SMART Treatment Decisions: Predicting 10-Year Cardiovascular Event Risks & Assessing Treatment Thresholds in a UK Population

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Outline

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  - Illustrative cases under 2 therapeutic interventions
- Conclusions & Practice Implications

Background

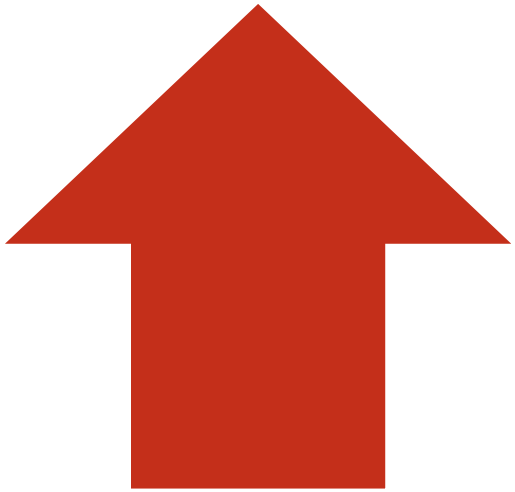
Motivation

- Prior diagnosis of atherosclerotic cardiovascular disease (ASCVD) leads to varying future vascular risks[1]
- Personalized future vascular risk assessment for secondary prevention population has clinical & financial advantages[2-5]
  - Clinical:
    - Providing (personalized) treatment only when vascular risks outweigh the risks associated with treatment
  - Financial:
    - Overtreatment of low-risk patients (treat all) can present a burden that may affect ability to treat higher risk patients, especially using novel, high cost treatments[6]
    - **Secondary prevention population risk estimation tools & thresholds for treatment** are needed to make high cost treatments (and alternatives) viable[7]
- Current guidance for treatment is vague (e.g., proprotein convertase subtilisin/kexin type 9 (PCSK9)) & not sufficiently individualized[1,8-13]
  - All individuals are assumed to be at sufficiently high risk that the benefits outweigh risks & costs[2,14,15]
- Novel tool for assessment of future vascular risks[16,17]: **external validation** necessary to test validity in routine primary care setting[18]

SMART ASCVD 10-year Risk Prediction Model

- SMART (Secondary Manifestations of ARTerial disease) Model:
  - [16] Dorresteijn JA, Visseren FL, Wassink AM, 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* 2013;99(12):866-72.
- **One of only two existing models** estimating 10-year risks of myocardial infarction, stroke, or cardiovascular death for secondary prevention population
- Model derived and internally validated using two cohorts (n=3,489 and n=2,299, respectively) of Dutch patients in one practice (University Medical Center Utrecht) in the Netherlands[16]
- External validation performed only in trial participants[17]
- **Model performance in routine populations unexplored to date**

SMART Risk Prediction Model:
Model Inputs[15]



Associated with Increased Risk of ASCVD Outcomes within 10-years:

- Age in years squared
- Male
- Diabetes Mellitus (Y)
- Smoking (Y)
- Systolic blood pressure
- Total cholesterol
- Log(hsCRP): High Sensitivity C-Reactive Protein (blood marker of systemic inflammation – lower is better)
- eGFR squared: Estimated Glomerular Filtration Rate (blood test for creatinine to measure kidney activity; the higher, the better the kidney's activity)
- Years since first diagnosis of vascular disease
- History of cerebrovascular disease (Y)
- History of coronary artery disease (Y)
- History of abdominal aortic aneurysm (Y)
- History of peripheral arterial disease (Y)

Associated with Decreased Risk:

- Age in years (age squared counteracts this effect)
- HDL-cholesterol
- eGFR

SMART Risk Prediction:

More on Model Inputs

Why the aforementioned risk factors?

- Hypothesis of researchers based on well-known risk factors
- Data-driven set of covariates included based on derivation cohort

> We acknowledge several limitations of the study. First, although our prediction models performed well in our own validation dataset, they would benefit from further external validation in other datasets. Nonetheless, we minimised the risk for over-fitting by including well known risk factors only, limiting the number of covariates, and through penalised maximum likelihood estimation of the model coefficients. Because an

Dorresteijn JAN, *et al. Heart* 2013;**99**:866–872. doi:10.1136/heartjnl-2013-303640

- We do not assess risk factor selection or model functional form in our UK external validation study

SMART Risk Prediction:

Model Functional Form

- 10-year risk (%) = $(1-0.81066^{\exp(\text{linear predictor} + 2.099)}) \times 100\%$
- Linear predictor =
  - - 0.0850 x age in years
  - + 0.00105 x (age in years)^2
  - + 0.156 [if male]
  - + 0.262 [if current smoker]
  - + 0.00429 x systolic blood pressure (mmHg)
  - + 0.223 [if diabetic]
  - + 0.140 [if history of coronary artery disease]
  - + 0.406 [if history of cerebrovascular disease]
  - + 0.558 [if abdominal aortic aneurysm]
  - + 0.283 [if peripheral artery disease]
  - + 0.0229 x years since first diagnosis of vascular disease
  - - 0.426 x HDL cholesterol in mmol/L
  - + 0.0959 x total cholesterol in mmol/L
  - - 0.0532 x eGFR in mL/min/1.73m^2
  - + 0.000306 x (eGFR in mL/min/1.73m^2)^2
  - + 0.139 x log(hsCRP in mg/dL)

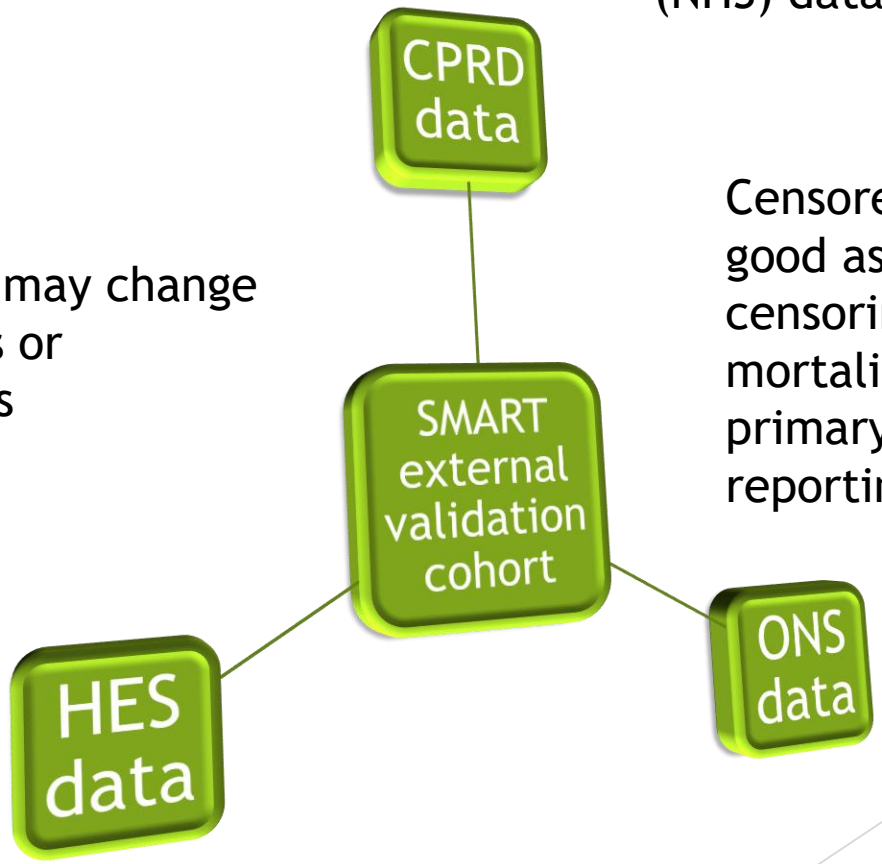
Study Purpose/Research Questions

- What is the SMART model performance using other populations outside the original derivation & validation cohorts?
  - Can the SMART model be applied to the UK population?
- Does the SMART model offer a net benefit over current treatment decision-making approaches (treat all/treat none)?
- Is SMART model performance overly affected by missing data & other covariate limitations?
- Can the SMART model be used to translate relative risk reductions associated with therapeutic interventions into estimated absolute individual event reductions?

Data, Outcomes, & Methods:
UK Population Data

External validation requires patient information from multiple sources.

Historical, longitudinal data spans 18 years (2000-2017) of UK National Health Service (NHS) data



Patients may change hospitals or providers

Censored data requires good assessment of censoring times (e.g., mortality data or primary care practice reporting patterns)

Data, Outcomes, & Methods:
Clinical Practice Research Datalink (CPRD)

- De-identified electronic health records (EHR) from patient **primary care visits**, including demographic information
- **Historical, longitudinal EHR data** from a network of NHS GP practices in the UK for 60 million patients across 30+ years
- Current data for 16 million registered patients with NHS practices
- Validated, quality data leading to 2,800+ publications
- Can be linked to other datasets, such as HES and ONS data
- Studies require protocol approval by CPRD Independent Scientific Advisory Committee (ISAC)
- See *www.CPRD.com* for more details

Data, Outcomes, & Methods: *HES & ONS Data*

- Hospital Episode Statistics (HES) data:
  - Collected by the National Health Service from **hospital visits (i.e., secondary care)**, including Accident & Emergency attendances and outpatient appointments
  - Socioeconomic & geographical information: age, sex, ethnicity, residency, etc.

- Office for National Statistics (ONS) data:
  - Includes **mortality information** (i.e., one of the study's censoring criteria)

Data, Outcomes, & Methods: *Study Cohort Entry Criteria*

- Patients for whom HES & ONS data could be linked to ensure outcomes & censoring times (e.g., mortality due to other causes) are captured
- Cohort entry on the first date that all the following criteria were met:
  - 1st January 2000
  - Past first anniversary of both database entry and registration with GP
  - 18 ≤ age < 80 years old
  - Six months post first record/diagnosis of vascular (ASCVD) event, including:
    - Coronary Heart Disease (CHD), including angina, myocardial infarction, and/or coronary revascularization
    - Cerebrovascular Disease (CVD), including transient ischemic attack, ischemic stroke, amaurosis fugax, retinal infarction, and/or carotid surgery
    - Peripheral Arterial Disease (PAD), including documented diagnosis and/or leg angioplasty, bypass, or amputation
    - Abdominal Aortic Aneurysm (AAA), including aneurysm and/or aneurysm surgery

Data, Outcomes, & Methods: *Study Cohort Exit Date*

- Cohort exit date was the **earliest** of:
  - Any vascular outcome occurrence
  - Last GP practice data upload to CPRD
  - Transfer of patient out of database
  - Patient's death
  - 31st December 2017

Data, Outcomes, & Methods:
Primary & Sensitivity Analyses

- Three cohorts defined from CPRD+HES+ONS data
  - **Primary Analysis: Primary cohort (n=244,578)**
    - Established ASCVD (> 6 months at time of cohort entry)
    - Defined to avoid recurring symptoms from initial ASCVD contaminating the study, and to match derivation cohort (several months post diagnosis)
    - Predictors defined to closely match SMART derivation study (e.g., smoking regardless of intensity; diabetes regardless of type; etc.)
    - Multiple imputation in R assuming missingness at random
  - **Sensitivity Analysis: Secondary cohort (n=136,445)**
    - Newly diagnosed ASCVD only – different from derivation cohort
    - Cohort entry defined as one week post diagnosis (all other entry & exit criteria the same)
  - **Sensitivity Analysis: Complete Case cohort (n=182,482)**
    - Defined to assess effects of imputation on model performance
    - Complete case (except for hsCRP, which is unavailable for everyone in the UK)
- Comparison with original SMART study cohorts
  - **Derivation cohort (n=3,489)**
  - **Validation cohort (n=2,299)**

Data, Outcomes, & Methods:
Baseline Population Differences

	PRIMARY COHORT (n=244,578) ^			DERIVATION COHORT (n=3,489) *	
	Median / n	IQR / %	Missing: n (%)	Median / n	IQR / %
Age	67.3	59.2 - 74.0	0	60	53-68
Sex (Male)	151,888	62.1%	0	2,575	74%
Date of cohort entry	1 Jan 2004	8 June 2000 – 21 May 2009	0	At baseline	100%
Vascular disease*			0		
Cerebrovascular Disease	73,520	30.1%		846	27%
Coronary Heart Disease	154,079	63.0%		1,892	60%
Peripheral Vascular Disease	32,459	13.3%		691	22%
Abdominal Aortic Aneurysm	7,048	2.9%		291	9%
Years since first vascular event			0		
<1 yr before enrolment	150,557	61.6%		2,065	59%
1-2 yrs before enrolment	10,098	4.1%		431	12%
>2 yrs before enrolment	83,923	34.3%		993	28%
Current smoking (Yes)	48,083	19.7%	24,449 (10.0%)	1,169	34%
Diabetes mellitus	38,717	15.8%	0	592	17%
Systolic blood pressure (mmHg)	140	126 - 150	12,605 (5.2%)	139	126-154
Total cholesterol (mmol/l)	4.7	4.0 - 5.6	28,610 (11.7%)	4.9	4.1-5.7
HDL cholesterol (mmol/l)	1.3	1.1 – 1.6	49,142 (20.1%)	1.2	1.0-1.4
hsCRP (mg/l)	N/A	N/A	244,578 (100.0%)	2.2	1.0-4.7
eGFR (ml/min/1.73m)	66.1	55.5 – 77.8	16,334 (6.7%)	76	66-87
Ethnicity			13,382 (5.5%)	N/A	N/A
Asian	5,589	2.3%			
Black	1,985	0.8%			
Mixed	557	0.2%			
White	220,850	90.3%			
Other	2,215	0.9%			

^ CPRD UK population data; 74.6% people had complete model information (except for hsCRP)

* Baseline numbers for derivation cohort taken from Table 1 in Dorresteijn et al., 2013

Data, Outcomes, & Methods:
Baseline Population Differences

- Population differences help validate SMART tool
  - UK-based population vs. single-hospital Dutch study
    - Study participation not required in the UK (retrospective study) vs. prospective nature of Dutch study (with written consent needed)
    - All-inclusive study in UK vs. potential biases in original study (Dutch-speaking & primarily white)
    - Data linked from multiple sources vs. required follow-up in the same hospital
  - Population age more representative in UK
    - Average age of 67.3 (range: 18-80) vs. 60 (range: 18-80) years
    - Average age of Dutch study is potentially affected by other exclusions that could bias sample toward younger & healthier populations:
      - Those not independent in daily activities
      - Those with terminal malignancy
      - Those without written consent to participate
  - More balanced population by sex in UK
    - 62.1% male vs. 74% male
  - Different vascular disease distribution
  - Differences in other behavioral characteristics
    - Smaller smoking prevalence in UK (19.7% vs. 34%)

Data, Outcomes, & Methods:
Imputation of hsCRP

	CVD		CHD		PAD		AAA	
Age	Male	Female	Male	Female	Male	Female	Male	Female
<=40	1.700	2.000	1.290	1.300	1.400	8.190	1.105	0.800
>40 & <=50	1.800	1.500	1.540	2.150	3.175	4.495	2.600	4.200
>50 & <=60	2.475	2.300	1.600	2.060	2.710	3.920	3.500	3.350
>60 & <=70	2.060	2.025	1.900	2.000	3.100	2.430	3.590	2.700
>70	2.700	2.400	2.300	2.460	3.350	3.035	5.085	2.950

- hsCRP unknown in UK: Use original derivation study baseline values & match by age group * sex * disease
- Median hsCRP by sex, age group, & disease from SMART derivation study was used for imputation of hsCRP in both UK primary & secondary cohorts
  - If multiple ASCVD events were present, the largest hsCRP value was selected
- Potential challenges:
  - Median values -> true variability of hsCRP (and information content) not captured
  - Some values from original study are based on low samples
  - Inconsistent across dimensions (e.g., female with AAA)

Data, Outcomes, & Methods:
Imputation of hsCRP (Cont.)

	CVD		CHD		PAD		AAA	
Age	Male	Female	Male	Female	Male	Female	Male	Female
<=40	1.700	2.000	1.290	1.300	1.400	8.190	1.105	0.800
>40 & <=50	1.800	1.500	1.540	2.150	3.175	4.495	2.600	4.200
>50 & <=60	2.475	2.300	1.600	2.060	2.710	3.920	3.500	3.350
>60 & <=70	2.060	2.025	1.900	2.000	3.100	2.430	3.590	2.700
>70	2.700	2.400	2.300	2.460	3.350	3.035	5.085	2.950

- Cannot just exclude variable from model -> Potential unintended effects on model outcomes
- SMART model assumes availability of all included risk factors
  - Not all risk factors may be available outside of Dutch study across other countries (e.g., hsCRP)
- Use derivation study hsCRP to 'fill the gaps'
  - This may bias our study making it less precise to assess individualized risks
  - If it still performs well, it will show robustness of the SMART tool to missing-ness of some inputs

Data, Outcomes, & Methods: *Outcome*

- First post cohort-entry occurrence (within 10 years) of:
  - Myocardial infarction (MI)
  - Stroke (ischemic or hemorrhagic)
  - Cardiovascular death (due to MI, congestive heart failure, ischemic stroke, intracerebral hemorrhage, ruptured abdominal aortic aneurysm, or sudden cardiac death)
- Outcome censored by multiple factors:
  - Practice not reporting data
  - Individuals moving away from practice
  - Death by non-ASCVD related causes
  - End of study period (cohort entry can occur at any point during the 2000-2017 study period)

Results:
Summary Statistics

- Primary Analysis/Cohort:
  - 244,578 individuals
  - 393 GP practices
  - Median follow-up: 5.25 years (IQR: 2.15-9.63)
  - 23.3% followed 10+ years - i.e., no events occurring <10 years
  - **1,284,035 patient-years** in our UK external validation study
  - 45,327 ASCVD outcome events observed
  - Observed 10-year Kaplan-Meier event risks:
    - 29.1% (95% CI 28.8-29.4%) for Males
    - 26.6% (95% CI 26.2-27.0%) for Females
  - Comparison to original SMART study:
    - **30,012 patient-years**
    - 483 (derivation) and 305 (validation) ASCVD outcome events observed

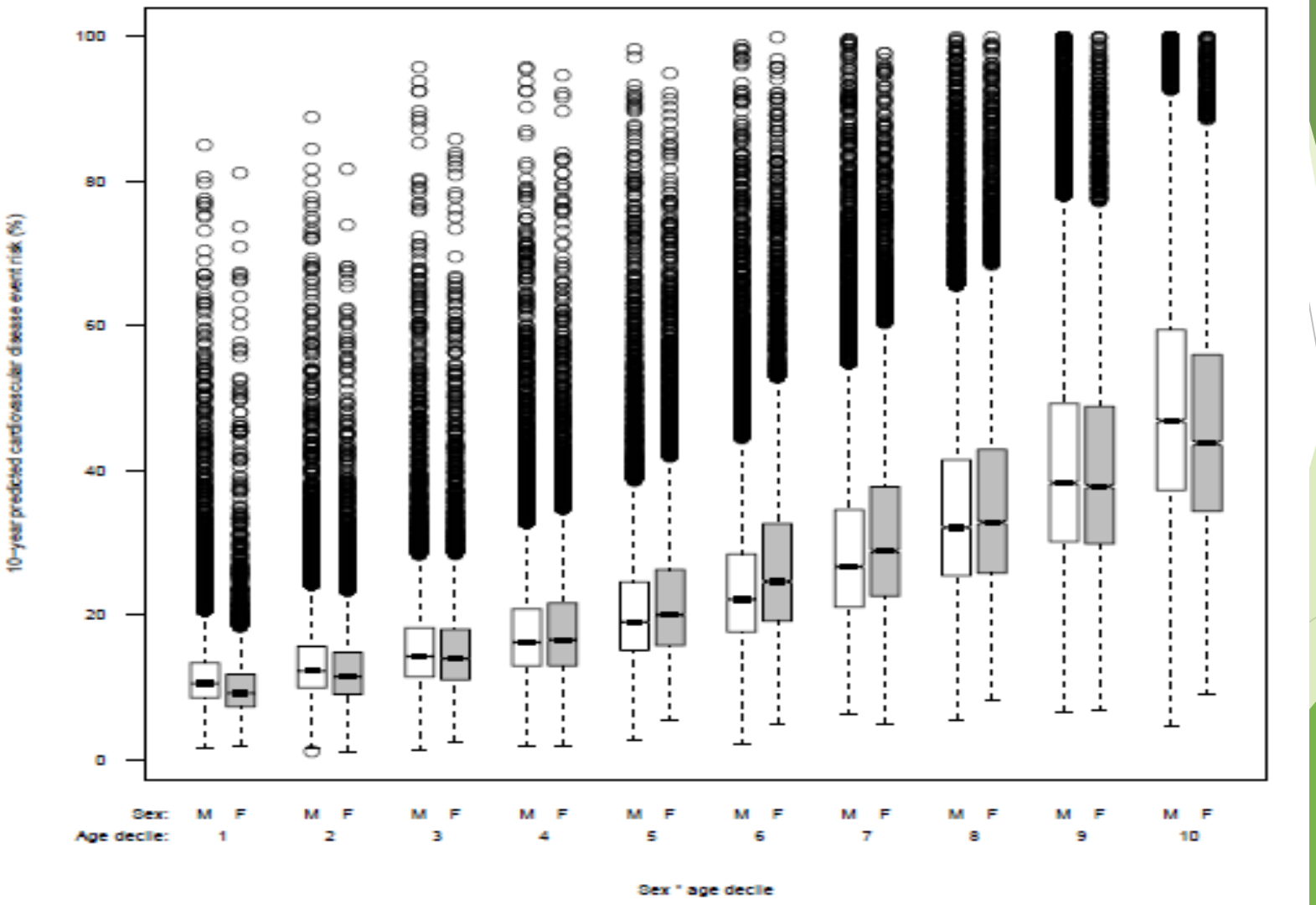
Results:
Summary Statistics (Cont.)

- Sensitivity Analysis/Secondary Cohort:
  - 136,445 people
  - 389 practices
  - Median follow-up: 3.74 years (IQR: 1.1-7.76)
  - 14.4% followed 10+ years - i.e., no events occurring <10 years
  - 28,115 ASCVD outcome events observed; 14,865 of which were within 6 months of diagnosis
  - Observed 10-year Kaplan-Meier event risks:
    - 29.6% (95% CI 29.2-30.1%) for Males
    - 27.9% (95% CI 27.4-28.4%) for Females

Results:

10-year Predicted Risk by Age Decile & Sex

Predicted 10-year Event Risks, for the Primary Cohort, by Age Decile & Sex.



Results:
Predicted vs. Observed

10-year Predicted Risk Range & Corresponding Kaplan-Meier Observed Risks (% & counts) for the Primary Cohort

10-year Predicted Risk (%)	Observed Risk (%)	n (%)
< 10	12	25,132 (10.3)
10 to < 20	19	86,483 (35.3)
20 to < 30	28	55,912 (22.9)
30 to < 40	36	34,501 (14.1)
≥ 40	49	42,550 (17.4)

- Observed risks fall within predicted ranges in all but the lowest risk range (slight under-predictive power)
- Demler et al., 2015[19] Calibration test: χ^2 = 1198.03, p<0.0001
- Example: Among those with 10-year predicted risks (measured at baseline) of a vascular event between 30% and 40% using the SMART tool, the observed Kaplan-Meier 10-year risk was 36%.
- 34,501 cohort individuals (14.1% of our study participants) were estimated to have a predicted risk in this range.

Results:
Comparison of Predicted vs. Observed Risks with Original Validation Study

10-year predicted risk (%)	Observed risk (%)	n (%)
< 10	12	25,132 (10.3)
10 to < 20	19	86,483 (35.3)
20 to < 30	28	55,912 (22.9)
30 to < 40	36	34,501 (14.1)
≥ 40	49	42,550 (17.4)

Cohort differences are visible in observed risks by predicted risk cluster:

- Every ***observed*** risk across predicted risk clusters is higher in our validation study than in the original validation cohort
- Age difference between original cohort & UK cohort
- Entry criteria in original validation study may have biased results to include those with healthier outcomes

SMART tool is still **very powerful to cluster individuals based on actual risk**.

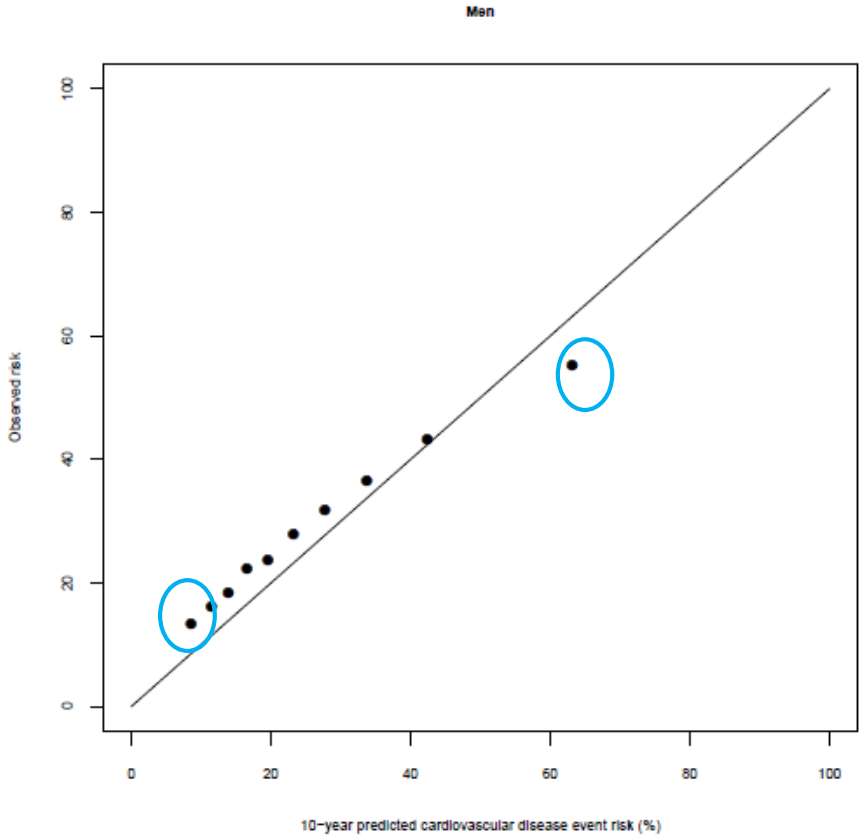
	Model A SMART risk score
Low 10-year risk (<10%):	
Patients (n; % of group)	417; 18%
Observed 10-year KM risk	6%
Moderate 10-year risk (10 to <20%):	
Patients (n; % of group)	930; 40%
Observed 10-year KM risk	15%
High 10-year risk (20 to <30%):	
Patients (n; % of group)	432; 19%
Observed 10-year KM risk	20%
Very high 10-year risk (30 to <40%):	
Patients (n; % of group)	221; 10%
Observed 10-year KM risk	26%
Extremely high 10-year risk (≥40%):	
Patients (n; % of group)	299; 13%
Observed 10-year KM risk	44%

model can be used to discriminate between low and high risk patients and to improve clinical decision making.

Dorresteijn JAN, *et al. Heart* 2013;**99**:866–872. doi:10.1136/heartjnl-2013-303640

Results:

Calibration Plot: Fit by Risk Decile & Sex



Validation Intuition:

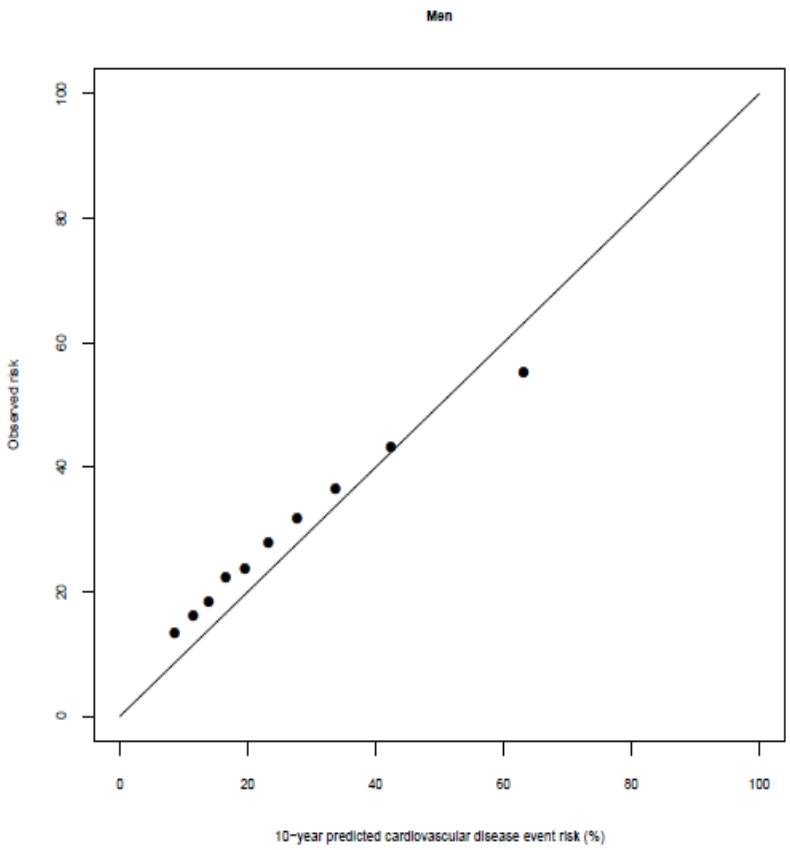
Do 10-year model predicted risks (x-axis) align with the actual observed risks (y-axis)?

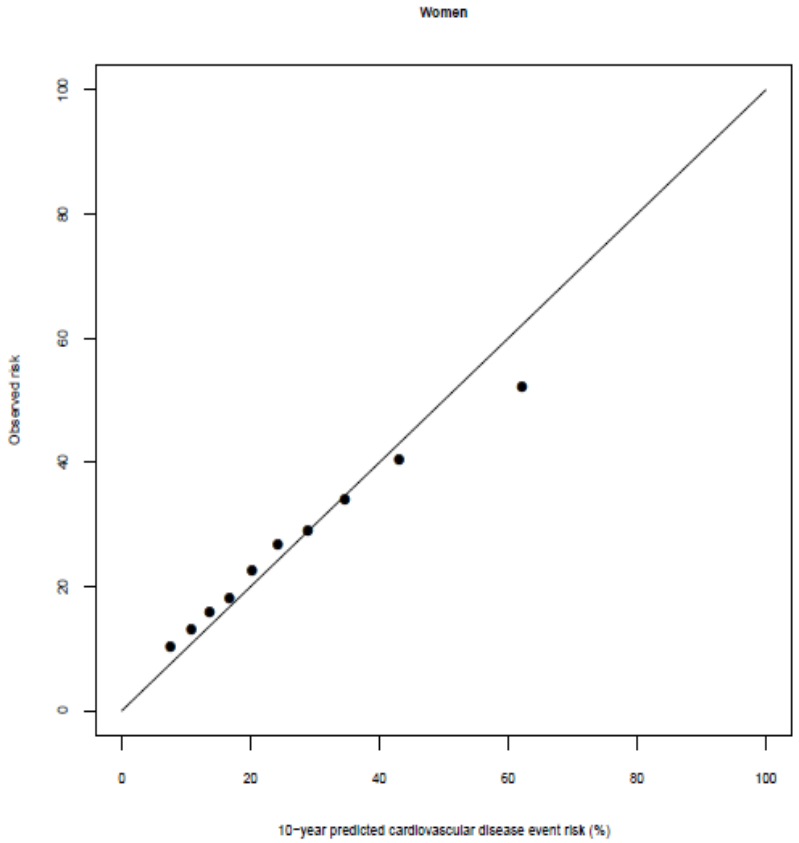
If not exactly, do predicted risks positively correlate with observed risks, so that thresholds can be used to **identify those at most risk**?

- The 10% of men predicted to have highest vascular event risk have a high observed risk (top right dot)
- The 10% of men predicted to have lowest risk, have low observed risk (bottom left dot)

Results:

Calibration Plots: Fit by Risk Decile & Sex





- 10-year Kaplan-Meier observed risk (y-axis) by 10-year predicted risk (x-axis), grouped by predicted risk decile
- Men (left) vs. Women (right)
- Slight under-prediction of risks for lower risk deciles, mainly for men
- Overall good predictive power

Results:

Calibration: Fit by Risk Decile & Sex

Decile	Risk Decile Men	Risk Decile Women
1	0.64	0.74
2	0.71	0.83
3	0.75	0.86
4	0.74	0.92
5	0.83	0.90
6	0.84	0.90
7	0.88	0.99
8	0.92	1.02
9	0.98	1.06
10	1.14	1.19
	χ^2=1048.42, p<0.0001	χ^2=352.6, p<0.0001

Worse prediction for those estimated to be at low risk, with consistent under-prediction, especially for men

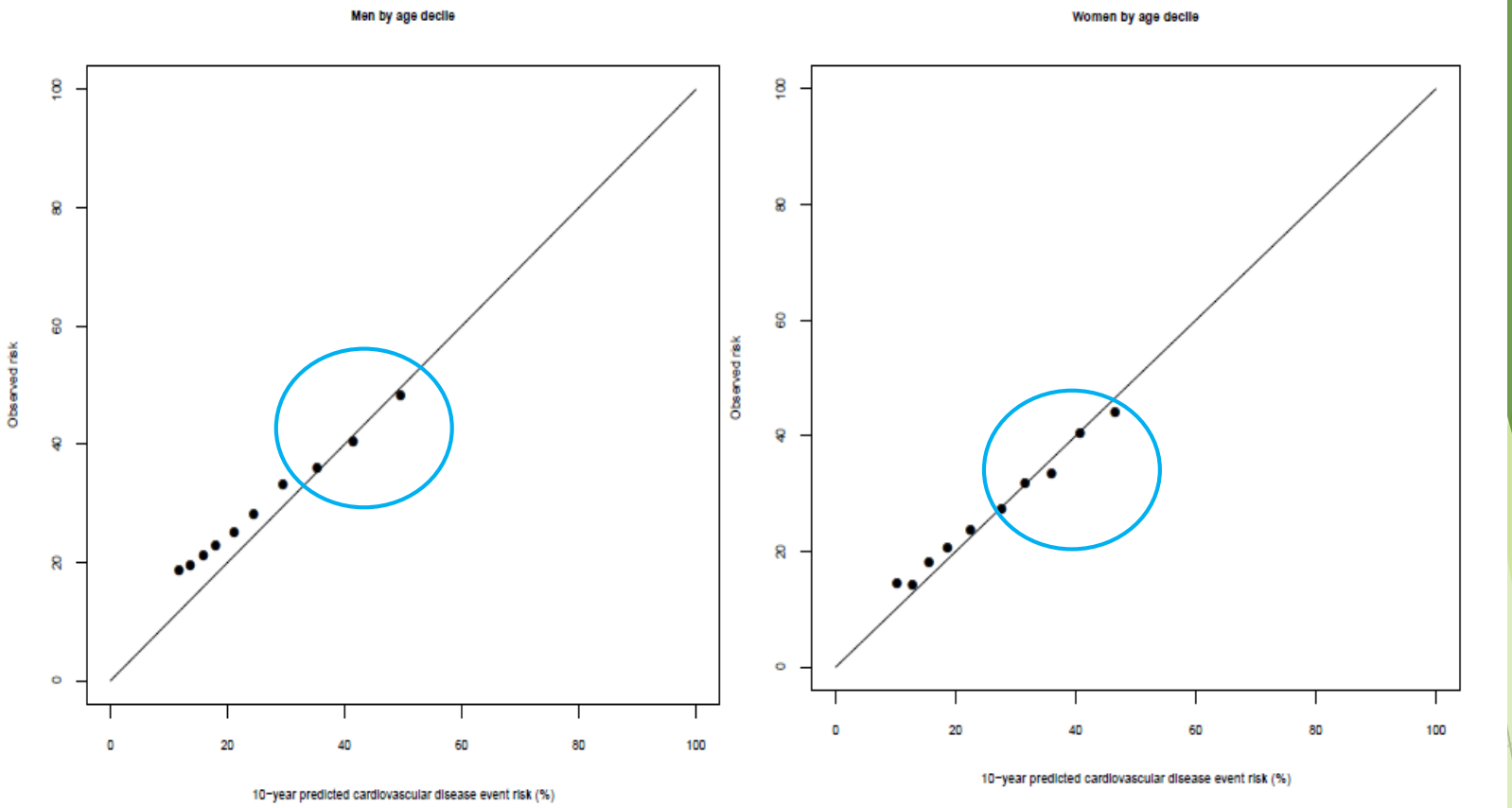
Better prediction for the half predicted at most risk

Ratios, by sex, of 10-year **predicted to observed risk,** ranked by 10-year predicted risk/sex score decile (where decile 1 = lowest predicted risk decile). 10-year predicted risks are defined as within-decile SMART-derived risk averages.

1 = SMART perfectly predicts risks (on average) for that sex*risk predicted decile
<1 = SMART under-predicts risks (on average)
>1 = SMART over-predicts risks (on average)

Results:

Calibration Plots: Fit by Age Decile & Sex



- 10-year Kaplan-Meier observed risk (y-axis) by 10-year predicted risk (x-axis), grouped by age decile
- Men (left) vs. Women (right)
- Small under-prediction of risks for lower age deciles, mainly for men
- Good predictive power among those predicted to have higher risks

Results:

Calibration: Fit by Age Decile & Sex

Decile	Age Decile Men	Age Decile Women
1	0.63	0.71
2	0.70	0.90
3	0.75	0.86
4	0.79	0.90
5	0.85	0.95
6	0.87	1.01
7	0.89	0.99
8	0.98	1.07
9	1.03	1.01
10	1.03	1.06

χ^2=901.33, p<0.0001 χ^2=148.31, p<0.0001

Under-prediction of risks for younger half of the population, especially for men

Reasonable risk predictions across sex & age deciles for older half of the population

Ratios, by sex, of 10-year **predicted to observed risk**, ranked by age decile (where decile 1 = lowest age decile). 10-year predicted risks are defined as within-decile SMART-derived risk averages.

1 = SMART perfectly predicts risks (on average) for that sex*age decile
<1 = SMART under-predicts risks (on average)
>1 = SMART over-predicts risks (on average)

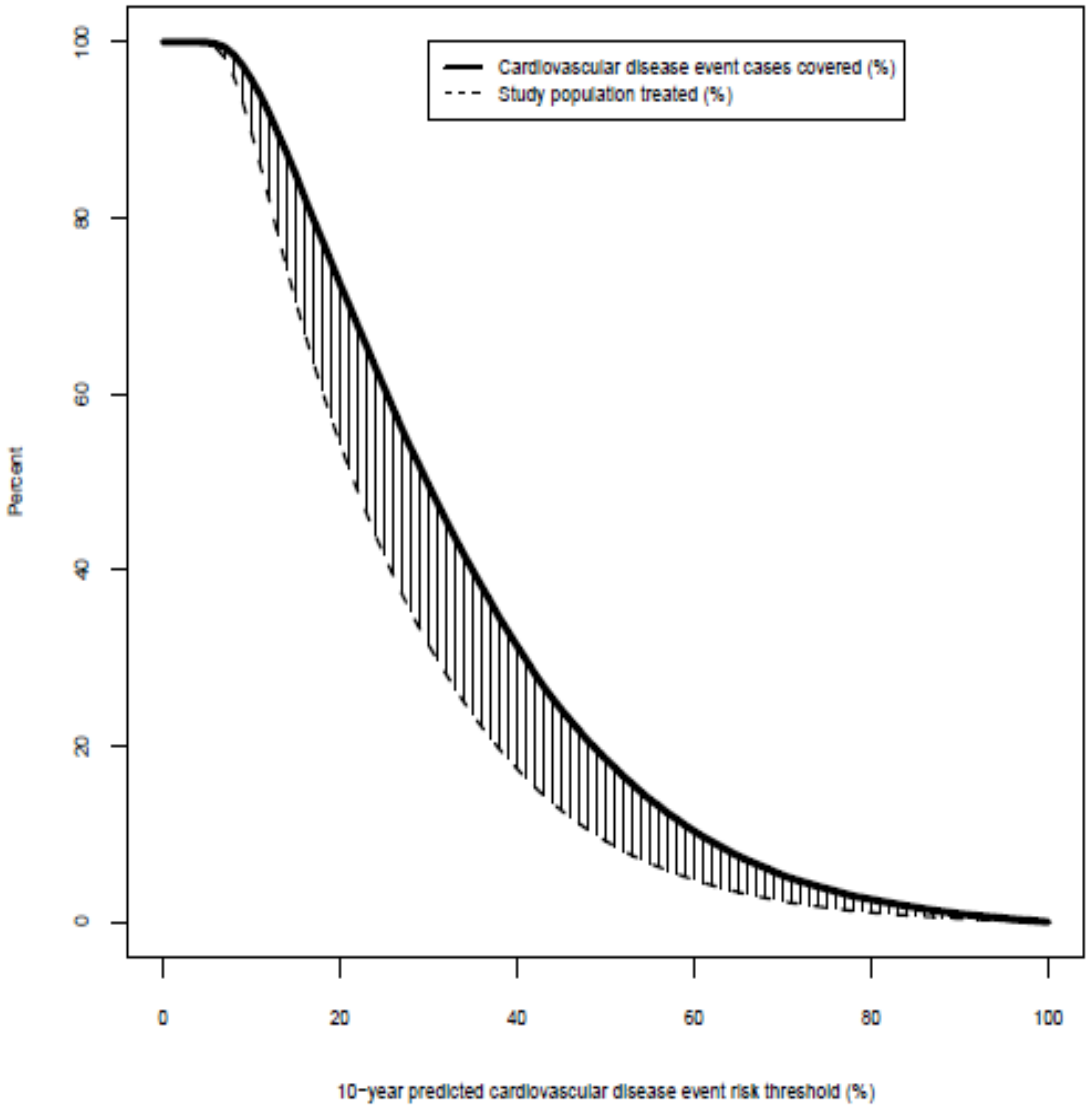
Results:
Model Performance: Discrimination

	C-statistic	95% Confidence Interval
Derivation cohort	0.706	0.679-0.733
Validation cohort	0.675	0.642-0.708
Primary cohort	0.639	0.636-0.642
Secondary cohort	0.559	0.555-0.562
Complete Case cohort	0.624	0.620-0.627

- Model performance:
  - Sensitive to cohort definition
  - Relatively robust to missing information (including hsCRP fully missing)
  - Aligned with lower bounds of validation cohort results

Results:

Risk Thresholds & Clinical Utility



Model predicts well across risk thresholds.

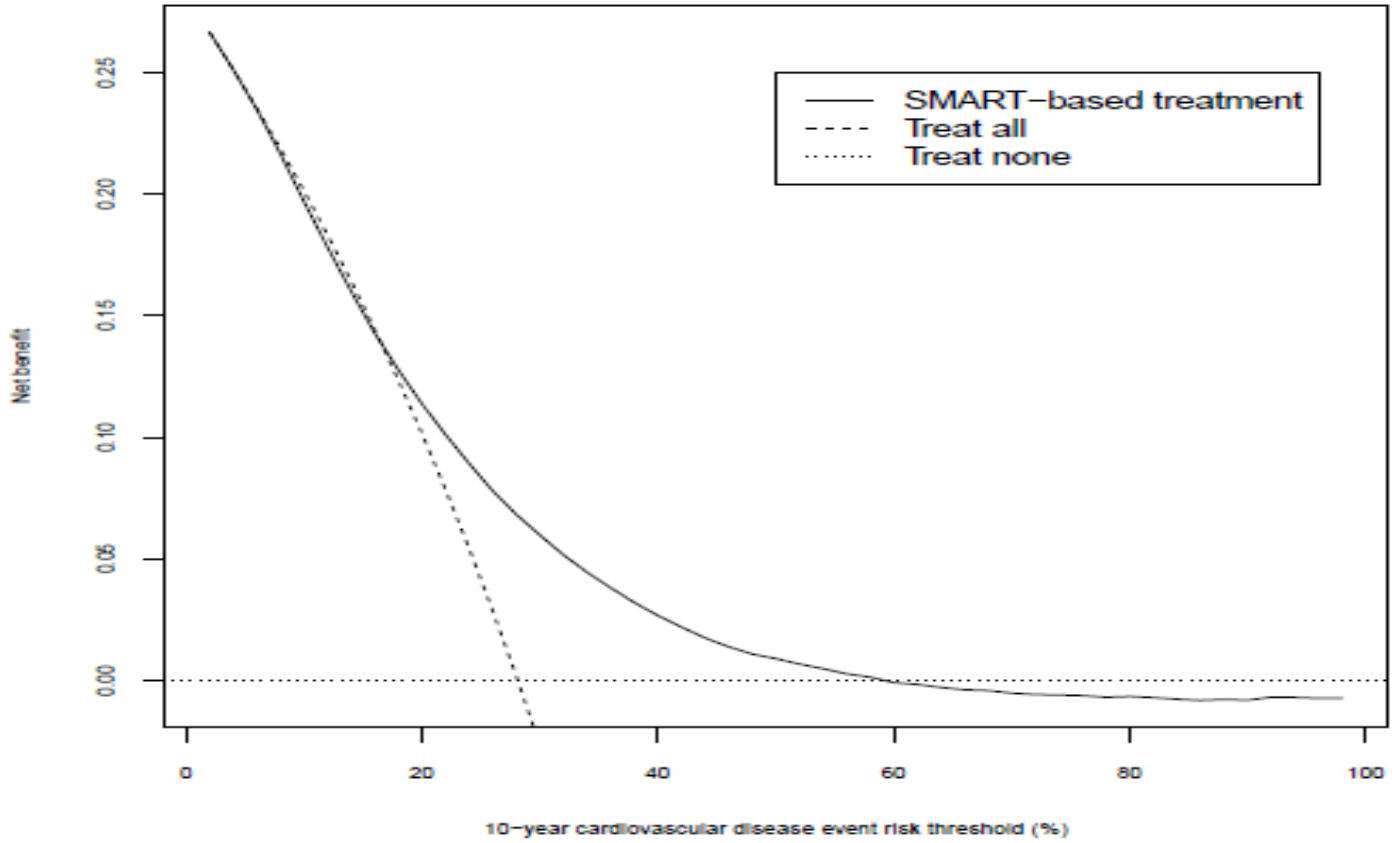
Upper curve represents CVD cases covered among those treated for a given threshold based on SMART risk predictions

Lower curve represents % of population treated for a given threshold based on SMART risk predictions

Curve difference provides information on the clinical utility of SMART & is a visual depiction of model outperformance over treatment at random

Results:

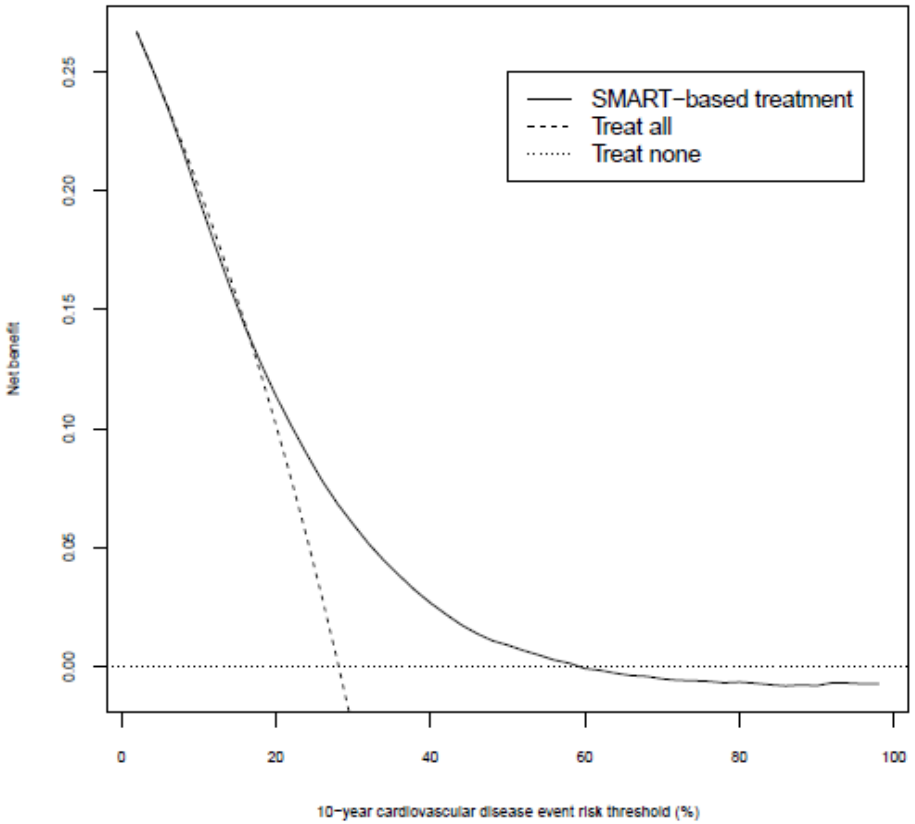
Net Benefit Decision Curve Analysis & Risk Thresholds



- Net benefit (y-axis) by 10-year predicted ASCVD risk threshold for treatment (x-axis) for:
  - Treat all: threshold=0% (dashed)
  - Treat none: threshold=100% (dotted)
  - SMART-based treatment: threshold=x-axis range (solid)
- SMART offers net benefits over current treatment decision-making approaches in the 20-60% predicted risk range, which are reasonable clinical thresholds

Results:

Net Benefit Decision Curve Analysis & Risk Thresholds (Cont.)



- For expensive treatments or those with undesired side effects, net benefits of high risk thresholds will be most relevant
- A threshold predicted risk of 40% would provide treatment to a segment of 17.4% of the population with observed risks of 49%

10-year predicted risk (%)	Observed risk (%)	n (%)
< 10	12	25,132 (10.3)
10 to < 20	19	86,483 (35.3)
20 to < 30	28	55,912 (22.9)
30 to < 40	36	34,501 (14.1)
≥ 40	49	42,550 (17.4)

Illustrative Example (Individual Level):

Measuring potential risk reduction associated with two different therapeutic interventions for patients with SMART 10-year predicted risks of 20%, 40%, or varied when metrics about relative risk reduction (RRR) upon treatment are available (overall or per unit reduction in non-HDL-C)

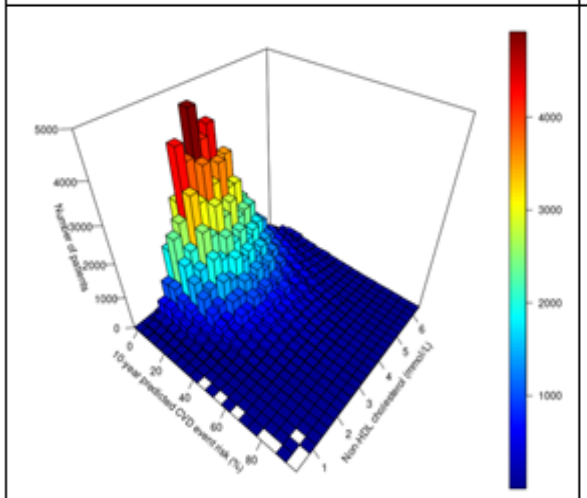
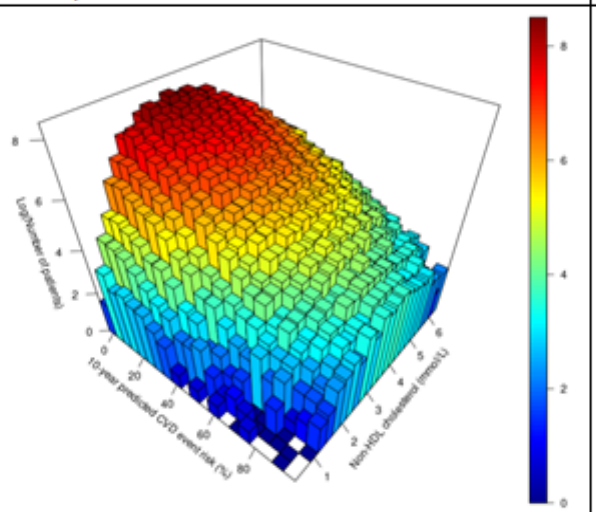
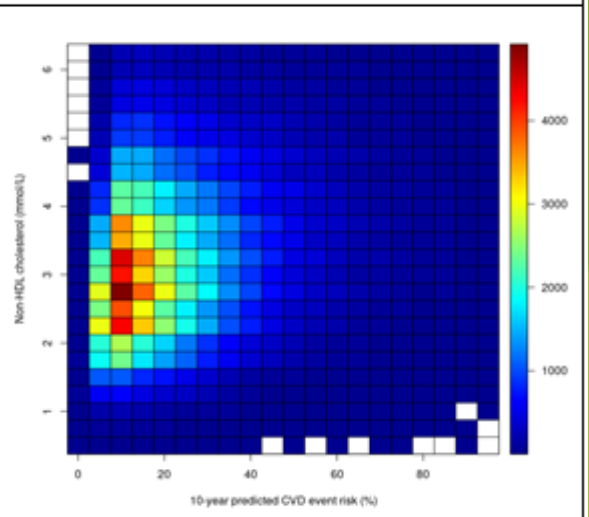
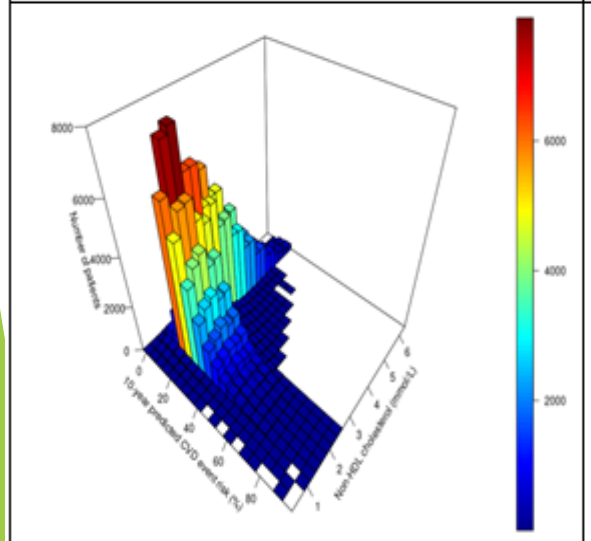
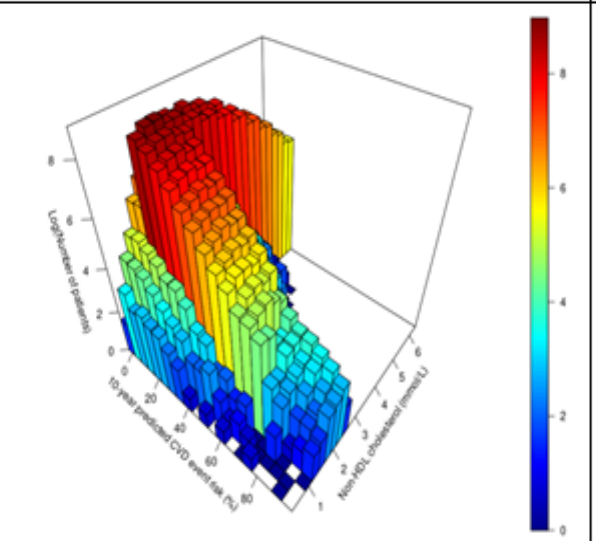
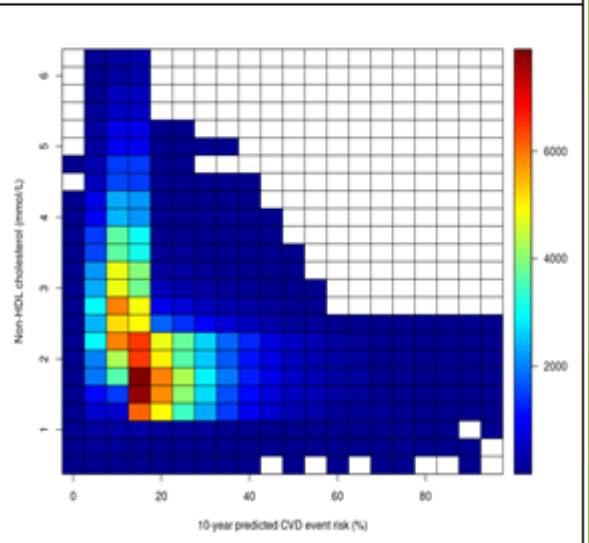
Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
non-HDL cholesterol (mmol/L)	2.79	3.26	2.95	3.07	2.89	2.61	2.79	3.20	3.49	3.49	3.49	3.49	3.49
HDL cholesterol (mmol/L)	0.517	0.517	0.491	0.698	0.646	0.698	0.698	0.517	0.749	0.646	0.465	0.517	0.646
Total cholesterol (mmol/L)	3.31	3.77	3.44	3.77	3.54	3.31	3.49	3.72	4.24	4.13	3.95	4.01	4.13
Age (years)	63.6	57.0	62.6	46.1	74.7	71.0	72.1	72.0	73.4	62.3	69.0	57.1	77.0
Sex	M	M	F	M	F	F	F	M	F	M	M	F	M
Current smoking status	No	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No	No
Systolic BP (mm Hg)	114	150	140	130	165	148	150	160	170	156	160	145	110
Diabetes Mellitus	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Coronary Heart Disease	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes
Cerebrovascular Disease	No	No	No	Yes	No	No	No	No	No	Yes	No	No	Yes
Abdominal Aortic Aneurysm	No	No	No	Yes	No	No	No	No	No	No	No	No	No
Peripheral Vascular Disease	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No
Years since ASCVD	-	-	2.2	-	11.8	-	12.6	14.5	23.9	4.5	7.5	-	21.5
eGFR (ml/min/1.73m)	67.7	71.0	54.1	71.5	78.6	48.4	59.9	75.3	30.9	85.7	54.2	53.1	91.1
hsCRP (mg/L) imputed	2.0	2.3	2.1	4.5	3.4	3.4	2.7	2.5	2.7	2.0	2.4	2.5	2.5
SMART 10-year predicted baseline risk (%)	20.0	20.0	20.0	20.0	40.0	40.0	40.0	40.0	75.7	23.8	45.4	18.1	61.7
Addition of rivaroxaban													
Predicted 10-year risk and 95% CI	15.2 (13.2-17.2)	15.2 (13.2-17.2)	15.2 (13.2-17.2)	15.2 (13.2-17.2)	30.4 (26.4-34.4)	30.4 (26.4-34.4)	30.4 (26.4-34.4)	30.4 (26.4-34.4)	57.5 (50.0-65.1)	18.1 (15.7-20.5)	34.5 (30.0-39.0)	13.8 (11.9-15.6)	46.9 (40.7-53.1)
Absolute risk reduction (%)	4.8	4.8	4.8	4.8	9.6	9.6	9.6	9.6	18.2	5.7	10.9	4.3	14.8
Addition of a PCSK9 MAb													
Estimated reduction in non-HDL cholesterol (mmol/L)	1.40	1.63	1.47	1.54	1.45	1.30	1.40	1.60	1.74	1.74	1.74	1.74	1.74
Predicted 10-year risk and 95% CI	15.5 (15.0-15.9)	14.8 (14.3-15.3)	15.2 (14.8-15.7)	15.1 (14.6-15.5)	30.6 (29.7-31.5)	31.4 (30.6-32.2)	30.9 (30.0-31.7)	29.7 (28.8-30.7)	54.8 (52.9-56.7)	17.2 (16.6-17.8)	32.9 (32.7-34.0)	13.1 (12.7-13.6)	44.7 (43.1-46.2)
Absolute risk reduction (%)	4.6	5.2	4.8	5.0	9.4	8.6	9.1	10.3	20.9	6.6	12.5	5.0	17.0

Hypothetical impact of two treatments:

- Rivaroxaban: anticipated absolute risk reduction is a fixed proportion of the starting risk (RRR=24% regardless of non-HDL-C[10])
- PCSK9 inhibitor: anticipated risk reduction dependent non-HDL-C reduction (16.90% risk reduction per unit of mmol/l – obtained from Cholesterol Treatment Trialists' Collaboration data)

Illustrative Example (Population Level):

Estimated impact of potential interventions for patients with SMART 10-year predicted risks above 20% and non-HDL-cholesterol above 2.6 mmol/L

[A] Histogram of 10-year predicted risk by non-HDL-C	[B] Log-scale histogram of 10-year predicted risk by non-HDL-C	[C] Heatmap of 10-year predicted risk by non-HDL-C
		
		

Strengths & Limitations

Strengths

- Big data -> Large population-based study, reasonably representative of all of UK population
- High quality, reliable data
- UK population-based study contains some differences in baseline characteristics vs. original study
- First external validation study of SMART model in a routine care population

Limitations

- Missing data
- hsCRP imputation unreliable for sub-populations with small counts (e.g., <40 years old among the original study)

Ongoing Research Using the SMART Model

- Expected risk impact of cholesterol-lowering drugs during RCTs
  - SMART can provide a baseline risk for patients across trial arms
  - Treatment effects (LDL-C/total cholesterol) across arms can be measured during trials
  - Relative and absolute 10-year risk reductions can be compared between arms across patients
  - Comparative 10-yr cardiovascular risk effectiveness of intervention arm vs. placebo can be compared with existing/alternative drugs
- See, for example: Ray K, Gunn L, McKay A, Feng A, Louie M, Ballantyne C. (2021) Estimated Cardiovascular Benefits of Bempedoic Acid in Patients with Established Cardiovascular Disease. *Journal of the American College of Cardiology*, 2021;77(18)S1,1460. [full manuscript currently under review]
- This approach can be used to evaluate the impact on 10-year CVD risks of treatments or interventions that modify sustainably any of the SMART model inputs (e.g. smoking, eGFR, etc.).

Conclusions

- Among those with established ASCVD (i.e., diagnosis > 6 months prior to cohort entry…Primary Cohort):
  - Slight under-prediction among lower risk & age groups, mainly for men
  - Overall model performance is similar to original study (validation cohort)

- Among those newly diagnosed with ASCVD (i.e., diagnosis a week prior to cohort entry…Secondary Cohort):
  - Model performance is weaker
  - ASCVD events within a few weeks/months can be linked to first event (e.g., relapse, related complications)

Conclusions (Cont.) & Practice Implications

- Model Performance
  - Relatively unaffected by missing data
  - Robust to the use of imputed hsCRP from different population
- SMART model is robust to transfer out of the original validation setting
- Viable tool for assessment of 10-year ASCVD predicted risks within population cohorts such as the UK
- Personalized medicine & treatment guidance -> Value in promoting shared decision-making between patients & providers
- Thinking about Next Steps
  - Use SMART model to create a desktop tool for primary care providers using EHR which may be useful in helping patients visualize ASCVD risk & impact of changes in different/multiple risk factors
  - Use SMART model to develop a tool that demonstrates how important potential treatments would modify risk

Thank You!

- For more detail, please see our manuscript in the ***European Journal of Preventive Cardiology***:
  - McKay AJ, Gunn LH, Ference BA, Dorresteijn JAN, Berkelmans GFS, Visseren FLJ, Ray KK. Is the SMART Risk Prediction Model Ready for Real World Implementation? A Validation Study in a Routine Care Setting of Approximately 380,000 Individuals. ***European Journal of Preventive Cardiology.*** **2021 epub ahead of print:**
  - https://doi.org/10.1093/eurjpc/zwab093

- Questions?
  - Contact: **laura.gunn@uncc.edu**

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