A simple risk model to predict cardiovascular death or myocardial infarction in patients with stable coronary artery disease

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on behalf of the CLARIFY investigators.

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Declaration of interest

- Research contracts (I have received research grants and Study Committee Honoraria from Servier)

Stable coronary artery disease

- Major cause of morbidity and mortality
- Risk stratification is recommended by the American and European guidelines
- There is a lack of a simple, contemporary, risk scoring system based on readily available risk factors that is applicable to a wide range of patients
- The CLARIFY registry provides an opportunity to develop such a score

CLARIFY registry

- Prospective, observational, longitudinal registry of a wide spectrum of patients with stable CAD
- Consecutive outpatients with stable CAD from 45 countries in Europe, the Americas, Africa, Middle East, and Asia/Pacific enrolled Nov 2009 - July 2010
- Follow-up of up to 5 years
- Collection of standardized data on e-CRF
- Complete data audits in 5% of randomly selected sites
- Independent Data Centre: Robertson Centre for Biostatistics, University of Glasgow

www.controlled-trials.com/ISRCTN43070564

CLARIFY Inclusion/ Exclusion criteria

Eligible patients had **stable CAD** defined as at least one of the following:

- documented MI > 3 months before enrolment
- angiographic demonstration of coronary stenosis ≥50%
- chest pain with evidence of myocardial ischaemia (stress electrocardiogram)
- CABG or PCI >3 months before enrolment

Exclusions:

- hospital admission for CV reasons in the past 3 months,
- planned revascularisation,
- conditions hampering participation or the 5-year follow-up
- severe heart failure

Development of risk model

- Study outcome: CVD death or non-fatal MI
- Subset of 15770 participants (1217 first events) who had assessment of eGFR and LVEF and other risk factors
- Model derived from a stepwise Cox proportional hazards model
- Discriminatory power assessed by Harrell's c-statistics and calibration lack of fit using approach described by May and Hosmer (1998), Lifetime Data Analysis
- Risk score evaluated in two external datasets
  - CORONOR stable CAD registry from northern France (n = 3624, events = 425)
  - Pooled placebo groups from the SIGNIFY and BEAUTIFUL trials of participants with stable CAD (n = 14356, events = 1365)
  - Partial calibration assessment, within the baseline hazard of the external dataset, comparing the calibration slope with the value 1, and applying the May and Hosmer test.
  - Calibration-in-the-large assessed using the method described by Crowson et al (2016), SMMR.

Factors included in the model

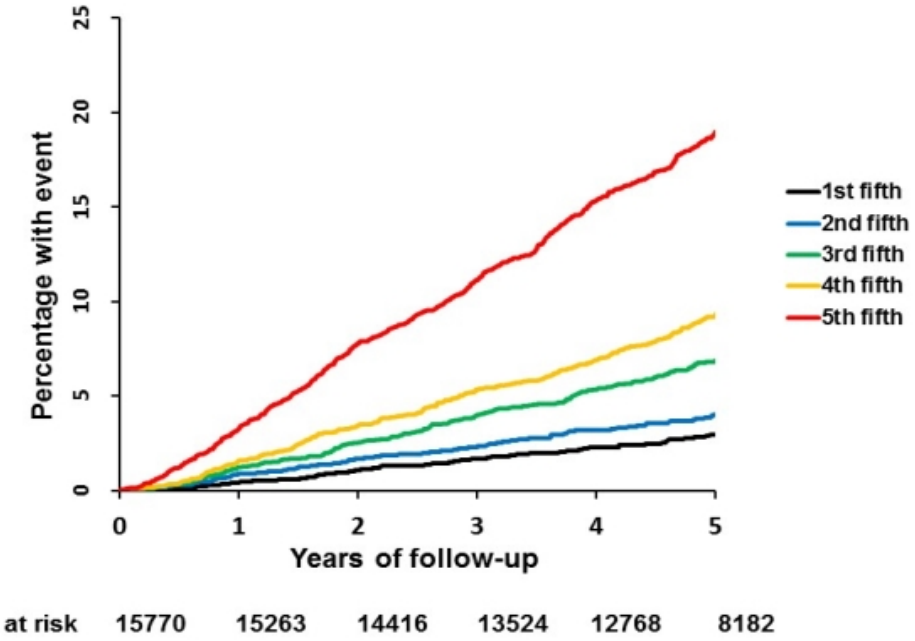
Predictor	HR (95% CI)
Age per 5 years	1.19 (1.15, 1.23)
Diabetes (insulin)	1.88 (1.58, 2.25)
Diabetes (not insulin)	1.30 (1.14, 1.48)
Current smoker	1.67 (1.39, 2.01)
Former smoker	1.33 (1.17, 1.51)
Current Angina	1.32 (1.17, 1.50)
AF/Flutter	1.54 (1.31, 1.82)
Myocardial Infarction	1.29 (1.13, 1.47)
Peripheral Arterial Disease	1.26 (1.08, 1.48)

Predictor	HR (95% CI)
PCI/CABG	0.78 (0.69, 0.88)
Stroke	1.51 (1.23, 1.84)
Hospitalisation for CHF	1.73 (1.46, 2.04)
eGFR < 30	2.73 (2.06, 3.61)
30 - 44.9	1.53 (1.26, 1.87)
45 - 59.9	1.27 (1.09, 1.48)
LVEF < 48%	1.85 (1.54, 2.22)
48 - 54.9%	1.35 (1.11, 1.65)

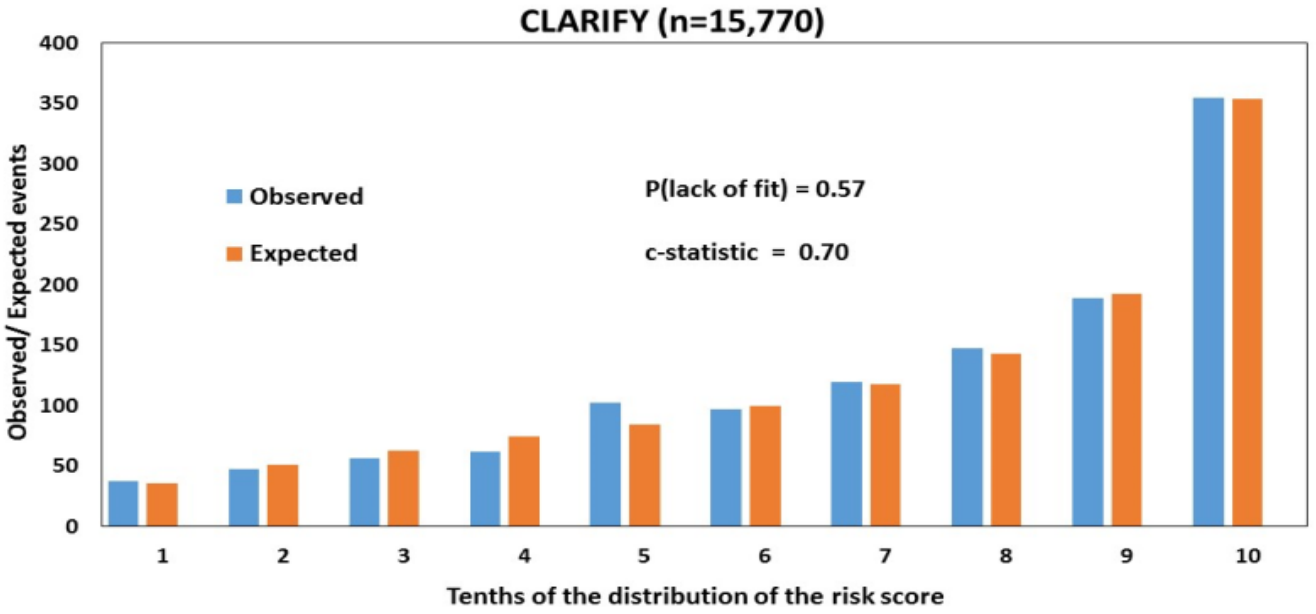
Calculation of risk

- The logarithms of the HRs are the weights assigned to each risk factor. A linear combination of the risk factors and the weights create a SCORE
- Prob (event before time T) = 1 - $[S_0(T)]^{\exp(\textbf{SCORE})}$
  - where $S_0(T)$ represents the baseline survival fuction
- $S_0(T)$ is estimated from the CLARIFY data

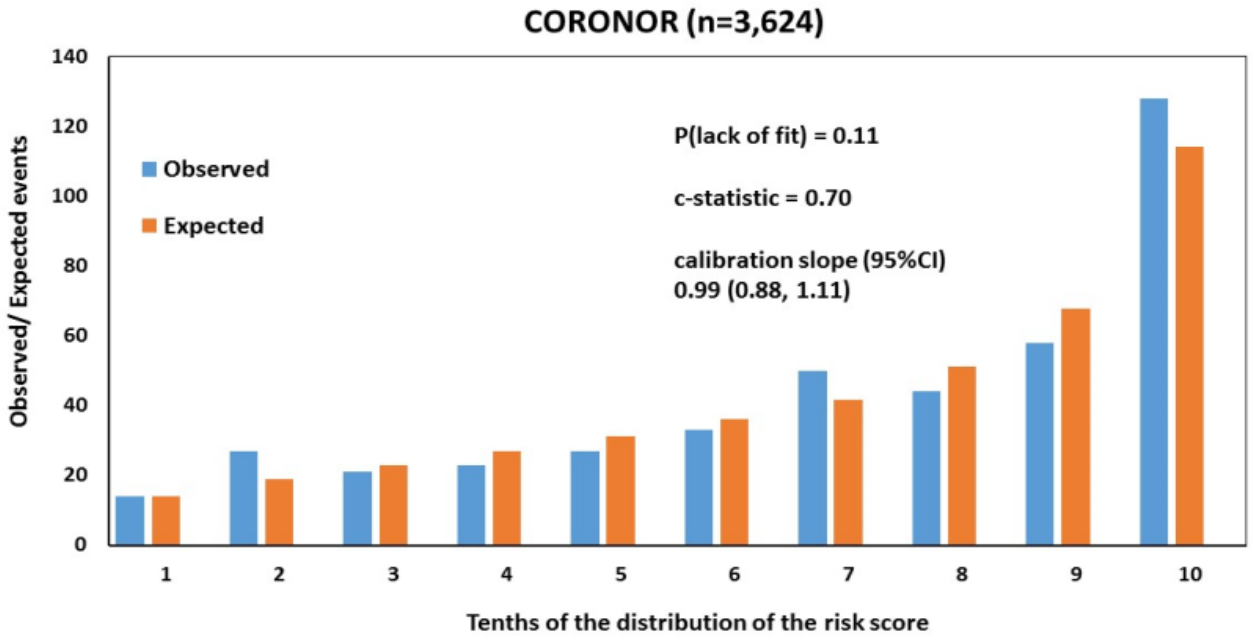
Cumulative incidence functions in CLARIFY split by fifths of the risk score



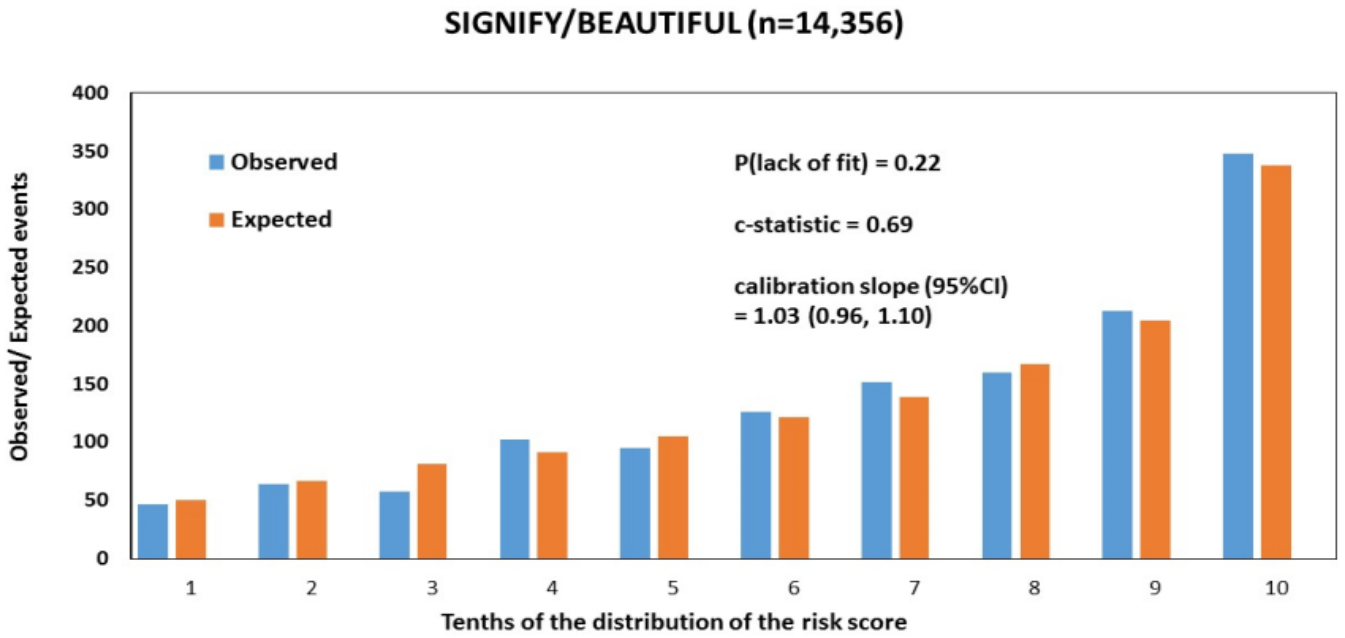
Observed and expected events in CLARIFY split by tenths of the risk score



Observed and expected events in CORONOR split by tenths of the risk score



Observed and expected events in SIGNIFY/BEAUTIFUL split by tenths of the risk score



Calibration-in-the-large

- When evaluated in SIGNIFY/BEAUTIFUL and in CORONOR there was evidence that the observed event rate was significantly higher overall (uniformly across the risk strata) in each external dataset compared to what was predicted by the CLARIFY risk model ($p < 0.001$)

Conclusions

- We have created a risk score for the outcome of CV death or non-fatal MI in patients with stable CAD based on readily available risk factors
- The score has been evaluated in two independent datasets covering a wide range of patients with stable CAD
- Although the score provides good discrimination, there is room for improvement, possibly with the addition of more sophisticated biomarker or imaging data
- The score needs to be calibrated. Further evaluation is required.

‘All statistical models are wrong, but some are useful’

George EP Box