Protocol and Statistical Analysis Plan for the CACD1 Study

This document has been prepared in accordance with the guidelines proposed by Yuan et al. (1).

1. SAP Version, Date, and Reason for Revision

Version #2: January 22, 2026

2. Study Title

Value of Coronary Artery Calcium Scoring for Guiding Statin Prescription in Primary Prevention Among Young Patients with Type 1 Diabetes

3. Study Acronym

CACD1

4. SAP Contributors, Roles, and Responsibilities

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5. Background and Rationale

Type 1 diabetes (T1D) accounts for approximately 5–10% of all diabetes cases (2), and its incidence continues to increase. In 2021, approximately 8.5 million people worldwide were living with T1D. The projected prevalence is expected to increase from 13.5 to 17.4 million by 2040 (3,4).

T1D is associated with reduced life expectancy and healthy life expectancy (5). Approximately one-third of this reduction is attributable to cardiovascular disease (CVD), which becomes the leading cause of death among patients with T1D after 20 years of disease duration, with an annual mortality rate of approximately 3% (6).

Accordingly, the latest ESC/EAS guidelines classify patients with T1D younger than 35 years as follows:

- Moderate cardiovascular risk for diabetes duration <10 years without additional cardiovascular risk factors;
- High cardiovascular risk for diabetes duration ≥10 years;
- Very high cardiovascular risk for diabetes duration ≥20 years.

These recommendations define progressively lower LDL cholesterol targets as cardiovascular risk increases and therefore support statin therapy when LDL cholesterol exceeds the recommended threshold. Coronary artery calcium (CAC) scoring, obtained from a non-contrast, low-radiation cardiac CT scan, is an effective complementary tool for cardiovascular risk assessment in primary prevention (7). This reproducible technique provides a more individualized assessment of cardiovascular risk and may help refine long-term statin prescribing decisions.

6. Study Design

Single-center, cross-sectional, interventional diagnostic study.

7. Primary Objective and Primary Endpoint

The primary objective is to evaluate the proportion of patients for whom the indication for statin therapy in primary prevention would change when cardiovascular risk is assessed using the coronary artery calcium (CAC) score instead of the 2019 ESC/EAS recommendations in patients aged 18–35 years with type 1 diabetes. According to the 2019 ESC/EAS Guidelines (8), statin therapy is recommended for the following categories:

1 Moderate cardiovascular risk
   - Age <35 years
   - Diabetes duration <10 years
   - No additional cardiovascular risk factors
   - LDL cholesterol target <1.0 g/L
2 High cardiovascular risk
   - Diabetes duration >10 years
   - No target-organ damage
   - No additional cardiovascular risk factors
   - LDL cholesterol target <0.7 g/L
3 Very high cardiovascular risk
   - Diabetes duration >20 years,
   - Presence of target-organ damage,
   - or more than three major cardiovascular risk factors (history of hypertension, dyslipidemia, current smoking, obesity/overweight, or premature family history of cardiovascular disease),
   - LDL cholesterol target <0.55 g/L.

According to the 2021 consensus statement from the French Societies of Cardiology and Diabetology (9), for patients younger than 50 years, cardiovascular risk categories are instead based on the coronary artery calcium (CAC) score:

1 Moderate cardiovascular risk
   - CAC ≤10
   - LDL cholesterol target <1.0 g/L
2 High cardiovascular risk
   - CAC 11–100
   - LDL cholesterol target <0.7 g/L
3 Very high cardiovascular risk
   - CAC >100
   - LDL cholesterol target <0.55 g/L

A modified indication for statin therapy (primary endpoint) will be considered when:

(i) the patient meets one of criteria a1–a3 but none of criteria b1–b3, corresponding to a false-positive recommendation (unnecessary statin prescription); or

(ii) the patient meets none of criteria a1–a3 but meets one of criteria b1–b3, corresponding to a false-negative recommendation (failure to prescribe statins when indicated).

8. Secondary Objective and Associated Endpoint

Few, if any, false-negative classifications are expected. We aim to develop an easy-to-use clinical tool that does not require systematic measurement of the coronary artery calcium (CAC) score, thereby reducing the number of false-positive classifications.

The secondary objective is to develop a prediction score based on clinical and biological parameters that identifies patients who would be recommended for statin therapy according to the CAC score.

9. Inclusion Criteria

Participants must meet all of the following criteria:

1. Age between 18 and 35 years, inclusive.
2. Diagnosis of type 1 diabetes, defined by positive T1D-specific autoantibodies or onset during childhood.
3. Eligible for primary cardiovascular prevention (no previous cardiovascular event).
4. Not currently receiving statin therapy.
5. Duration of diabetes greater than 5 years.
6. Use of a continuous glucose monitoring (CGM) system for at least the previous 14 days.
7. Covered by the French National Health Insurance system, either directly or through a third party.
8. Provision of written informed consent to participate in the study.

10. Non-Inclusion Criteria

Participants meeting any of the following criteria will not be eligible:

1. Secondary cardiovascular prevention (history of a previous cardiovascular event).
2. Electrocardiographic abnormalities suggestive of myocardial ischemia.
3. Contraindication or intolerance to statin therapy.
4. Individuals belonging to a protected population, including:
    - minors;
    - individuals deprived of liberty by judicial or administrative decision;
    - persons residing in healthcare or social care institutions;
    - adults under legal protection.
5. Pregnant or breastfeeding women.

11. Sample Size Calculation

Based on the available medical records, the prevalence of a change in the indication for statin therapy was estimated at 40%. Assuming a 95% confidence interval and an absolute precision of 10%, approximately 92 evaluable patients are required. To account for missing data, unevaluable records, and losses to follow-up, a total sample size of 100 patients has been planned.

12. Interim Analysis

No interim analysis is planned.

13. Study Timeline

- Inclusion period: 36 months.
- Participant follow-up duration: 1 day.
- Total study duration: 26 months and 1 day.

14. Participant Withdrawal and Data Follow-up

Participants may be withdrawn prematurely from the study for the following reasons:

- Withdrawal of informed consent;
- Any reason considered by the investigator to be in the participant's best interest.

The investigator will document the reasons for premature discontinuation. The date and reason for study withdrawal will be recorded in both the participant's medical record and the case report form (CRF). Participants withdrawn from the study will not be replaced.

15. Description of the Study Population

A participant flow diagram will be constructed according to the inclusion and non-inclusion criteria and the final analysis population. Because the proportion of missing data is expected to be very low, complete-case analyses will be performed. Patients with missing data for any variable defining categories a1–a3 or b1–b3, as well as patients who withdraw their consent during the study, will be excluded from the analysis population.

16. Significance Level

Statistical significance will be declared for two-sided p-values <0.05.
All hypothesis tests will be two-sided, and 95% two-sided confidence intervals will be reported.

17. Type I Error Control (Multiplicity)

No adjustment for multiplicity will be applied; therefore, no correction for inflation of the type I error rate is planned.

18. Subgroup Analyses and Interaction Tests

No subgroup analyses or interaction tests are planned.

19. Assessment of Potential Selection Bias Due to Complete-Case Analysis

A first table will describe and compare the characteristics of the complete-case analysis population and the excluded patients. Continuous variables will be summarized using means and standard deviations, whereas categorical variables will be summarized using counts and percentages. The following categorical variables will be described:

- Sex (male/female)
- Current smoking (yes/no)
- Family history of premature coronary artery disease (yes/no)
- Overweight (yes/no)
- Obesity (yes/no)
- Diabetic retinopathy (yes/no)
- Diabetic neuropathy (yes/no)
- Diabetic nephropathy (yes/no)
- Positive spot urine microalbuminuria (yes/no)
- Antidiabetic treatment (multiple daily injections or insulin pump)
- Coronary artery calcium (CAC) score category ($\leq$10, 11–100, >100)

The following continuous variables will be described:

- Body mass index (kg/m²)
- Duration of diabetes (years)
- HbA1c (%)
- Total cholesterol (g/L)
- HDL cholesterol (g/L)
- LDL cholesterol (g/L)
- Serum creatinine (µmol/L)
- Estimated glomerular filtration rate (eGFR, MDRD equation; mL/min/1.73 m²)
- Spot urine microalbuminuria (mg/L)
- Continuous glucose monitoring (CGM) metrics over the preceding 14 days:

Time in Range (%)
Time Above Range (%)
Time Below Range (%)
Coefficient of Variation (%)

P-values will be reported without adjustment for multiple testing, given the descriptive nature of these analyses Categorical variables will be compared using the Chi-square test (or Fisher's exact test when the expected cell count is less than five). Continuous variables will be compared using Student's t-test (or the Wilcoxon rank-sum test if the total sample size across the two groups is less than 30).

20. Baseline Characteristics

A second table will describe and compare the baseline characteristics listed above for the overall analysis population; and according to the primary endpoint (change in the indication for statin therapy: yes/no).

21. Description of the Primary Endpoint

A third contingency table (3 × 3) will present the number of patients according to the cross-classification between categories a1–a3 and b1–b3.

A fourth contingency table (2 × 2) will summarize the numbers and proportions of true positives, true negatives, false positives, and false negatives, using the recommendations from the French Societies of Cardiology and Diabetology as the reference standard ("gold standard").

22. Evaluation of Discriminative Performance

A multinomial logistic regression model will be developed to predict the cardiovascular risk category defined by the coronary artery calcium (CAC) score (three categories: CAC ≤10, 11 ≤ CAC ≤100, and CAC >100) using the following clinical characteristics of patients with type 1 diabetes:

- age;
- sex;
- duration of diabetes;
- body mass index;
- blood pressure;
- dyslipidemia;
- smoking status;
- family history of premature coronary artery disease;
- presence of microvascular complications;
- HbA1c;
- antidiabetic treatment modality;
- continuous glucose monitoring (CGM) metrics collected during the preceding 14 days.

The assumption of log-linearity will first be assessed, and the transformation of each continuous predictor minimizing the Bayesian Information Criterion (BIC) will be retained. Predictor selection will subsequently be performed using a backward stepwise selection procedure. The discriminative performance of the final model will be assessed using the Volume Under the ROC Surface (VUS)for three-class classification (10), with correction for optimism by bootstrap cross-validation (11). For each validation sample (subjects not included in the bootstrap sample), the proportions of false-negative and false-positive classifications will be estimated both

for the proposed prediction model and for the 2019 ESC/EAS recommendations. A statistically significant reduction in the false-positive rate would provide internal validation of the proposed prediction tool.

23. References

1. Yuan I, Topjian AA, Kurth CD, Kirschen MP, Ward CG, Zhang B, et al. Guide to the statistical analysis plan. Paediatr Anaesth. mars 2019;29(3):237-42.

2. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014 Jan 4;383(9911):69-82. doi: 10.1016/S0140-6736(13)60591-7. Epub 2013 Jul 26. PMID: 23890997; PMCID: PMC4380133

3. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010 Sep;39(3):481-97. doi: 10.1016/j.ecl.2010.05.011. PMID: 20723815; PMCID: PMC2925303

4. Cai X, Li J, Cai W, Chen C, Ma J, Xie Z, Dong Y, Liu C, Xue R, Zhao J. Meta-analysis of type 1 diabetes mellitus and risk of cardiovascular disease. J Diabetes Complications. 2021 Apr;35(4):107833. doi: 10.1016/j.jdiacomp.2020.107833. Epub 2021 Jan 2. PMID: 33514477.

5. Rawshani A, Sattar N, Franzén S, Rawshani A, Hattersley AT, Svensson AM, Eliasson B, Gudbjörnsdottir S. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet. 2018 Aug 11;392(10146):477-486. doi: 10.1016/S0140-6736(18)31506-X. Epub 2018 Aug 9. PMID: 30129464; PMCID: PMC6828554.

6. Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, Magge SN, Marx N, McGuire DK, Orchard TJ, Zinman B, Eckel RH. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2014 Oct;37(10):2843-63. doi: 10.2337/dc14-1720. Epub 2014 Aug 11. PMID: 25114297; PMCID: PMC4170130.

7. Mortensen MB, Dzaye O, Steffensen FH, Bøtker HE, Jensen JM, Rønnow Sand NP, Kragholm KH, Sørensen HT, Leipsic J, Mæng M, Blaha MJ, Nørgaard BL. Impact of Plaque Burden Versus Stenosis on Ischemic Events in Patients With Coronary Atherosclerosis. J Am Coll Cardiol. 2020 Dec 15;76(24):2803-2813. doi: 10.1016/j.jacc.2020.10.021. PMID: 33303068

8. Cosentino F, Grant P, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. ESC Scientific Document Group. Eur Heart J 2020;41:255-323 9. Valensi P, Henry P, et al. Risk stratification and screening for coronary artery disease in asymptomatic patients with diabetes mellitus: Position paper of the French Society of Cardiology and the French-speaking Society of Diabetology. Diabetes Metab. 2021 Mar;47(2):101185. doi: 10.1016/j.diabet.2020.08.002. Epub 2020 Aug 23. PMID: 32846201.

10. Waegeman W, Baets BD, Boullart L. On the scalability of ordered multi-class ROC analysis. Computational Statistics & Data Analysis. 2008;52(7):3371-88. 11. Schomaker M, Heumann