATIN_365 = 0;
IF HD120=1 AND HD365=1 AND HD730=0 THEN HIGH_DOSE_STATIN_365 = 1;

d) 121 to 365 days of current cumulative exposure to LPS* medication (***Low_Dose_Statin_365***):
LOW_DOSE_STATIN_365 = 0;
IF LD120=1 AND LD365=1 AND LD730=0 THEN LOW_DOSE_STATIN_365 = 1;

e) 366 to 730 days of current cumulative exposure to HPS* medication (***High_Dose_Statin_730***):

HIGH_DOSE_STATIN_730 = 0;
IF HD120=1 AND HD365=1 AND HD730=1 THEN HIGH_DOSE_STATIN_730 = 1;

f) 366 to 730 days of current cumulative exposure to LPS* medication (***Low_Dose_Statin_730***):

LOW_DOSE_STATIN_730 = 0;
IF LD120=1 AND LD365=1 AND LD730=1 THEN LOW_DOSE_STATIN_730 = 1;

g) Past exposure to HPS* medication (***Past_High_Dose_Statin***):

PAST_HIGH_DOSE_STATIN = 0;
IF HD120=0 AND LD120=0 AND HD365=1 THEN PAST_HIGH_DOSE_STATIN = 1;
IF HD120=0 AND LD120=0 AND HD365=0 AND LD365=0 AND HD730=1
THEN PAST_HIGH_DOSE_STATIN = 1;

h) Past exposure to LPS* medication (***Past_Low_Dose_Statin***):

PAST_LOW_DOSE_STATIN = 0;
IF HD120=0 AND LD120=0 AND LD365=1 THEN PAST_LOW_DOSE_STATIN = 1;
IF HD120=0 AND LD120=0 AND HD365=0 AND LD365=0 AND LD730=1
THEN PAST_LOW_DOSE_STATIN = 1;

* There are 6 categories of current exposure and 2 categories of past exposure. Assuming YES=1 and NO=0. Every case and control must contribute to 1 and only 1 exposure category.

Permutations and Categorization of Current Cumulative and Past Statin Exposures

1 to 120 days	121 to 365 days	366 to 730 days	Exposure Categorization
H	H	H	High_Dose_Statin_730
H	H	L	High_Dose_Statin_365
H	H	•	High_Dose_Statin_365
H	L	H	High_Dose_Statin_120
H	L	L	High_Dose_Statin_120
H	L	•	High_Dose_Statin_120
H	•	H	High_Dose_Statin_120
H	•	L	High_Dose_Statin_120
H	•	•	High_Dose_Statin_120
L	H	H	Low_Dose_Statin_120
L	H	L	Low_Dose_Statin_120
L	H	•	Low_Dose_Statin_120
L	L	H	Low_Dose_Statin_365
L	L	L	Low_Dose_Statin_730
L	L	•	Low_Dose_Statin_365
L	•	H	Low_Dose_Statin_120
L	•	L	Low_Dose_Statin_120
L	•	•	Low_Dose_Statin_120
•	H	H	Past_High_Dose
•	H	L	Past_High_Dose
•	H	•	Past_High_Dose
•	L	H	Past_Low_Dose
•	L	L	Past_Low_Dose
•	L	•	Past_Low_Dose
•	•	H	Past_High_Dose
•	•	L	Past_Low_Dose
•	•	•	Not Possible by Cohort Definition

• Means no dispensing

H. Analytic Steps

1. Assemble three study populations as per Sections D-F above: We will essentially be defining three separate case-control populations: 1) Incident diabetes, 2) all-cause mortality, and 3) SAE.

   According to Section G, define each study patient as:

   i. Exposed to HPS medications (binary; Exposure=1) NOTE: For the purpose of calculating the initial propensity scores in the simulated data, follow-up end-date was used in place of index date and a patient was considered exposed to HPS if HD 120=1 or HD365=1 or HD730=1 rather than basing it on first statin prescription), or
   ii. Exposed to LPS medications (binary; Exposure=0)
   iii. Define the **Cohort Entry Date** as the date the patient started a statin after an OVD diagnosis.
   iv. Apply cohort exclusion criteria

2. Generate high dimensional propensity scores for HPS versus LPS statin exposure at cohort entry (note: this only needs to be done ***once*** on the entire nested cohort, but using the primary outcome (diabetes)). We will use the same propensity scores in all five analyses. Use data in the one-year period prior to the Cohort Entry Date. Do not use data from after the end of the CDE episode in the PS model. Trim (i.e. exclude) patients with the bottom 5 percent and top 5 percent of propensity scores (use >5 percent if needed to remove any remaining non-overlap in PS score among HPS and LPS patients).
   i. Generate PS histograms (This should be a single graph where the PS histogram for HPS patients is overlapped on the PS histogram for LPS patients.
   ii. Assign each patient to one of 10 categorical propensity score deciles (PSD1, PSD2, etc.), with a value of 1 for the decile to which they belong, and 0 for the other deciles.
   iii. Assign each patient an ordinal propensity score decile value between 1 and 10 (PSD0)

3. Create binary indicator variables for each type of CDE event. MI=1 if MI, 0 otherwise; Stroke=1 if stroke, 0 otherwise; variables.

4. Compute baseline characteristics of the whole trimmed study populations (**Table 1, 'Full Cohort' columns)**. Use data from up to 1 year before the Cohort Entry Date. For diagnoses, the following diagnostic codes should be used:
   i. Hypertensive Disease (ICD9 401.x - 405.x, ICD10 I10.x-I15.x)
   ii. Hypercholesterolemia (ICD9 272.x, ICD10 E78.x)
   iii. Peripheral Vascular Disease (ICD9 443.x, ICD10 I73.x)
   iv. Congestive Heart Failure (ICD9 428.x, ICD10 I50.x)
   v. Diabetes (ICD9 250.x, ICD10 E10.x, E11.x-E14.x)
   vi. Injury or poisoning (ICD9 800.x - 999.x, ICD10 S00.x - T98.x)

For drug utilization, see the list of drugs in **Appendix III**. For health care utilization in **Table 1**, use the same time periods that were used for generating the HDPS. That is, use the one-year period prior to the Cohort Entry Date.

5. Define the End of Follow Up date for each patient and outcome as per the definition in Section D.4. Note, patients can have up to 3 unique end-of-follow-up dates depending on their outcome pattern.

6. Identify outcome events for each of the 3 analyses. Cases are defined as per Section-F Outcomes.

7. For the analysis of each outcome, match controls to cases as follows:
   Controls will be randomly selected as follows (repeat steps (i) though (v) for each case):

    a. For each case (caco=1), identify all patients, regardless of caco status, who were at-risk of having the event on the case's *Index_Date*. However, patients who became a case on or before the case date are not eligible to be controls.
    b. Generate a random number between 0 and 1 for each patient from (i). For example, the RANUNI function in SAS generates random numbers between 0 and 1 from a uniform distribution. Use a positive, non-zero seed value. If you use a positive seed, you can always replicate the stream of random numbers by using the same DATA step.
    c. Sort all patients from (ii) by ascending random number.
    d. Select as the controls for the case the first 10 non-cases in the sorted list of patients from (iii) who have the same sex, age within ±2 years, and day of cohort entry ±90 days.
        i. (**Note**: For cases where there are fewer than 10 patients in the list to serve as controls (with the same matching factors) then, for those cases, select the whole list)

        ii. (**Note**: For cases where there are no patients in the list to serve as controls (with the same matching factors) then, for those cases, widen the age matching criterion from ±2 years to ±5 years to obtain at least one match to avoid losing the case)

        iii. (**Note**: it is okay if a case serves as another case's control so long as the patient was free of the outcome [i.e. in the risk set] at the time he/she was selected as a control, and only later became a case).

        iv. (**Note**: it is okay if a patient serves as a control for more than one case).

v. (**Note**: If you have carried forward the caco variable, you will need to make sure to change caco to equal 0 if a case is serving as another cases's control (only where it is acting as a control though).)

e. Assign each control within the matched set an *Index_Date* equal to the matched case's *Index_Date*.

f. For each case, assign a matching number (***Match_Num***) to the case and its 10 controls. For example, the first case and 10 matched controls will be assigned a *Match_Num* of 1. The second case and matched controls will be assigned a matching number of 2, etc.

8. Compute baseline characteristics of the study population (x3) at the Cohort Entry Date (**Table 2**). For health care utilization in **Table 2**, use the same time periods that were used for generating the HDPS and for Table 1.

9. Outcome: Estimate odds ratios

i. Create multi-level exposure variable (repeat 3 times, once for each analysis)

```
DATA SD.REGDATA;
SET SD.COHORT_OUTCOME;
STATIN_EXPOSURE=9;
IF HIGH_DOSE_STATIN_120  =1 THEN STATIN_EXPOSURE=1;
IF LOW_DOSE_STATIN_120   =1 THEN STATIN_EXPOSURE=2;
IF HIGH_DOSE_STATIN_365  =1 THEN STATIN_EXPOSURE=3;
IF LOW_DOSE_STATIN_365   =1 THEN STATIN_EXPOSURE=4;
IF HIGH_DOSE_STATIN_730  =1 THEN STATIN_EXPOSURE=5;
IF LOW_DOSE_STATIN_730   =1 THEN STATIN_EXPOSURE=6;
IF PAST_HIGH_DOSE_STATIN =1 THEN STATIN_EXPOSURE=7;
IF PAST_LOW_DOSE_STATIN  =1 THEN STATIN_EXPOSURE=8;
 RUN;
```

ii. Conditional logistic regression (repeat 3 times, once for each analysis)

```
PROC LOGISTIC DATA=sd.REGDATA DESCENDING;
CLASS STATIN_EXPOSURE ;
MODEL OUTCOME =
                        STATIN_EXPOSURE
                        PSD1 PSD2 PSD3 PSD4 PSD6 PSD7 PSD8 PSD9 PSD10
                        STROKE; *PSD5 AND MI EXCLUDED AS THE REFERENCE
                        CATEGORIES;
STRATA MATCH_NUM;
CONTRAST 'HIGH 120 V LOW 120'   STATIN_EXPOSURE  1 -1  0  0  0  0  0 /
ESTIMATE=BOTH;
CONTRAST 'HIGH 365 V LOW 365'   STATIN_EXPOSURE  0  0  1 -1  0  0  0 /
ESTIMATE=BOTH;
```

```
CONTRAST 'HIGH 730 V LOW 730'   STATIN_EXPOSURE  0 0 0 0 1 -1 0 /
ESTIMATE=BOTH;
CONTRAST 'PAST HIGH V PAST LOW' STATIN_EXPOSURE  1 1 1 1 1 1 2 /
ESTIMATE=BOTH;
RUN;
```

Each province to provide logistic regression output from SAS for each outcome model. Output for the outcome models only is required (There is no need to include logistic regression output from propensity score regressions).

Some provinces may be unable to run logistic regressions due to small numbers. When this happens, in place of each logistic regression model compute summary Mantel-Haenszel odds ratios and RGB (Robins-Greenland-Breslow) variances for the natural logs of those summary odds ratios (A SAS template will be provided).

Tables

→ Link to Tables for Analytic Protocol M3.0

Download these Excel tables to output your results (double click on the icon below).

CNODES_Analytic Protocol_Statins DM_1

Appendix I– Exclusion Drugs

C10	**C10**		**LIPID MODIFYING AGENTS**
C10A	C10A		LIPID MODIFYING AGENTS, PLAIN
C10AA	*C10AA*		*HMG CoA reductase inhibitors*
	C10AA01	01	simvastatin
	C10AA02	02	lovastatin
	C10AA03	03	pravastatin
	C10AA04	04	fluvastatin
	C10AA05	05	atorvastatin
	C10AA06	06	cerivastatin
	C10AA07	07	rosuvastatin
	C10AA08	08	pitavastatin
C10AB	*C10AB*		*Fibrates*
	C10AB01	01	clofibrate
	C10AB02	02	bezafibrate
	C10AB03	03	aluminium clofibrate
	C10AB04	04	gemfibrozil
	C10AB05	05	fenofibrate
	C10AB06	06	simfibrate
	C10AB07	07	ronifibrate
	C10AB08	08	ciprofibrate
	C10AB09	09	etofibrate
	C10AB10	10	clofibride
C10AC	*C10AC*		*Bile acid sequestrants*
	C10AC01	01	colestyramine
	C10AC02	02	colestipol
	C10AC03	03	colextran
	C10AC04	04	colesevelam

continued above and to right...

... continued

C10AD	*C10AD*		*Nicotinic acid and derivatives*
	C10AD01	01	niceritrol
	C10AD02	02	nicotinic acid
	C10AD03	03	nicofuranose
	C10AD04	04	aluminium nicotinate
	C10AD05	05	nicotinyl alcohol (pyridylcarbinol)
	C10AD06	06	acipimox
	C10AD52	52	nicotinic acid, combinations
C10AX	*C10AX*		*Other lipid modifying agents*
	C10AX01	01	dextrothyroxine
	C10AX02	02	probucol
	C10AX03	03	tiadenol
	C10AX05	05	meglutol
	C10AX06	06	omega-3-triglycerides incl. other esters and acids
	C10AX07	07	magnesium pyridoxal 5-phosphate glutamate
	C10AX08	08	policosanol
	C10AX09	09	ezetimibe
	C10AX10	10	alipogene tiparvovec
C10B	C10B		LIPID MODIFYING AGENTS, COMBINATIONS
C10BA	*C10BA*		*combination with other lipid modifying agents*
	C10BA01	01	lovastatin and nicotinic acid
	C10BA02	02	simvastatin and ezetimibe
	C10BA03	03	pravastatin and fenofibrate
C10BX	*C10BX*		*HMG CoA reductase inhibitors, other combinations*
	C10BX01	01	simvastatin and acetylsalicylic acid
	C10BX02	02	pravastatin and acetylsalicylic acid
	C10BX03	03	atorvastatin and amlodipine

Appendix II– Exposure Drugs

EXPOSURE DRUGS	
STATINS	
C10AA01	simvastatin
C10AA02	lovastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA07	rosuvastatin
C10BA01*	lovastatin and nicotinic acid
C10BA02*	simvastatin and ezetimibe
C10BA03*	pravastatin and fenofibrate
C10BX01*	simvastatin and acetylsalicylic acid
C10BX02*	pravastatin and acetylsalicylic acid
C10BX03*	atorvastatin and amlodipine

*Combination drugs Cohort Entry Date is an exclusion criterion. However, use of combination statins after cohort entry is allowed and should be measured as exposure in the case control analysis.

Appendix III– Drugs for Baseline Characteristics and Outcomes Tables

Acetaminophen:	WHO ATC N02BE01, 51 and 71
NSAIDs:	All WHO ATC M01A
ACE Inhibitors:	All WHO ATC C09A and C09B
ARBS:	All WHO ATC C09C, C09D and C09X
Diuretics:	All WHO ATC C03
Thiazide Diuretics	All WHO ATC C03A
Loop Diuretics	All WHO ATC C03CA, C03CB01, C03CB02, C03EB01, C03EB02
Potassium Sparing Agents	All WHO ATC C03D and C03E
Other Diuretics	All WHO ATC C03B, C03C (excluding C03CA, C03CB01, C03CB02), C03X
Beta Blockers:	All WHO ATC C07
Calcium Channel Blockers:	All WHO ATC C08
Systemic Antibiotics:	All WHO ATC J01

Appendix IV – Matching Macro

Click on the file icon below to download the SAS matching macro (double click on the icon below).