

BACKGROUND

- Coronary Artery Disease (CAD) is the leading cause of death worldwide.
- Clinical risk scores, such as Atherosclerotic Cardiovascular Disease Pooled Cohort Equations (ASCVD-PCE), are used routinely in primary prevention to identify individuals at elevated CAD risk and guide preventive interventions.
- Polygenic risk scores (PRS) can enhance the precision of clinical risk scores, especially for individuals with uncertain (borderline/intermediate) clinical risk, but the evidence supporting their utility in primary prevention is limited.
- We developed a cross-ancestry PRS model for CAD and integrated it with the Pooled Cohort Equations (PCE), a standard clinical tool used to predict the risk of atherosclerotic cardiovascular disease (ASCVD), to derive the caIRS, which estimates 10-year absolute CAD risk.
- In order to assess the utility of the caIRS model in primary prevention of CAD:
  - We retrospectively validated the performance of the caIRS in comparison to the standard of care ASCVD-PCE model using the diverse, US based Penn Medicine Biobank (PMBB) cohort.
  - Designed and initiated a randomised clinical trial to assess the impact of returning the caIRS based risk estimates on patient outcomes and management.

METHODS

**Retrospective model validation**

We validated the performance of the caIRS in comparison to ASCVD-PCE model among **14182** PMBB participants (**1158** incident cases):

- eligible for risk assessment using the ASCVD-PCE model
- with no history of CAD or CAD diagnosis within 30 days from enrollment
- not using cholesterol lowering medication

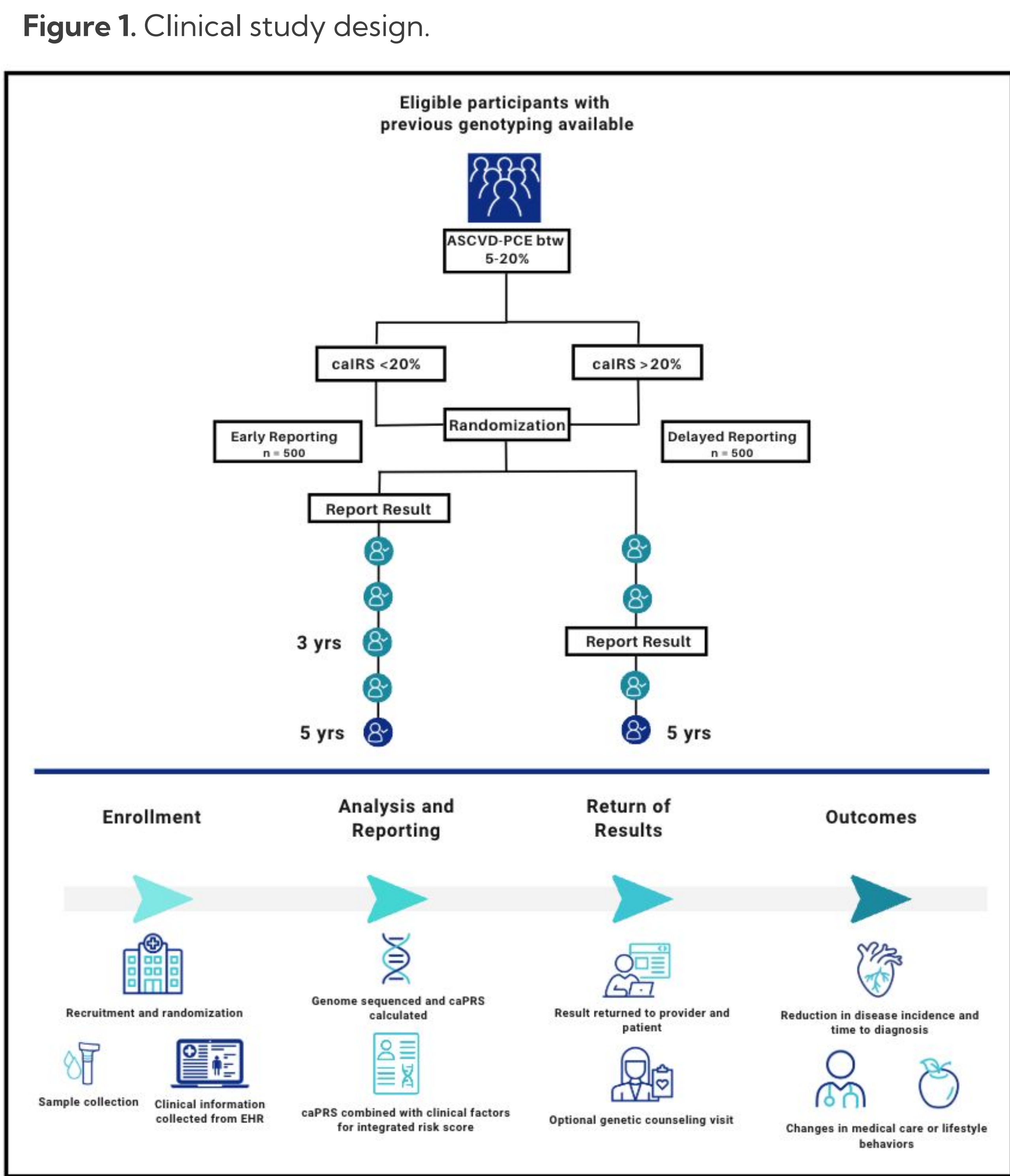
We compared the classification performance of the ASCVD-PCE and caIRS in predicting incident CAD by using 20% as a high risk threshold and assessed the reclassification of individuals at uncertain clinical risk (borderline/intermediate category; 5–20% ASCVD-PCE) risk using caIRS.

**Prospective clinical study**

The clinical study will recruit 1000 CAD-free participants with borderline/intermediate clinical risk (ASCVD-PCE: 5–20%) across 3 US health centers.

Participants will be stratified into high (≥20%) and average (<20%) risk categories using caIRS and randomised into early (2–3 months) and delayed (3 years) reporting arms.

CAD incidence, statin use and lab results will be tracked over 5 years to evaluate the impact of elevated caIRS score on disease incidence, lifestyle behaviours and changes in medical care.



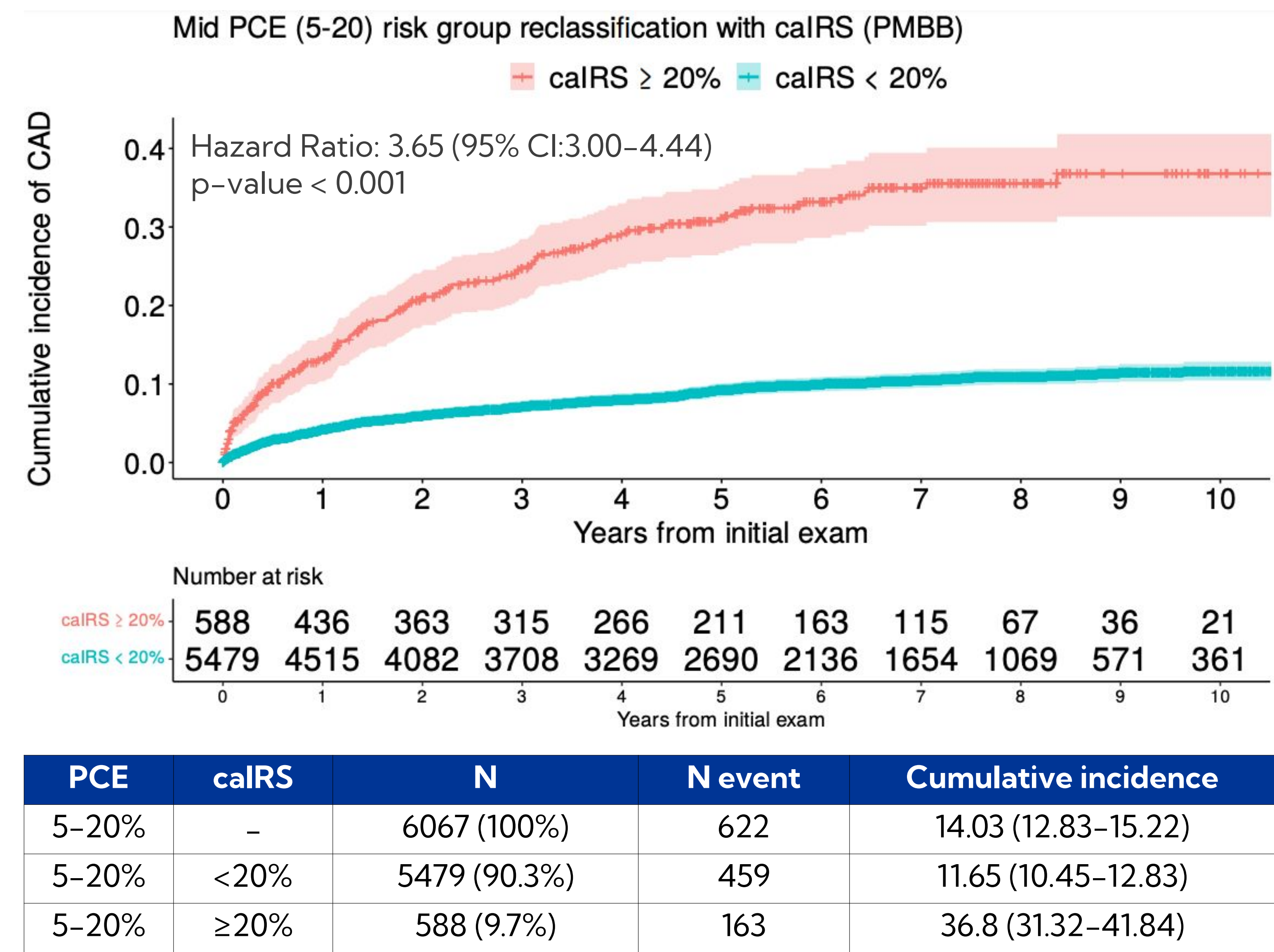
Integrating CAD PRS with clinical risk scores enhances the identification of individuals at high risk and has the potential to increase the effectiveness of primary prevention

RESULTS

**Table 1.** Comparative performance of the PCE and caIRS in the PMBB cohort. The Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Net Reclassification Improvement (NRI) values correspond to the 20% risk classification threshold.

| Model | NRI               | Sensitivity | Specificity | PPV  | NPV  | C-index             |
|-------|-------------------|-------------|-------------|------|------|---------------------|
| PCE   | –                 | 29.4        | 91.3        | 23.1 | 93.6 | 0.732 (0.719–0.746) |
| caIRS | 9.08 (6.63–11.59) | 39          | 90.8        | 27.4 | 94.4 | 0.761 (0.747–0.774) |

**Figure 2.** 10-year cumulative incidence of CAD among PMBB individuals identified as borderline or intermediate risk using PCE and those reclassified into high and low risk groups by caIRS with the corresponding 10-year cumulative incidence rates (+/- 95% CI), counts of individuals (N) and events (N event) for each group.



CONCLUSIONS AND FUTURE DIRECTIONS

- Retrospective validation study of the CAD caIRS score, which combines genetic and traditional clinical risk factors, demonstrated the potential to refine clinical risk estimates and improve treatment guidance in a primary prevention setting.
- The results from the (on-going) prospective trial will provide further insights into how the integration of genetic risk factors into routine CAD risk assessment, using the caIRS model, influences long-term cardiovascular outcomes and personalized treatment strategies.