

Come stimare il rischio cardiovascolare nel DMT2

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Department of Systems Medicine

Center for Atherosclerosis
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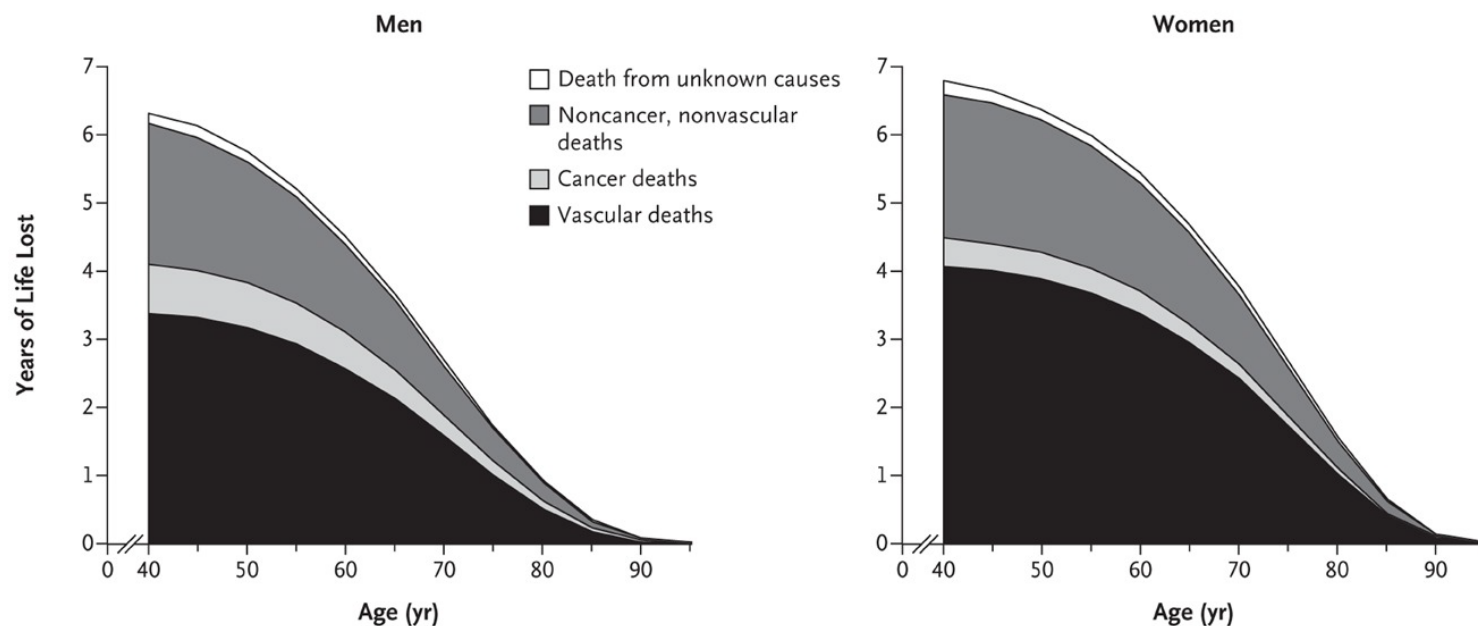


Massimo Federici

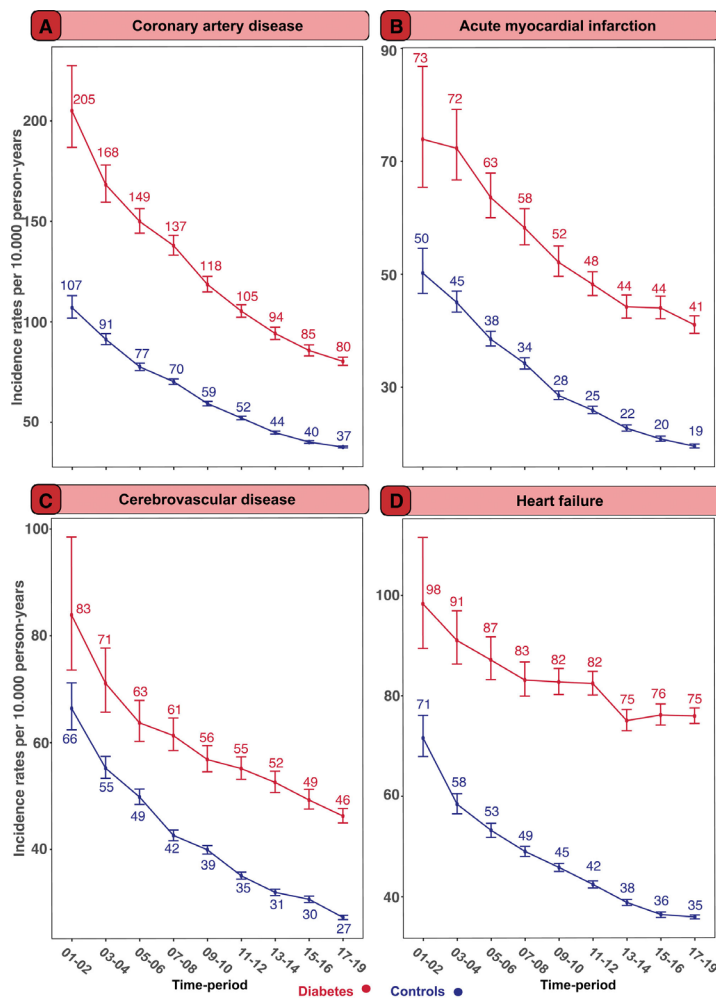
- received unrestricted research grant by EFSD/Sanofi initiative;
- has given lectures for Novo Nordisk, Lilly & Co, Boehringer Ingelheim, Daiichi-Sankyo, Amgen, and Merck Sharp & Dohme;
- and has served as an advisor for Novo Nordisk, Lilly & Co, Boehringer Ingelheim, Amarin, Amgen, Merck Sharp & Dohme, and Organon;
- all fees were approved by the University of Rome Tor Vergata (according to Italian law n. 165/2001, art. 53)

Type 2 diabetes and life expectancy

On average, type 2 diabetes reduces life expectancy by ~6 years



Katpoge S et al, *NEJM* 2011

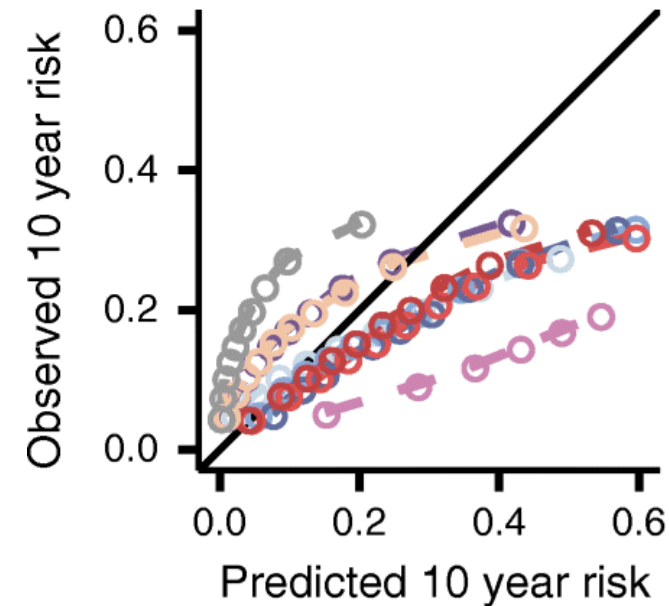
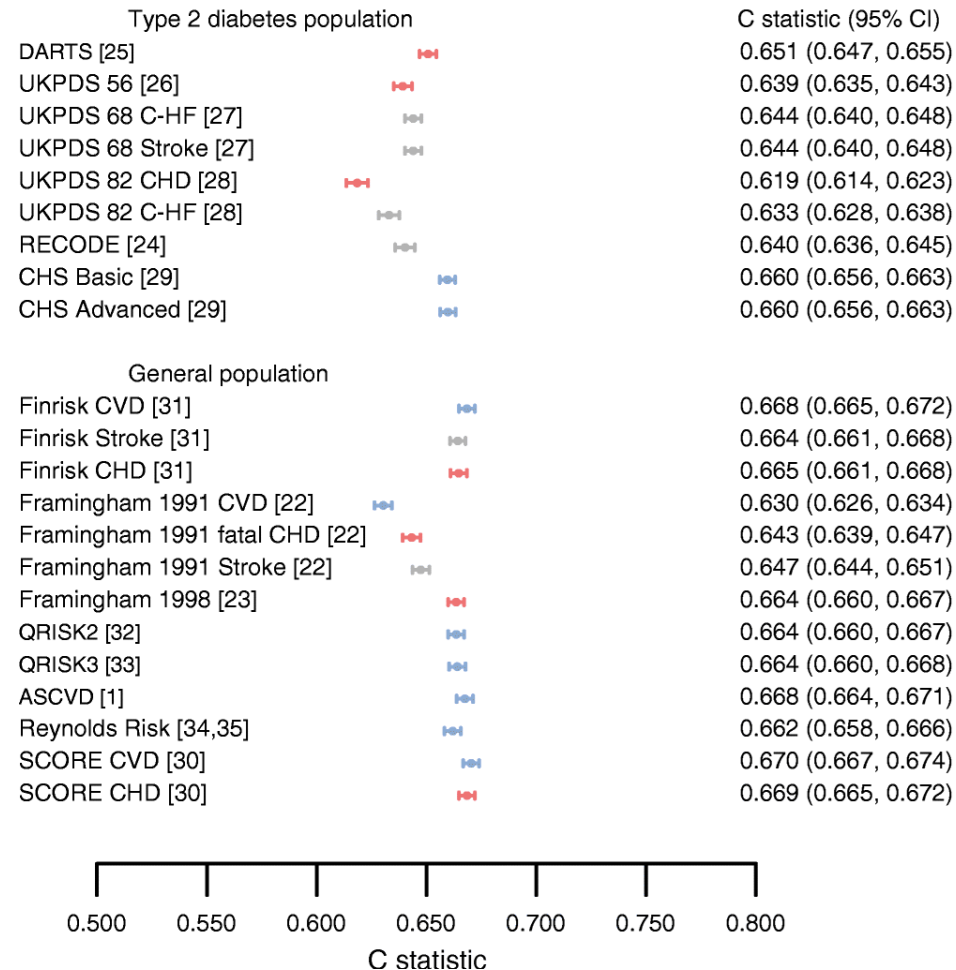


Diabetes-specific risk prediction models

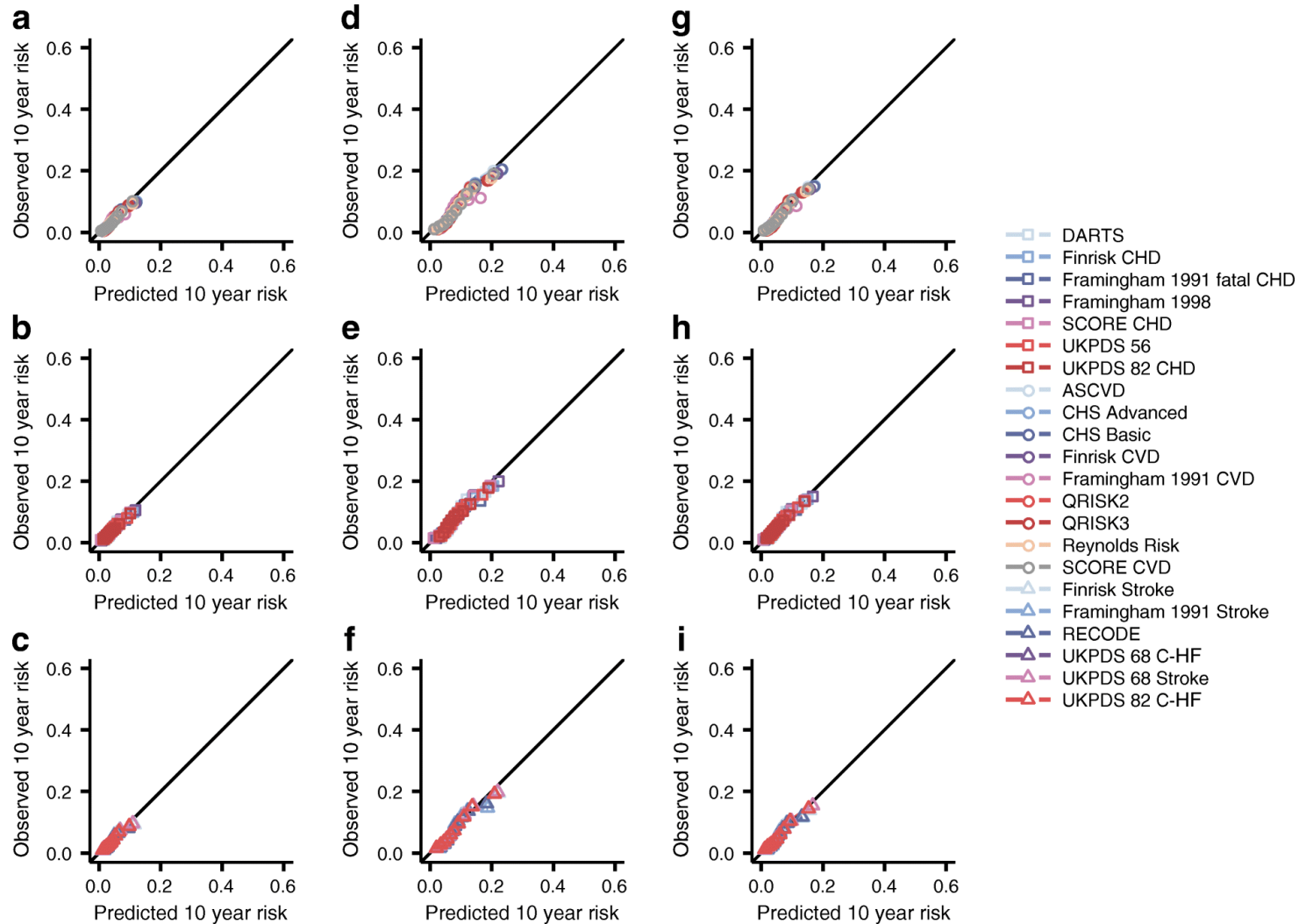
- Risk models help refine CVD risk estimations and identify patients who will benefit most from treatment
- Include duration of diabetes, glycated haemoglobin (HbA1c), and TOD
- Examples are:
 - ADVANCE predicts 4-year CVD risk
 - UKPDS predicts CVD risk in the UK
 - DIAL prediction of life-time risk

**Limitations: based on older cohort data,
not geographically recalibrated**

Good discrimination but poor calibration of CVD risk prediction tools in type 2 diabetes



Improved performance after “re-calibration”



Development process and key features of SCORE2

1. Model development

Sex-specific, competing risk-adjusted risk models derived in 45 prospective cohorts in 13 countries (~680,000 individuals, and ~30,000 CVD events)



Recalibration to four risk regions in Europe using age-, sex-, and region-specific risk factor values and CVD incidence rates (derived using data on ~10.8 million individuals)



2. Model validation

External validation in 25 prospective cohorts in 15 European countries (~1.1 million individuals, and ~43,000 CVD events)



C-indices ranged from 0.67 (95% confidence interval [CI] 0.65-0.68) to 0.81 (95% CI 0.76-0.86)

SCORE2 risk prediction algorithms key features



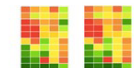
Sex-specific risk prediction models



Estimate 10-year risk of fatal and non-fatal CVD



Calibrated to the most contemporary and representative CVD rates



Available for four distinct European risk regions



Can be rapidly updated to reflect future CVD incidence and risk factor profiles

Individual example

Patient risk factors:

50 years old

Smoker

SBP: 140 mmHg

Cholesterol: 5.5 mmol/L

HDL-c: 1.3 mmol/L

10-year risk depending on risk region

Female				Male			
Low risk	Moderate risk	High risk	Very high risk	Low risk	Moderate risk	High risk	Very high risk
4.2%	5.1%	6.9%	13.7%	5.9%	7.5%	8.1%	14.0%

SCORE2-Diabetes: a risk tool for T2D

Development process

Original SCORE2 algorithms:

Predictors: age, sex, smoking, diabetes, SBP, total and HDL cholesterol

Calibrated to predict CVD risk in:

low, moderate, high and very high risk regions of Europe



Adaptation of SCORE2 for individuals with type-2 diabetes:

Added predictors: age at diabetes diagnosis, HbA1c and eGFR

→ SCORE2-Diabetes

Data used: 229,460 individuals with type-2 diabetes from electronic health records, diabetes registry, cohort studies



Validation of SCORE2-Diabetes:

External validation in 217,036 individuals with type-2 diabetes from Sweden, Spain, Malta and Croatia



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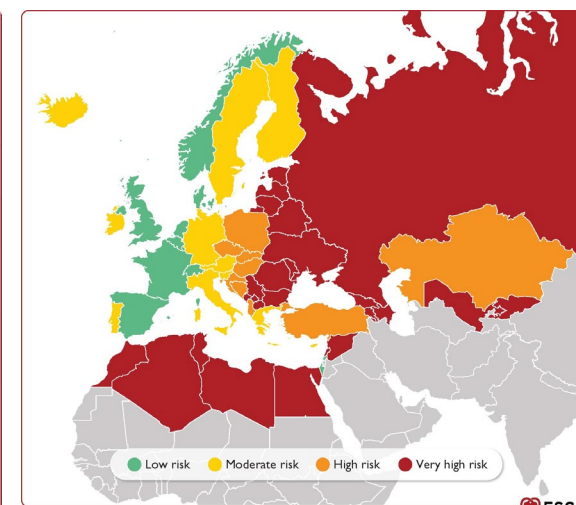
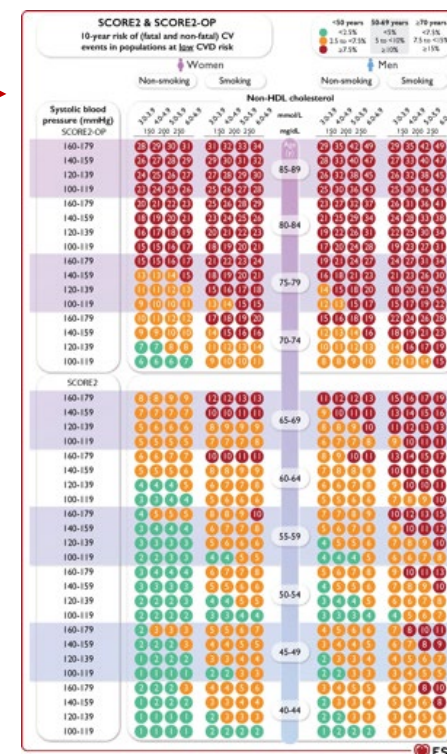


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SCORE2 10-year risk of (fatal and non-fatal) CV events



SCORE2-Diabetes

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CPRD

ERFC



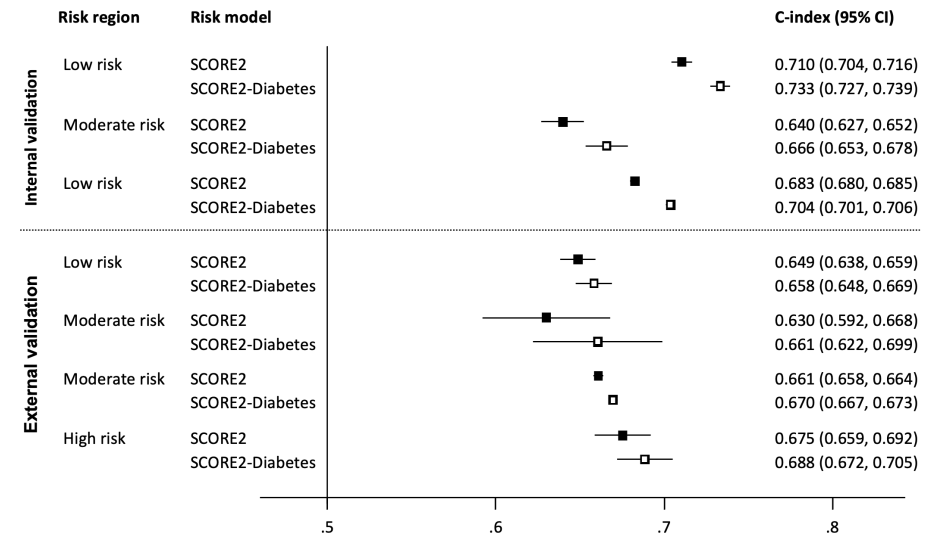
~230K individual with type 2 diabetes and information on age at diagnosis, HbA1c and eGFR



SCORE2-Diabetes

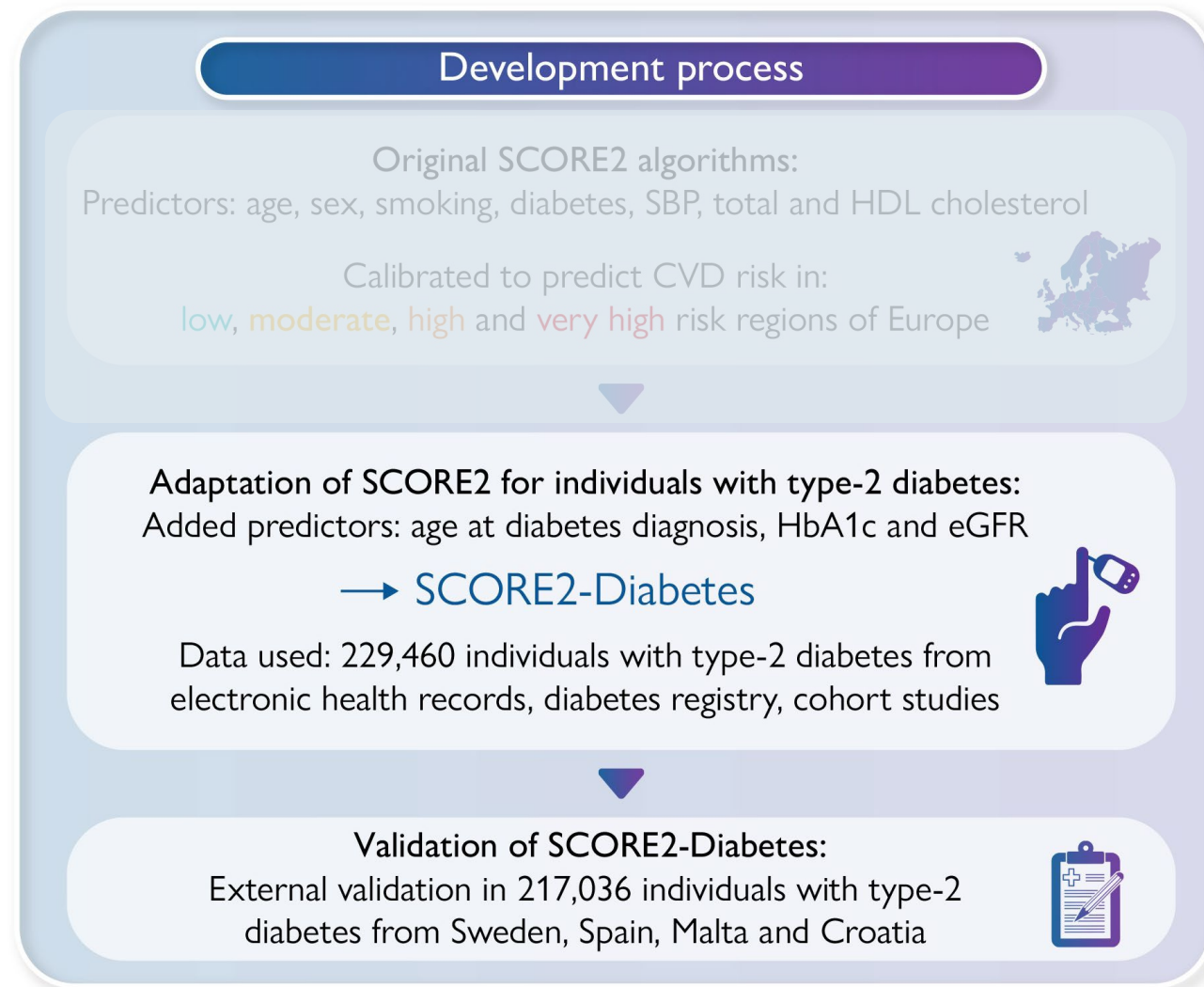


Internal and external validation across Europe



Pennells L et al, Eur Heart J 2023 Eur Heart J. 2023 Jul 21;44(28):2544-2556

SCORE2-Diabetes: a risk tool for T2D



CPRD

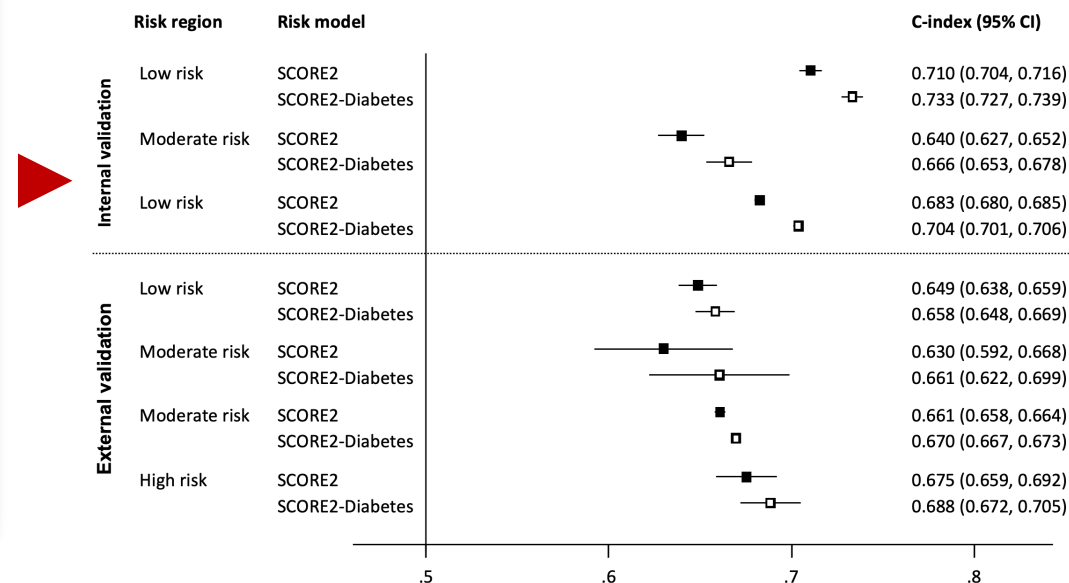
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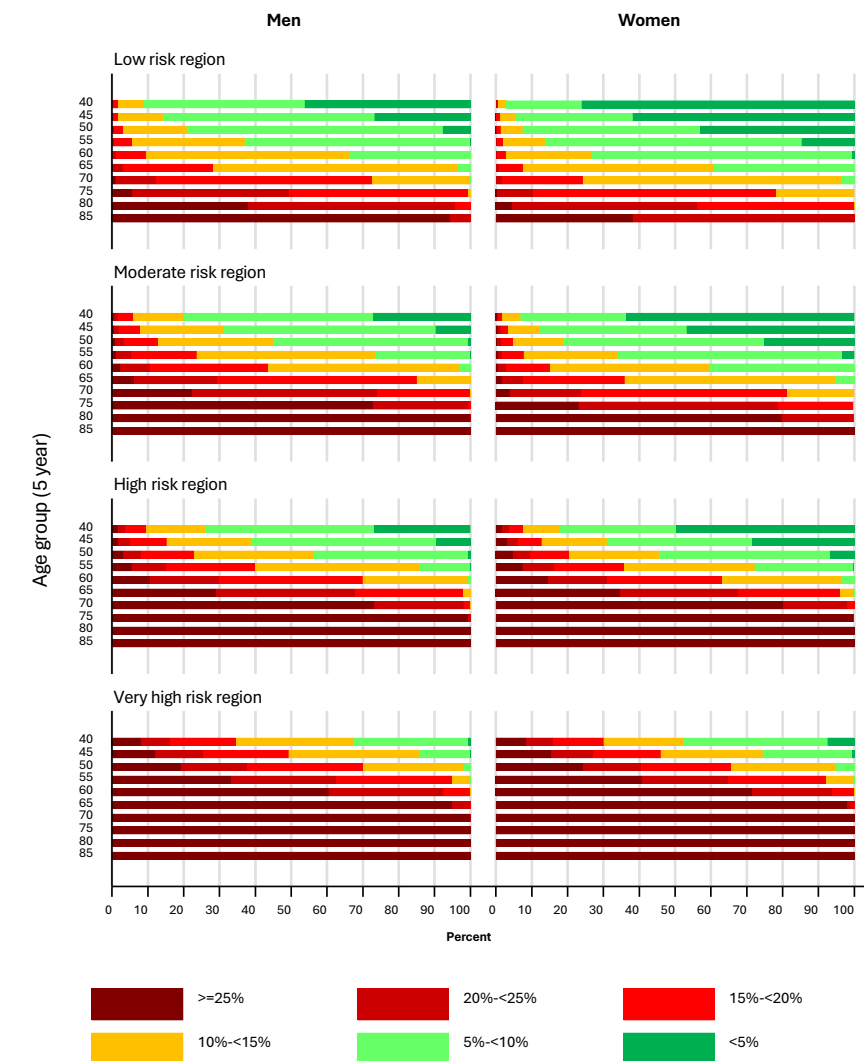


Validation of SCORE2-Diabetes:

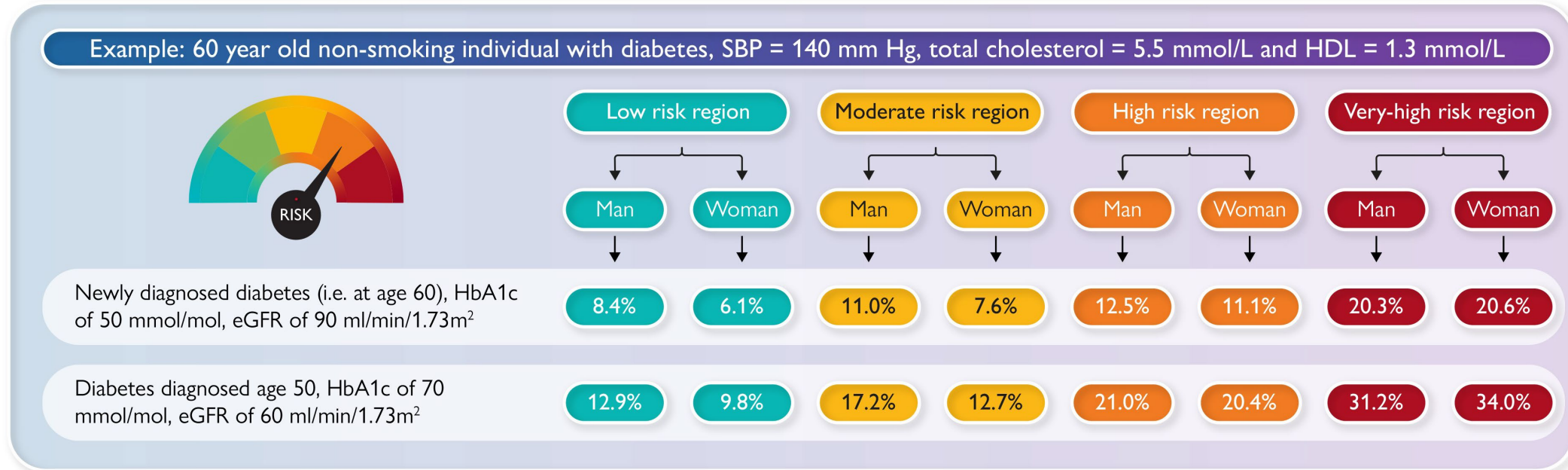
External validation in 217,036 individuals with type-2 diabetes from Sweden, Spain, Malta and Croatia



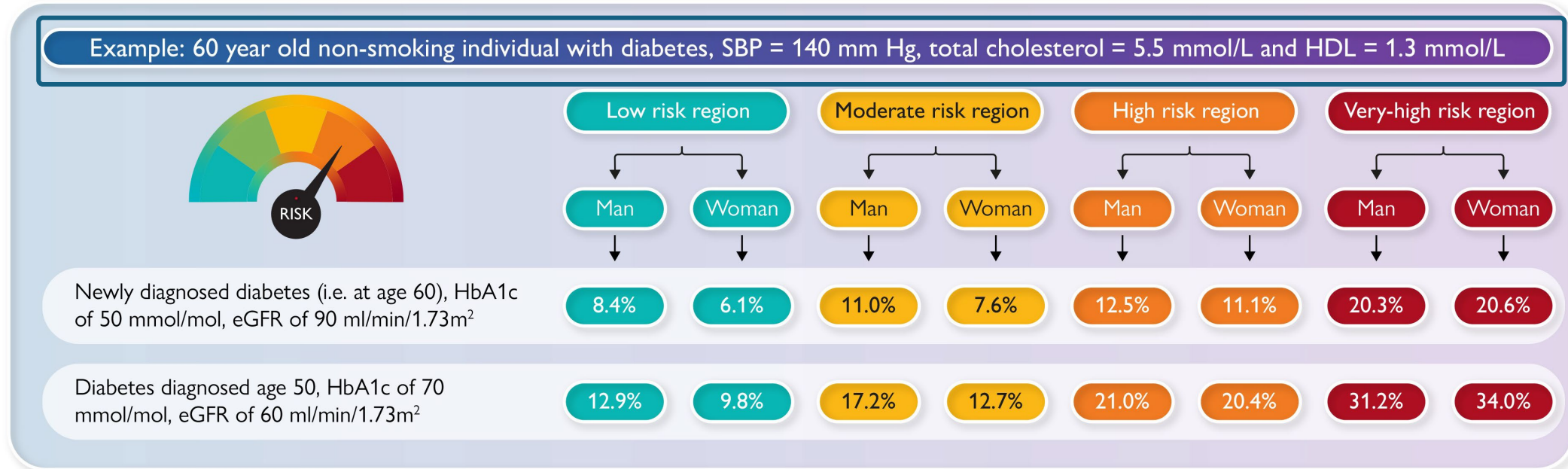
Expected CVD risk distribution across Europe



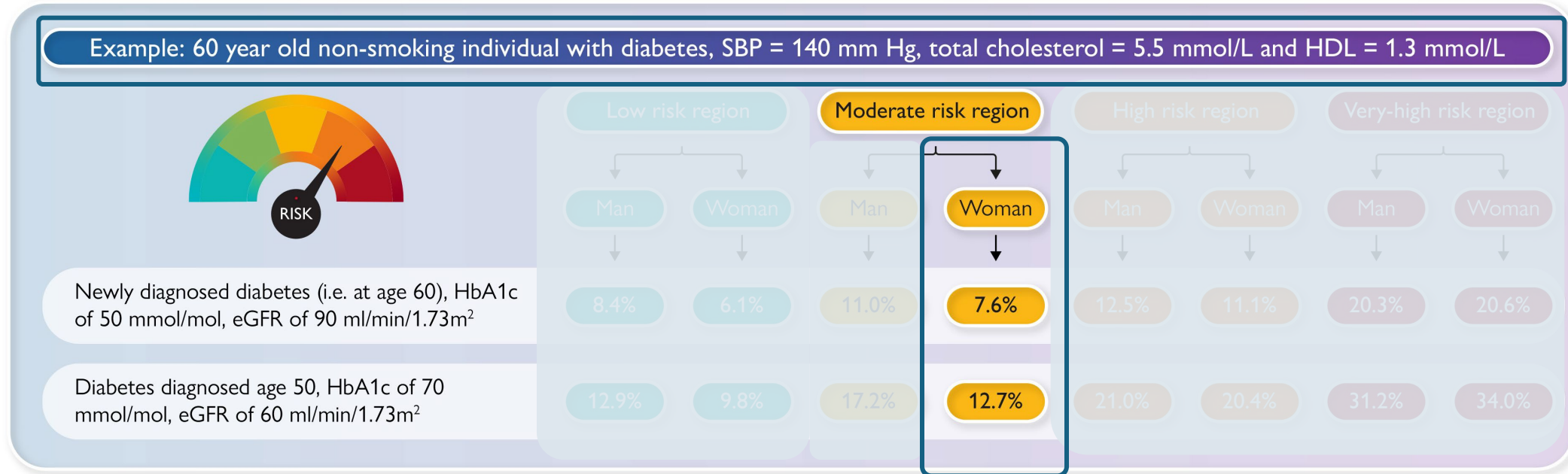
SCORE2-Diabetes: example of risk estimation



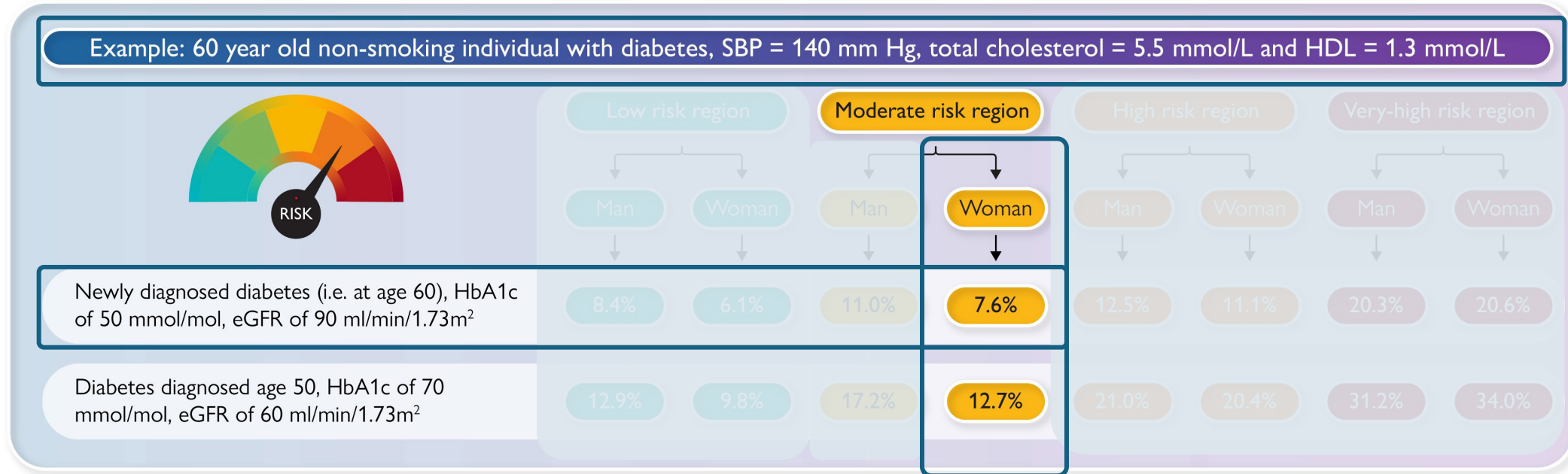
SCORE2-Diabetes: example of risk estimation



SCORE2-Diabetes: example of risk estimation



SCORE2-Diabetes: example of risk estimation



SCORE2-Diabetes: example of risk estimation

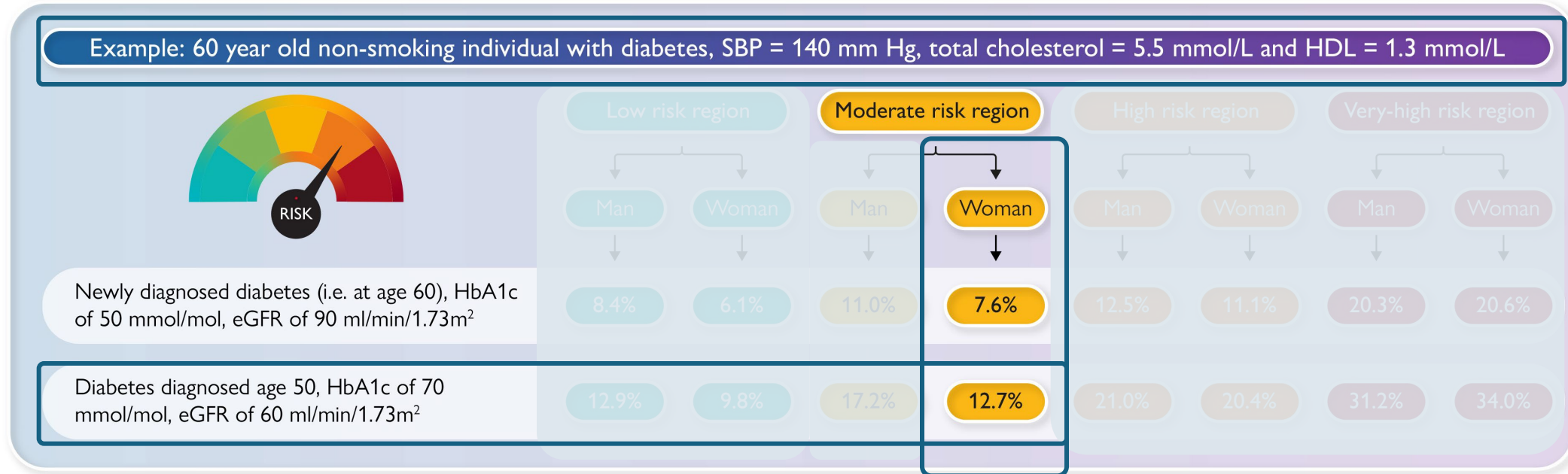
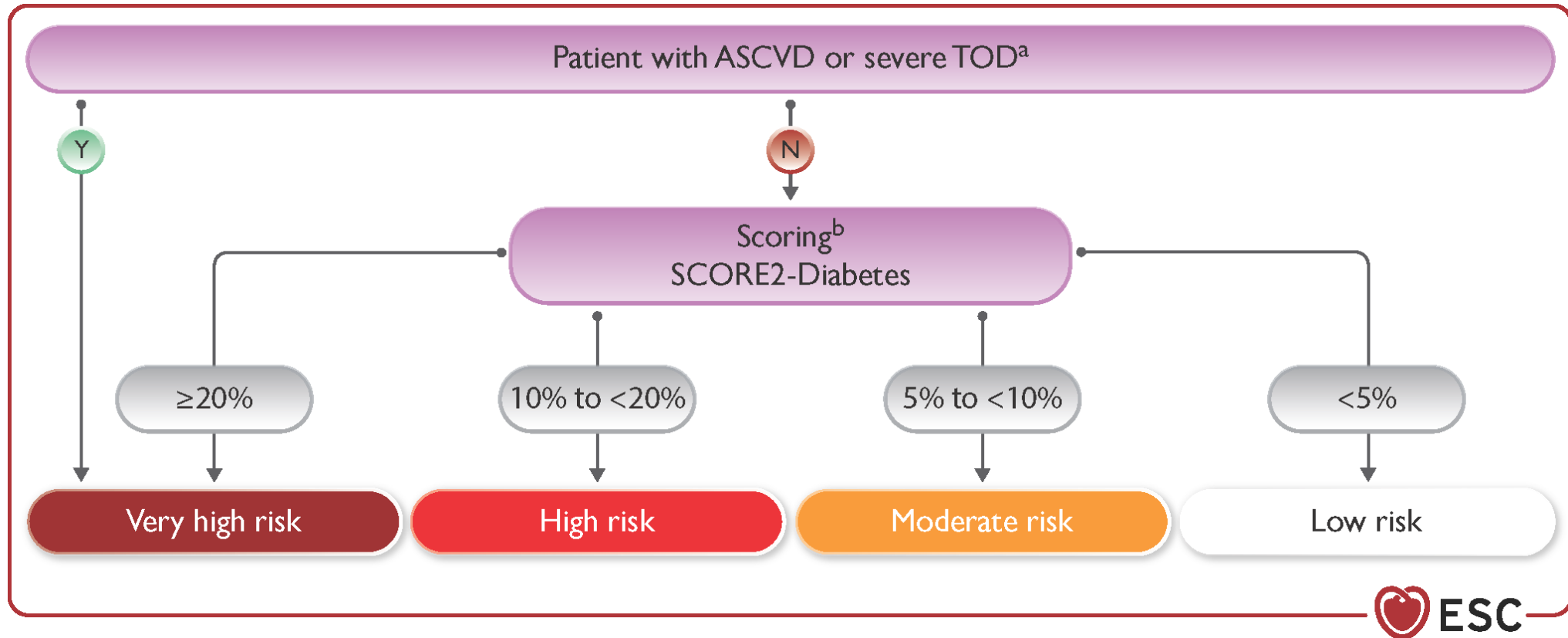


Figure 3

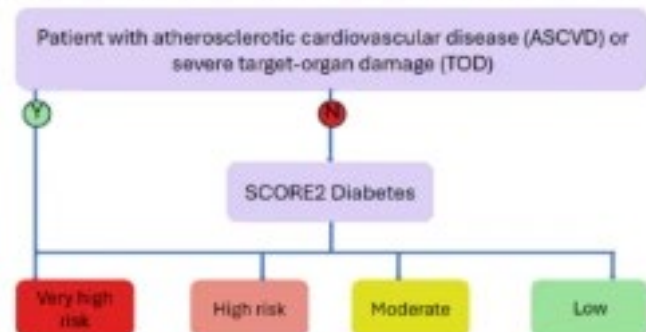
Cardiovascular risk categories in patients with type 2 diabetes



Cardiovascular risk profile in subjects with diabetes: is SCORE2-Diabetes reliable?

Background

People living with type 2 diabetes are at a two- to four-fold higher risk of developing cardiovascular (CV) disease, making early assessment of their CV risk essential



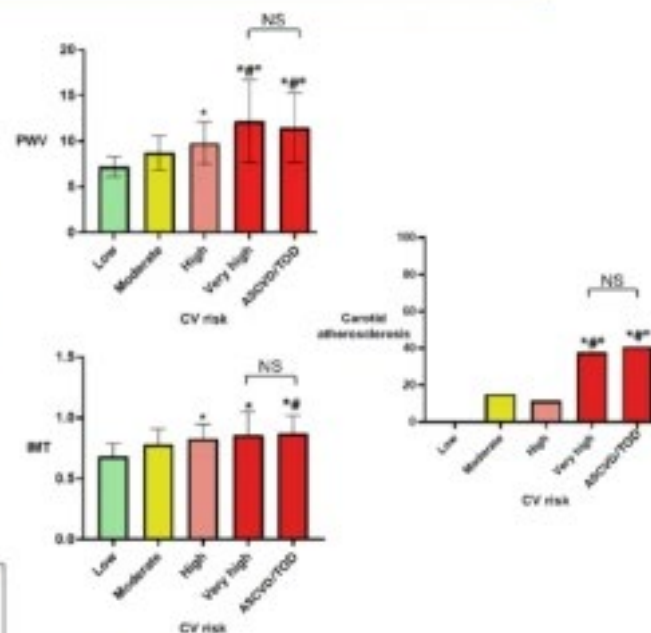
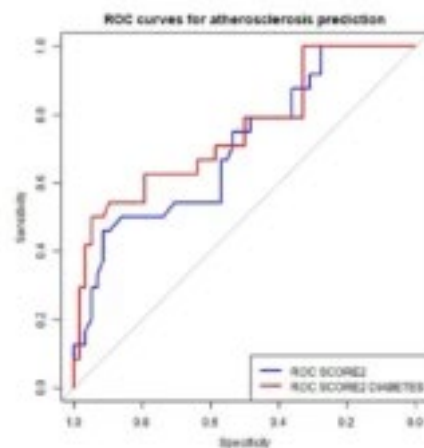
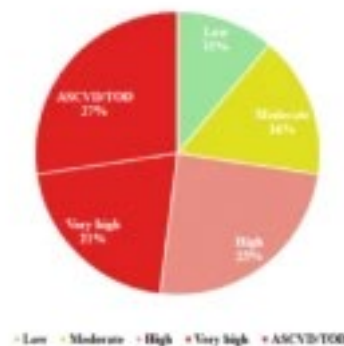
Adapted from "2023 ESC guidelines for management of cardiovascular disease in patients with diabetes"

Methods

-  179 participants
-  Intima-Media Thickness (IMT) and carotid atherosclerosis
-  Arterial stiffness (Pulse Wave Velocity, PWV)
-  SCORE2 Diabetes

Results

SCORE2 Diabetes



PWV, IMT and carotid atherosclerosis were significantly increased from Low to Very high and ASCVD/TOD groups

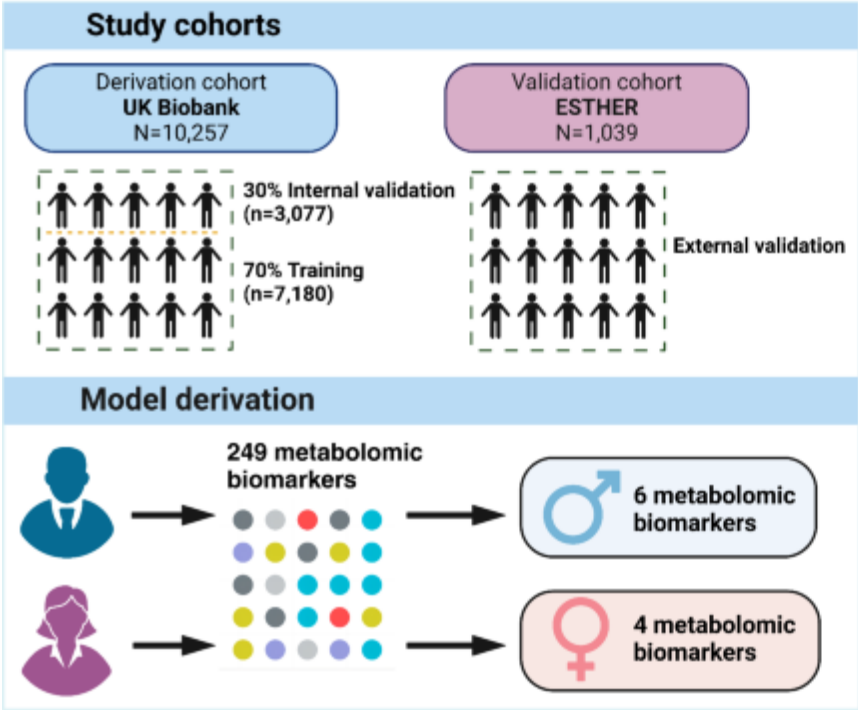


No significant differences were found between the Very High and ASCVD/TOD groups in any parameter



SCORE2-Diabetes had superior predictive performance for carotid atherosclerosis and high PWV compared to SCORE2

Improving 10-year cardiovascular risk prediction in patients with type 2 diabetes with metabolomics



Performance evaluations

Base model:
SCORE2-Diabetes

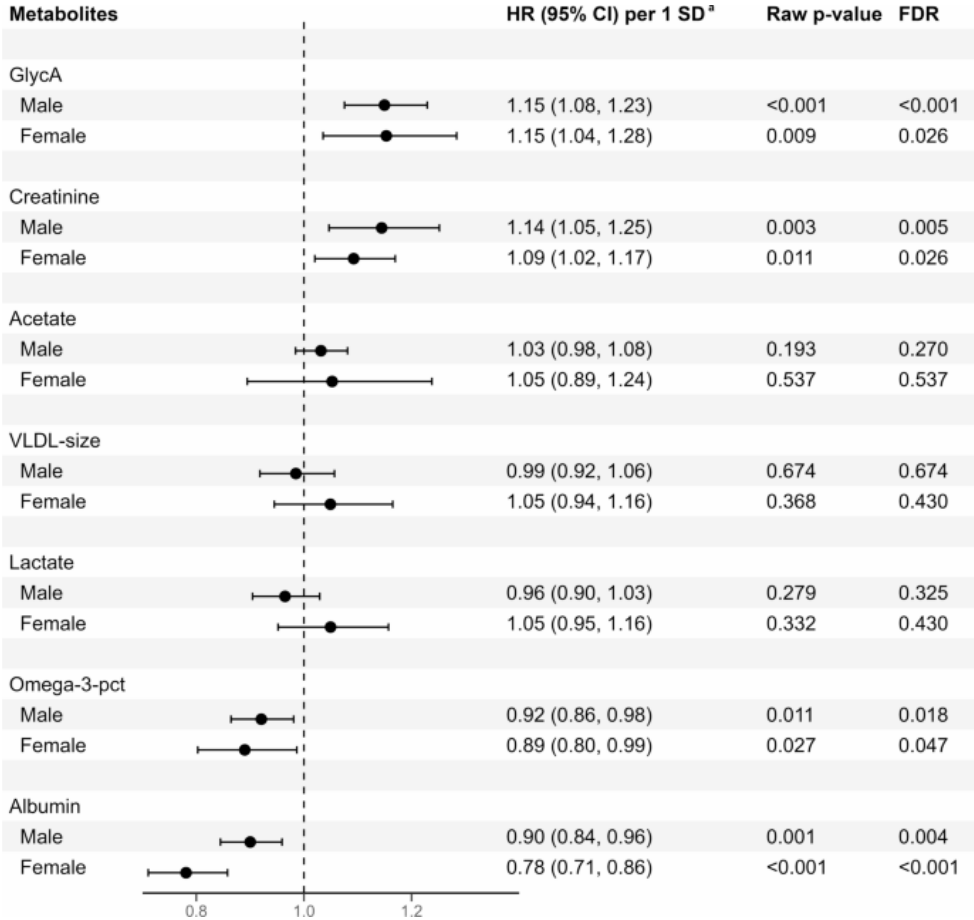
Outcomes:
10-year MACE risk

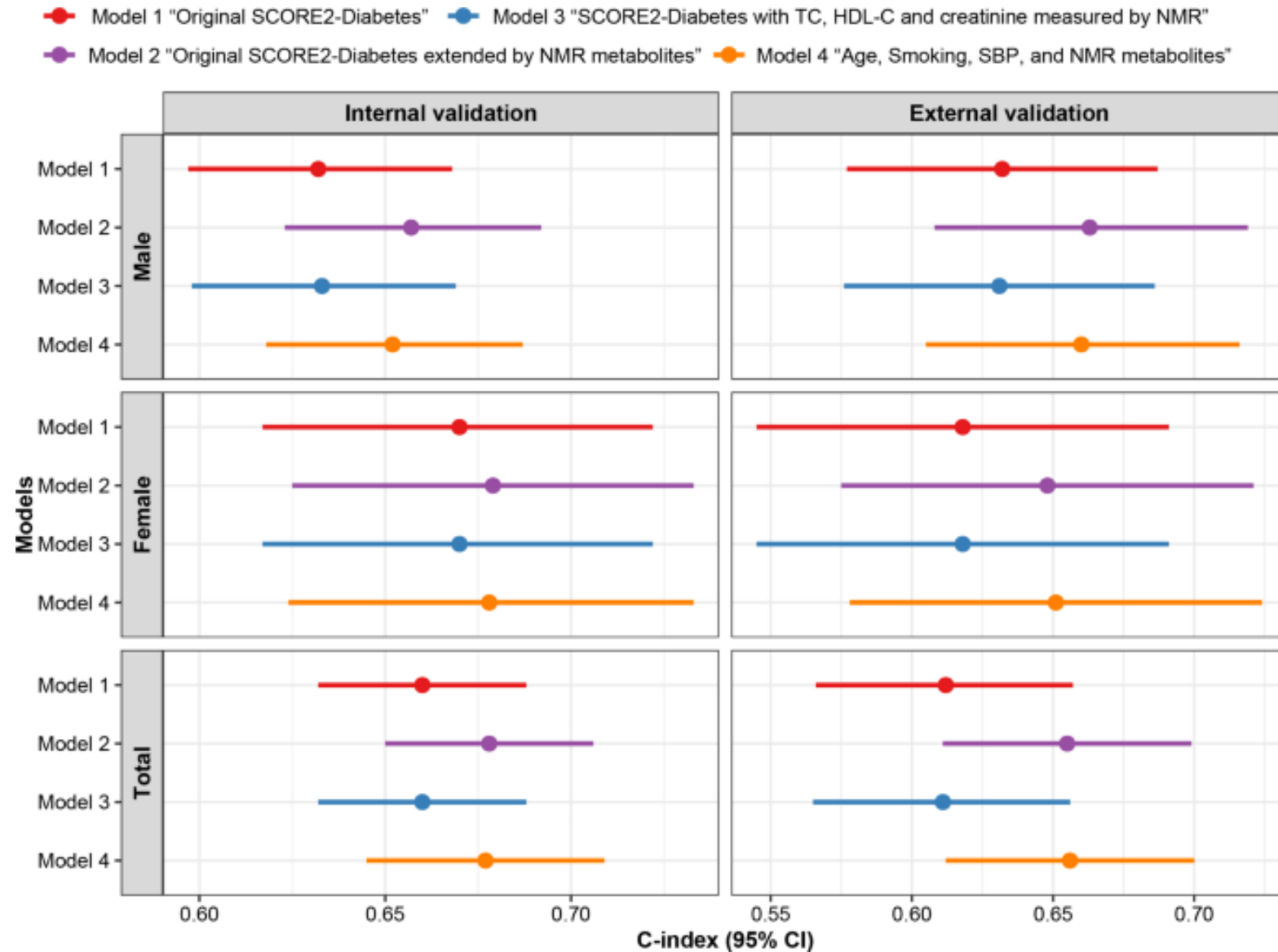
Discrimination (C-index) Internal validation

SCORE2-Diabetes: 0.660
Extended by metabolomics: 0.678
ΔC-index: +0.018; P = 0.037

Discrimination (C-index) External validation

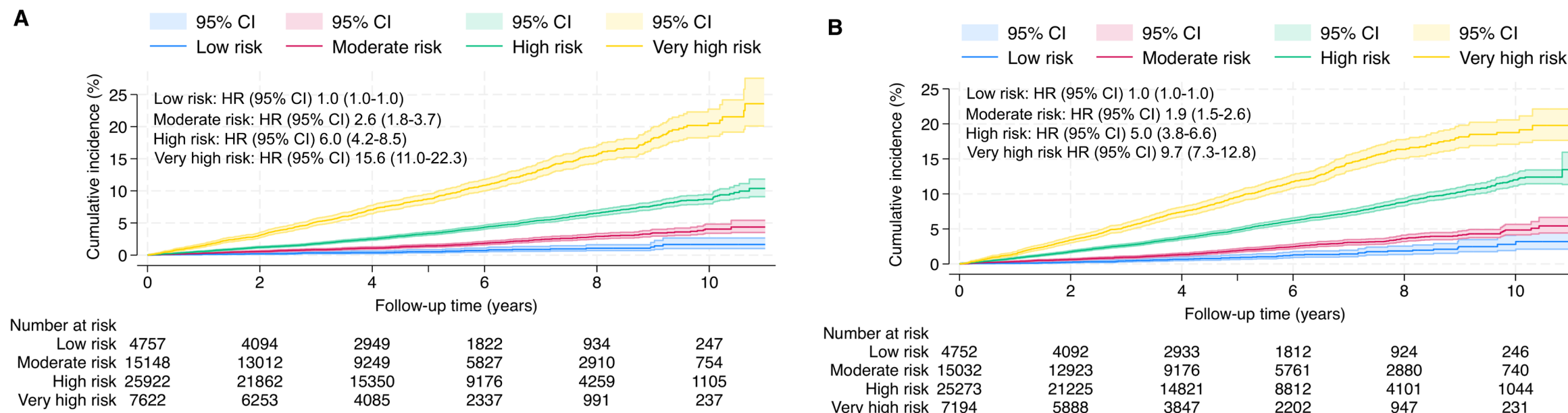
SCORE2-Diabetes: 0.612
Extended by metabolomics: 0.655
ΔC-index: +0.043; P = 0.011





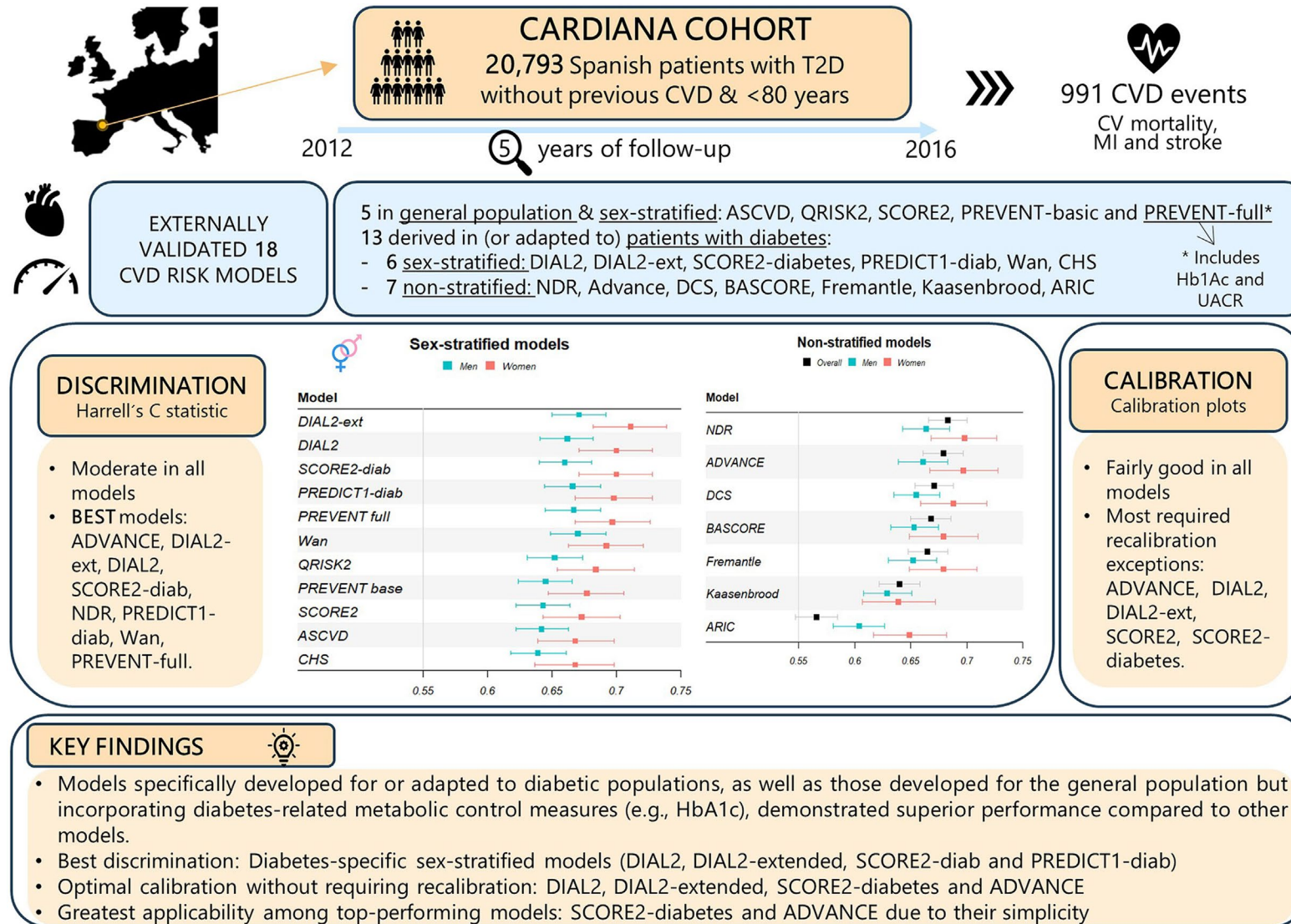
SCORE2-Diabetes

Predicts the Risk of Heart Failure and Atrial Fibrillation in Individuals With Newly Diagnosed Type 2 Diabetes



Cumulative incidence and HRs for HF (A) and AF (B) with stratification by risk group according to SCORE2-Diabetes.

SCORE2 DIABETES better performance than other scores



Can SCORE2-Diabetes Improve Pre-Test Probability Assessment and Clinical Management of Coronary Artery Disease?

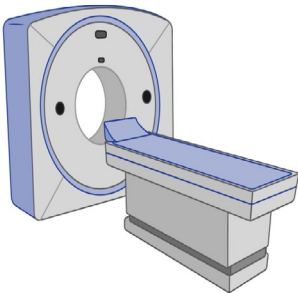
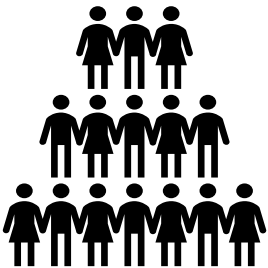
Mollace et al. *Cardiovascular Diabetology* (2025) 24:464
<https://doi.org/10.1186/s12933-025-03000-3>

Cardiovascular Diabetology

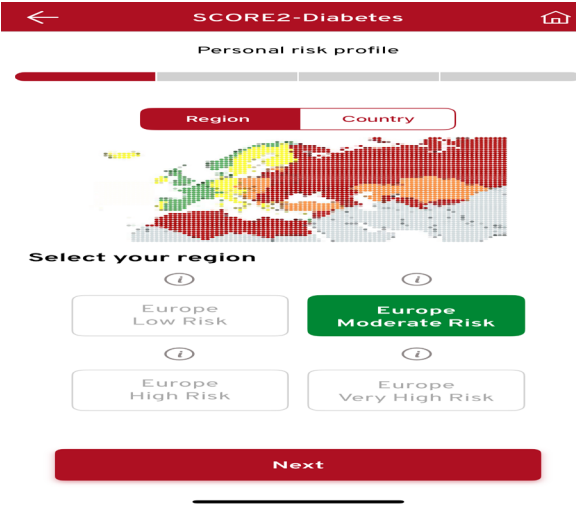
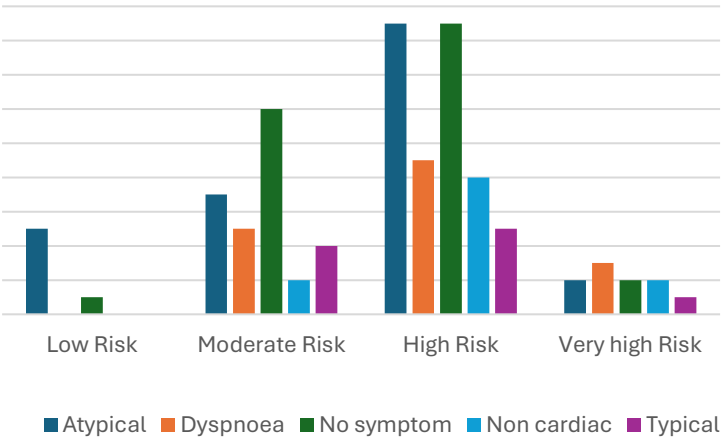
RESEARCH Open Access

SCORE2-diabetes for predicting coronary artery disease: a cardiac CT study in a diabetic moderate-risk region population

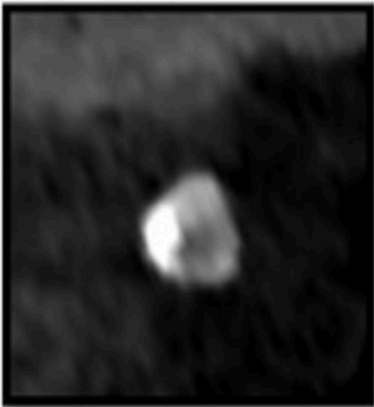
Rocco Mollace^{1,2*}, Matteo Nardin^{3,4}, Matteo Arzenton⁵, Federica Testerini³, Anita Fumagalli⁶, Flavia Nicoli¹, Margherita Celeste Licastro¹, Alessandro Nudi¹, Valentina Bernardini³, Federica Frascaro⁵, Silvana Di Maio⁷, Rossella Menghini⁸, Elona Collaku⁹, Giorgio Agati⁹, Eleonora Corghi⁹, Maria Lo Monaco¹, Davide Cao^{1,3}, Antonio Cardamone¹⁰, Cristina Carresi¹¹, Anna Rita Coppoletta¹¹, Eugenio Martelli¹², Gianluca Campo⁵, Giulio Stefanini^{3,7}, Erika Bertella¹ and Massimo Federici^{8,13}



Low to moderate PTP following current guidelines



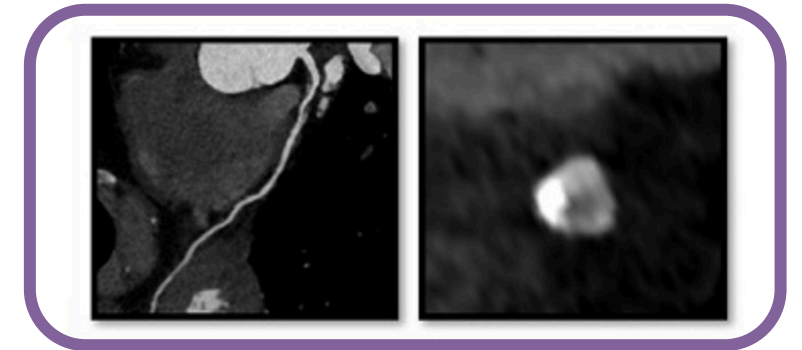
Extension and severity of CAD



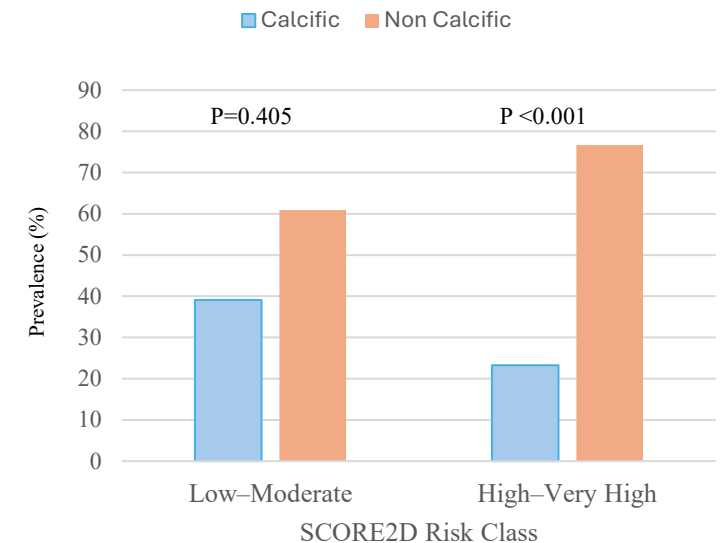
Plaque morphology

SCORE2-Diabetes and CAD prediction

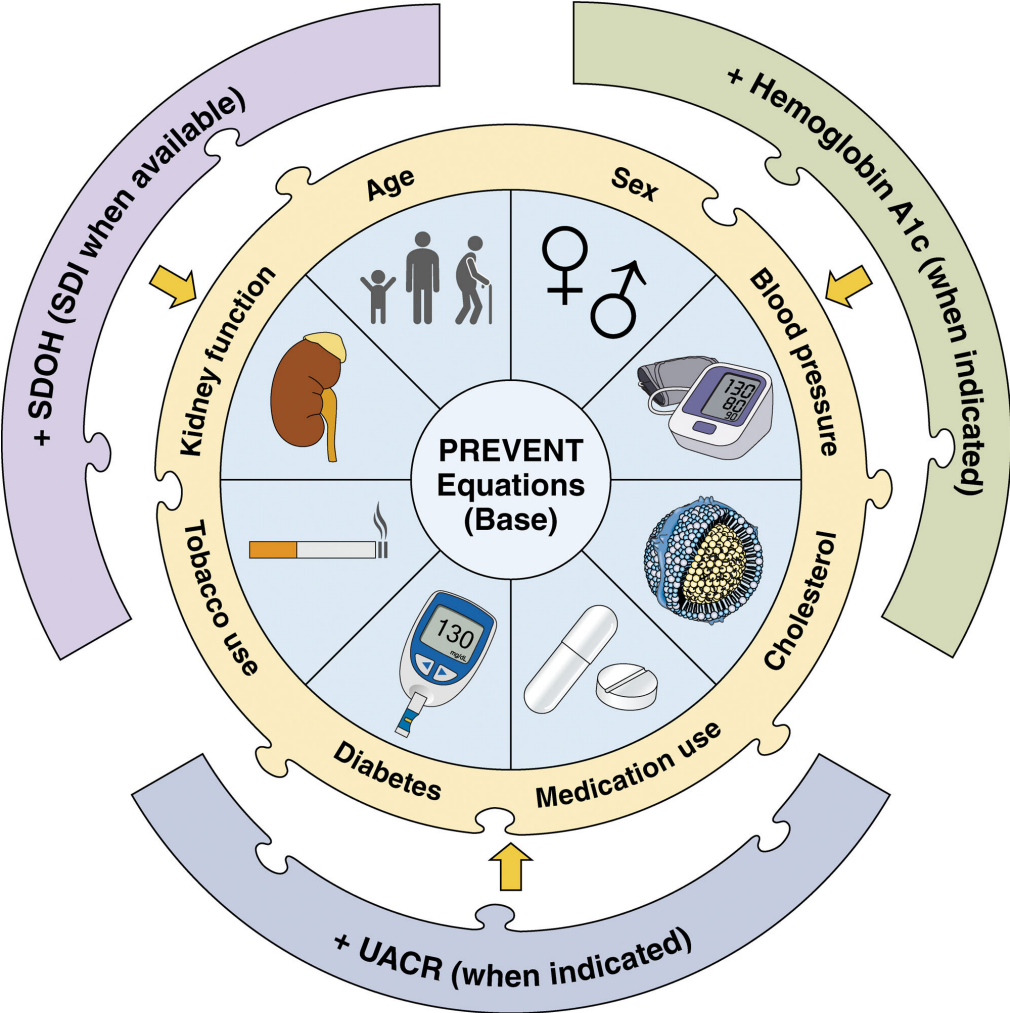
Higher SCORE2-D scores correlate with greater CAD burden, more severe stenosis, and a predominance of high-risk plaque features in patients with T2DM. These findings suggest that SCORE2-D may be a valuable tool in refining cardiovascular risk stratification and guiding clinical decision-making in diabetic populations.



Plaque assessment by CCTA



Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health



CKM Stages	Stage 0	Stage 1	Stage 2	Stage 3
CVD Risk				

Low risk

Borderline to intermediate risk

High risk

Lifetime cardiovascular disease risk calculators

Lifetime cardiovascular disease risk calculators		
Categories	Risk-Calculator	
Apparently healthy < 70 years 	LIFE-CVD Model	Sex, age, geographic region, smoking, diabetes mellitus, parental history of MI prior to age 60, systolic blood pressure, BMI, total cholesterol, HDL-C, LDL-C, HbA1c, lipid-lowering drug and antithrombotic treatment.
Type 2 Diabetes Mellitus 	Dial 2 Model	Sex, age, geographic region, current smoking, history of vascular disease, duration of diabetes mellitus, insulin therapy, systolic blood pressure, BMI, total cholesterol and HDL-C, LDL-C, HbA1c, eGFR, albuminuria, lipid-lowering drug and antithrombotic treatment.
Previous Cardiovascula Diseases 	SMART REACH Model	Sex, age, geographic region, current smoking, history of vascular disease, duration of diabetes mellitus, insulin therapy, systolic blood pressure, BMI, total cholesterol and HDL-C, LDL-C, HbA1c, eGFR, albuminuria, lipid-lowering drug and antithrombotic treatment.

C-indices of the core DIAL2 core model for assessing lifetime CVD events and non-CVD mortality (Swedish National Register)

DIAL2 Diabetes Lifespan Calculator

Tool Related Share

Age

Sex

Male

Smoking Status

Never

Body Mass Index (BMI)

HbA1c (%)

Systolic Blood Pressure (mmHg)

LDL Cholesterol (mg/dL)

Calculate

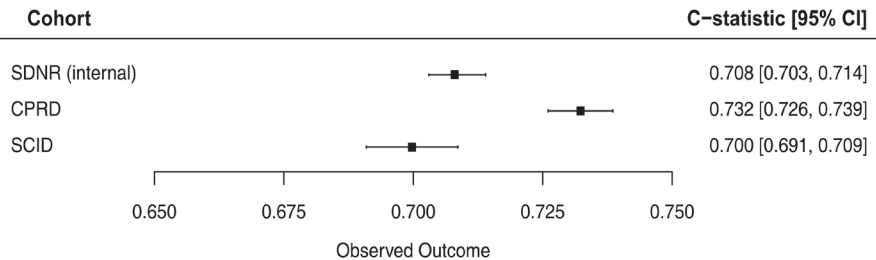
DIAL2 Score: Explanation and Clinical Context

The DIAL2 (Diabetes Lifespan) model estimates the lifetime risk of cardiovascular disease (CVD) and CVD-free life expectancy in individuals with type 2 diabetes without prior CVD history. Developed using data from the Swedish National Diabetes Register, the model incorporates factors such as age, sex, smoking status, BMI, HbA1c, systolic blood pressure, and LDL cholesterol levels. It has been recalibrated for European low- and moderate-risk regions and externally validated in Scottish and UK populations. The model assists clinicians in shared decision-making by providing individualized long-term risk assessments, aligning with the 2021 ESC CVD prevention guidelines.

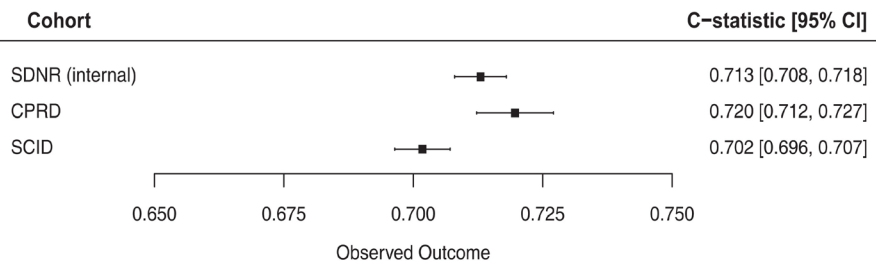
Reference:

Østergaard HB, et al. Estimating individual lifetime risk of incident cardiovascular events in adults with type 2 diabetes: an update and geographical calibration of the DIAbetes Lifespan perspective model (DIAL2). *Eur J Prev Cardiol.* 2023;30(1):61-69. doi:10.1093/eurjpc/zwac126.

Core model, CVD events



Core model, non-CVD mortality



DARE Spoke 3 – Digitally-enabled secondary and tertiary prevention

DARE BAC APPRENDI

DEVELOPMENT OF A 10 YEARS RISK
PREDICTIVE ALGORITHM BASED ON SCORE2
DIABETES

DARE BAC INsu-LINE

DEVELOPMENT OF A LIFETIME RISK
PREDICTIVE ALGORITHM BASED ON SCORE2
DIABETES



AMD data from
2005 to 2024 for
over 1 million
patients



Creation of a
longitudinal
database



Calculation of the
cardiovascular risk
score

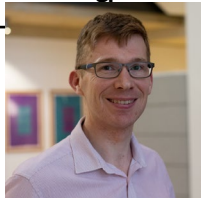


Algorithm integrated into
the MetaClinic platform

Take home message

- The clinical value of SCORE2-Diabetes lies in its application with the context for which it was developed, namely, individuals with T2DM in countries where the model has been appropriately calibrated.
- When used outside this target population, its predictive accuracy may be reduced, potentially leading to misclassification of risk and an underestimation or overestimation of the tool's performance.
- Importantly, additional recalibration to local epidemiology and risk factor distributions is feasible and may improve performance when the model is implemented in new countries or subpopulations, provided appropriate data are available.
- In addition, although SCORE2-Diabetes is an evaluated and validated tool, prospective evaluation, e.g. by incorporation into CV outcome trials (CVOTs), is needed.

Task Force Members

						
Katharina Schütt (TF-Co)	Dirk Müller-Wieland (TF-Co)	Ramzi A. Ajjan	Manuel J. Antunes	Ruxandra M. Christodorescu	Carolyn Crawford	Emanuele Di Angelantonio
						
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Maciej Lesiak	Maddalena Lettino	Darren K. McGuire	Wilfried Mullens	Bianca Rocca	Naveed Sattar	

(TF-Co: TF Coordinators)

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad192)



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Thank You!

Josè Manuel Fernandez Real

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