Development of Cardiovascular Risk Equations: Clinical Expertise x Data from the SELECT Trial

MSR73

A. B. Bojesen[1], M. Bøg[1], M. Ivkovic[1]
[1] Novo Nordisk A/S, Denmark

Introduction

Cost-effectiveness models (CEMs) for cardiovascular therapies typically require long-term predictions derived from clinical trial data. To address evidence gaps, CEMs incorporate risk equations for specific clinical outcomes, balancing statistical rigor with clinical relevance.

Objective: to derive equations for the risk of acute coronary syndrome (ACS*) and stroke based on the SELECT[2] trial data.

*ACS: myorcardial infarction or unstable angina

Methods

Using a prospective cohort design, we estimated risk equations from SELECT trial data for ACS and stroke outcomes. Expert elicitation identified and prioritized risk factors for the SELECT population.

Clinical experts ranked potential risk factors by importance, followed by discussions to incorporate their insights. We used a least absolute shrinkage and selection operator (LASSO) approach combined with clinical input to identify predictors based on both clinical and statistical relevance.

Cox regression was used for development, then final models were refitted with appropriate parametric models for long-term extrapolation. Only risk factor observations at trial baseline were used.

The SELECT trial

A multicentre, double-blind, randomised, placebo-controlled, event-driven superiority trial with 17,604 participants.

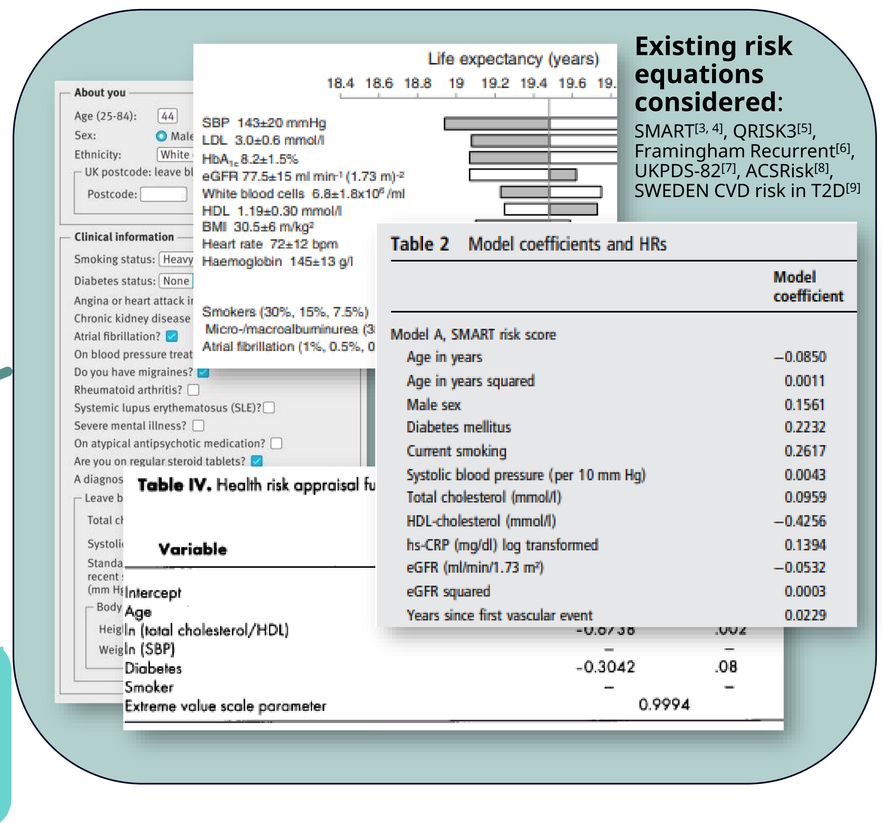
Intervention:
Once-weekly semaglutide 2.4 mg subcutaneous vs. placebo

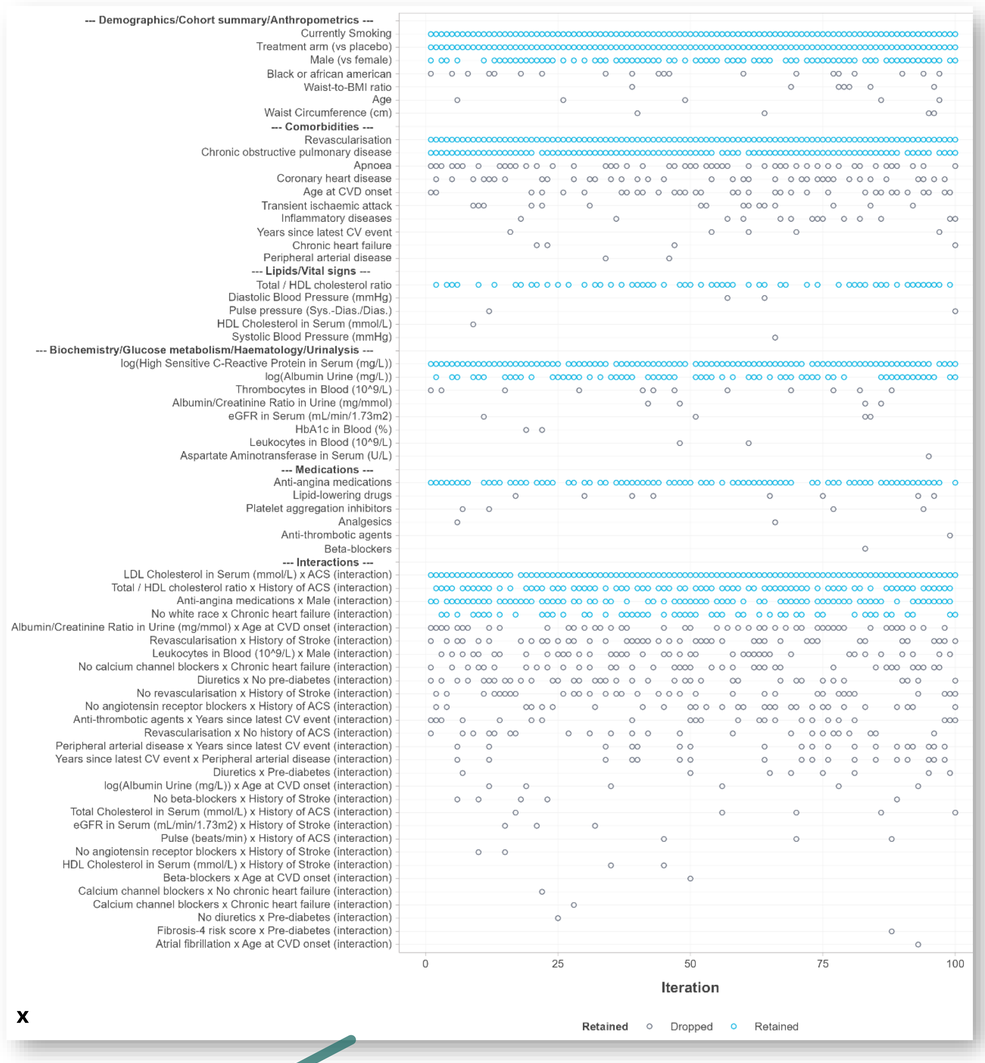
Key Inclusion Criteria:
✓ Age ≥45 years
✓ BMI ≥27 kg/m²
✓ Prior myocardial infarction or prior stroke or peripheral arterial disease

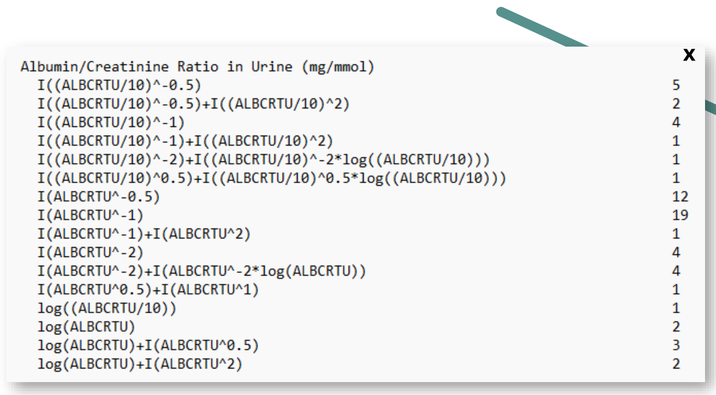
Key Exclusion Criteria:
✗ HbA1c ≥48 mmol/mol (≥6.5%)
✗ History of type 1 or type 2 diabetes
✗ Recent CV events (<60 days before screening)

Risk factor pool:
- Exisiting risk equations
- Pragmatic literature review
- Highlighted by clinicians

Ranking of risk factors by clinicians







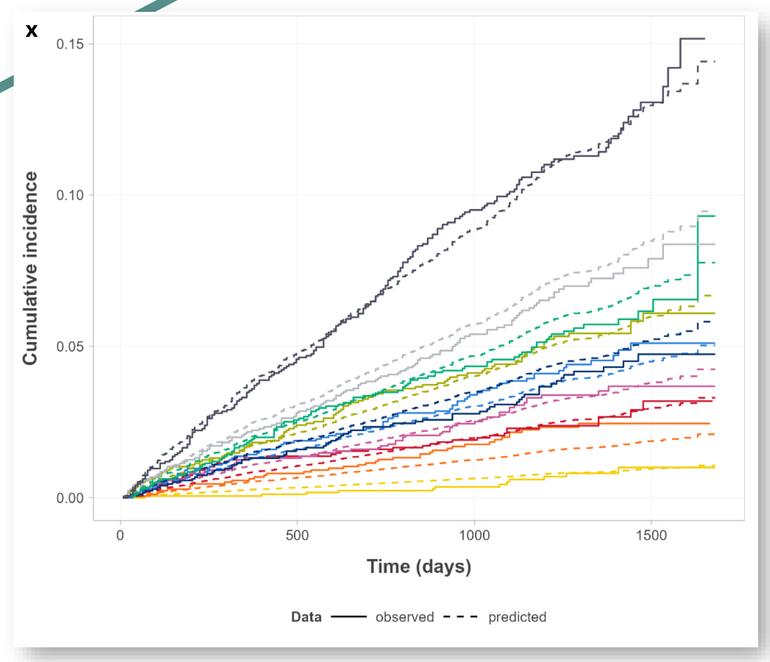
```
Albumin/Creatinine Ratio in Urine (mg/mmol)                          x
  I((ALBCRTU/10)^-0.5)                                               5
  I((ALBCRTU/10)^-0.5)+I((ALBCRTU/10)^2)                             2
  I((ALBCRTU/10)^-1)                                                 4
  I((ALBCRTU/10)^-1)+I((ALBCRTU/10)^2)                               1
  I((ALBCRTU/10)^-2)+I((ALBCRTU/10)^-2*log((ALBCRTU/10)))            1
  I((ALBCRTU/10)^0.5)+I((ALBCRTU/10)^0.5*log((ALBCRTU/10)))          1
  I(ALBCRTU^-0.5)                                                   12
  I(ALBCRTU^-1)                                                     19
  I(ALBCRTU^-1)+I(ALBCRTU^2)                                         1
  I(ALBCRTU^-2)                                                      4
  I(ALBCRTU^-2)+I(ALBCRTU^-2*log(ALBCRTU))                           4
  I(ALBCRTU^0.5)+I(ALBCRTU^1)                                        1
  log((ALBCRTU/10))                                                  1
  log(ALBCRTU)                                                       2
  log(ALBCRTU)+I(ALBCRTU^0.5)                                        3
  log(ALBCRTU)+I(ALBCRTU^2)                                          2
```

Development process

x Illustrated using results for ACS

Candidate risk factors
→ Transformations
→ Interactions/Stratification
→ Proportionality
→ Selection (*LASSO penalisation + bootstrapping*)
→ Review by clinicians
→ Final model (*estimation, fit evaluation*)

Clinical review of preliminary risk equations considered the clinical rationale for predictors, with suggestions to add or remove predictors as well as discussions on functional forms and the composition of the trial population.



Final models

Predictors	ACS	Stroke
TREATMENT		
Semaglutide 2.4 mg	✓	✓
DEMOGRAPHICS		
Age	✓	✓
Sex (Male)	✓	
CARDIOVASCULAR HISTORY		
Apnoea	✓	
History of ACS	✓	
Coronary heart disease	✓	
Prior revascularisation	✓	
History of stroke		✓
History of TIA		✓
Cerebrovascular disorder		✓
Atrial fibrillation		✓
COPD	✓	
CLINICAL MEASUREMENTS		
Systolic blood pressure		✓
Total/HDL cholesterol ratio	✓	
log(hsCRP)	✓	
LIFESTYLE FACTORS		
Current smoking	✓	
MEDICATIONS		
Anti-angina medications	✓	
INTERACTIONS		
Angina medications × Male	✓	
Total / HDL cholesterol ratio × History of ACS	✓	
Platelet aggregation inhibitors × No stroke		✓

Conclusion

We developed robust risk equations for cardiovascular events from the SELECT trial by integrating clinical expertise throughout the process.

The modelling approach combined robust statistical approaches (cause-specific, Cox proportional hazards models, LASSO penalisation, and bootstrapping) with expert clinical knowledge, resulting in parsimonious, representative, and clinically valid risk equations. This collaborative approach aligns with CEM requirements in HTA settings while emphasizing clinical validity. To enhance the validity and transparency of future risk equations that rely on clinical expertise, it is essential for risk factors to be consistently measured and reported in clinical trials.

The risk equations can be applied in long-term health economic models or in general models for population-level risk.

References

This study: M. Bøg et al: “Development of SELECT trial-based cardiovascular risk equations”, in review in PharmacoEconomics.
[2] Lincoff AM et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med [Internet]. 2023 Dec 14;389(24):2221–32.
[3] Dorresteijn JAN et al. Development and validation of a prediction rule for recurrent vascular events based on a cohort study of patients with arterial disease: the SMART risk score. Heart [Internet]. 2013 Apr 10;99(12):866–72.
[4] Klooster CC van et al. Predicting 10-year risk of recurrent cardiovascular events and cardiovascular interventions in patients with established cardiovascular disease: results from UCC-SMART and REACH. International Journal of Cardiology [Internet]. 2021 Feb;325:140–8.
[5] Hippisley-Cox J et al. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ [Internet]. 2017 May 23;j2099.
[6] Agostino RB et al. Primary and subsequent coronary risk appraisal: New results from The Framingham Study. American Heart Journal [Internet]. 2000 Feb;139(2):0272–81.
[7] Hayes AJ et al. UKPDS Outcomes Model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia [Internet]. 2013 June 22;56(9):1925–33.
[8] Steen DL et al. Event Rates and Risk Factors for Recurrent Cardiovascular Events and Mortality in a Contemporary Post Acute Coronary Syndrome Population Representing 239 234 Patients During 2005 to 2018 in the United States. JAHA [Internet]. 2022 May 3;11(9).
[9] Cederholm J et al. Risk Prediction of Cardiovascular Disease in Type 2 Diabetes. Diabetes Care [Internet]. 2008 Oct 1;31(10):2038–43.

Presenter: Anders Bo Bojesen, Clinical Data Science Specialist, Launch Evidende Generation & Orchestration, qabj@novonordisk.com