Simple risk models to predict cardiovascular death in patients with stable coronary artery disease

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Aims
Risk estimation is important to motivate patients to adhere to treatment and to identify those in whom additional treatments may be warranted and expensive treatments might be most cost effective. Our aim was to develop a simple risk model based on readily available risk factors for patients with stable coronary artery disease (CAD).

Methods and results
Models were developed in the CLARIFY registry of patients with stable CAD, first incorporating only simple clinical variables and then with the inclusion of assessments of left ventricular function, estimated glomerular filtration rate, and haemoglobin levels. The outcome of cardiovascular death over ~5 years was analysed using a Cox proportional hazards model. Calibration of the models was assessed in an external study, the CORONOR registry of patients with stable coronary disease. We provide formulae for calculation of the risk score and simple integer points-based versions of the scores with associated look-up risk tables. Only the models based on simple clinical variables provided both good c-statistics (0.74 in CLARIFY and 0.80 or over in CORONOR), with no lack of calibration in the external dataset.

Conclusion
Our preferred model based on 10 readily available variables [age, diabetes, smoking, heart failure (HF) symptom status and histories of atrial fibrillation or flutter, myocardial infarction, peripheral arterial disease, stroke, percutaneous coronary intervention, and hospitalization for HF] had good discriminatory power and fitted well in an external dataset.

Study registration
The CLARIFY registry is registered in the ISRCTN registry of clinical trials (ISRCTN43070564).

Keywords
Risk model • Validation • Stable coronary artery disease • Cardiovascular death
Introduction

Stable coronary artery disease (CAD) is a major cause of death and disability and a growing component of the global cardiovascular (CV) burden. According to the American Heart Association report 2017, CAD remains responsible for one-third or more of all deaths in individuals over age 35 years. Stable CAD encompasses a spectrum of syndromes with heterogeneous risks, including patients who may or may not have experienced a previous acute coronary syndrome or undergone revascularization. Given this diversity, stratification of risk has been recommended by European and American guidelines to help guide the management of patients. Estimates of risk can be used in discussions with patients to help motivate the need for risk reduction interventions and encourage adherence to evidence-based therapies including lifestyle modification and secondary prevention drugs. The increasing cost of care is a major challenge for all healthcare systems. Health economic analysis plays an important role particularly for novel therapies. Treatments that provide the same relative benefit, independent of absolute risk, will be most cost effective when used to treat the highest risk patients. Risk models can be used for cost-effectiveness stratification.

The objective of this article is to develop a risk model for adverse outcomes in patients with stable CAD. To have widest applicability, the ideal risk model should be relatively simple and based on risk factors routinely recorded in clinical practice. Risk models derived from older cohorts have been criticized. Since CV event rates have been falling, a successful risk model must reflect contemporary risk. Risk models have been developed for patients with stable CAD, some derived for specific subpopulations such as patients with anginal symptoms, patients with suspected angina attending a chest pain clinic, survivors of acute coronary syndromes, populations including less stable participants with recent myocardial infarction (MI), and patients recruited to clinical trials. Many of these models do not reflect current clinical practice or absolute CV risk. A model has been developed for a UK primary care context using routinely collected data from a large UK general practice population as has a model incorporating N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT). A model has been reported based on a cohort of patients from a specific geographic area in northern France. Likewise, a simple point-based model was based on the REDuction of Atherothrombosis for Continued Health (REACH) registry. However, REACH included 27% of participants without a history of CAD and started enrolment in 2003.

We have created models for patients with stable CAD based on readily available risk factors collected in the prospective observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY), with validation in an external dataset, the ‘Suivi longitudinal des patients avec un trouble du rythme’ (CORONOR) observational study.

Methods

The CLARIFY registry

The CLARIFY registry has been described in detail elsewhere. Briefly, CLARIFY was an observational registry of over 33,000 patients with stable CAD, enrolled in 45 countries between 2009 and 2010 with a target follow-up of 5 years. Consecutive patients were enrolled by 2,898 investigators, with each investigator enrolling 10–15 consecutive patients over a short time period. The first patient was included on 26 November 2009 and recruitment was completed on 30 June 2010. Inclusion required any of the following four criteria (not mutually exclusive): previous MI (at least 3 months prior to enrolment), evidence of coronary stenosis >50%, proven symptomatic MI, or prior revascularization procedure. The main exclusion criteria were serious non-CV disease and conditions interfering with life expectancy or severe other CV disease [including advanced heart failure (HF)]. Follow-up visits were annually for five years, although some final visits were conducted late, interspersed with 6-month telephone calls. Baseline characteristics of the population included in our risk models and numbers of CV deaths observed in subgroups are given in Supplementary material online, Table S1.

Risk model derivation

Our aim was to provide a contemporary risk model based on risk factors that have been identified previously. We expected left ventricular ejection fraction (LVEF) and available laboratory variables in the CLARIFY dataset to potentially be important predictors. However, current estimates of these quantities were not always available in patients’ notes, particularly in participants recruited in primary care. Hence, we decided to develop models, both including and excluding LVEF and laboratory markers. We restricted our populations to participants who had complete assessments of the parameters relevant to each model. Most participants in CLARIFY had complete data when LVEF and laboratory markers were excluded. Laboratory markers investigated were estimated glomerular filtration rate (eGFR), haemoglobin, total cholesterol, and low and high density lipoprotein cholesterol levels. There was a significant degree of non-availability of recent measurements of LVEF and laboratory markers. In addition, varying combinations of total, low, and high density lipoprotein cholesterol levels were recorded, further reducing availability of these measurements. In the reduced datasets, these cholesterol measurements had limited independent prognostic value and hence were not considered further. The participants provided written informed consent for participation in the study. All of the study data were collected, managed, and analysed at the Robertson Centre for Biostatistics, University of Glasgow.

The clinical outcome evaluated in this study was CV death. This outcome included deaths of unknown cause in the derivation and validation cohorts. We were concerned that there would be heterogeneity in the use of coronary revascularization across the countries included in CLARIFY and, as the outcomes in CLARIFY were not adjudicated, stroke and hospitalization for HF would represent less reliable events. Initial analyses including MI in the endpoint resulted in models with reduced discriminatory power. Cardiovascular death is a key outcome for patients with stable CAD. It is defined more reliably in a study without endpoint adjudication and is more relevant than all-cause mortality in terms of possible modification in a population with CAD.

Statistical methods

To make our model more useful in clinical practice, we were advised to minimize the number of variables included in the model, with an objective of including no more than 10 variables. To this end we fitted stepwise Cox proportional hazards regression models using P-values of 0.05 to enter or remove variables. If the model contained more than 10 variables we focused on the first 10 variables selected. Stepwise fitting of models has been criticized, particularly with relatively small datasets relative to the number of variables investigated. However, it has been noted that selected predictor variables with very small P-values (say, <0.001) are
The ability of the models to discriminate between those with and without an outcome was assessed using Harrell’s c-statistic. A risk score was calculated for each participant based on each fitted model. The population was divided into 10 categories split by the deciles of the risk score. Observed numbers of events were calculated and expected numbers of events were calculated for each participant based on each fitted model. The population was divided into 10 categories split by the deciles of the risk score. After the fitting of models, categories were merged where there was little evidence of variation in risk.

### Results

#### Risk score derivation

In the main paper we focus on the results for top 10 predictor models. Results for the additional models containing all variables included in the stepwise regression fits are given in the Supplementary material online, Appendix. The CLARIFY population used for deriving the risk scores excluding LVEF and laboratory variables comprised 32 361 patients (1619 CV deaths, median (lower quartile–upper quartile) follow-up 5 (4.4–5.1) years, total follow-up 143 747 person-years) for the top 10 predictor model. When LVEF and laboratory variables were allowed to enter the model, the corresponding numbers were 15 768 patients (839 CV deaths, median (lower quartile–upper quartile) follow-up 5 (4.8–5.1) years, total follow-up 71 421 person-years) for the top 10 predictors model. Summary statistics, hazard ratios,
population. For each model, there was a stepwise increase in the primary endpoint in each fifth of risk, as would be expected in a stable demonstrated an approximately linear cumulative incidence of the outcome of CV death (shown in for the outcome of CV death (shown in Table 2) for Models 1 and 2. The plots visually suggest good calibration with borderline evidence of lack of calibration in the statistical tests for Model 1. More detailed analysis suggests that any lack of calibration is only evident for patients with very low risk. There is no evidence of lack of calibration for Model 2. The almost linear separation of the cumulative incidence curves for each model supports the proportional hazards assumptions as do the P-values when testing the interaction between the risk score and the logarithm of time, with all P-values >0.22. As a sensitivity analysis we also investigated the discriminatory power of the models in subgroups based on male/female and Caucasian/non-Caucasian splits. The c-statistics were very similar in the subgroups for all models.

### Table 2  Multivariable risk model incorporating the top 10 predictors of cardiovascular death, including left ventricular ejection fraction and laboratory variables (N = 15 768)

| Statistic | HR (95% CI) | P<sub>HR</sub> | P<sub>Group</sub> | \( \chi^2 \) |
|-----------|-------------|----------------|-----------------|-------------|
| Age (per 5 years) | 63.3 (10.5) | 1.28 (1.23–1.33) | <0.0001 | 161 |
| Diabetes | On insulin | 1152 (7.3) | 1.87 (1.52–2.30) | <0.0001 | <0.0001 |
| Referent: not diabetic | Not on insulin | 3774 (23.9) | 1.34 (1.15–1.56) | 0.0003 |
| Current angina | 4160 (26.4) | 1.23 (1.06–1.42) | 0.0067 | 7 |
| AF/flutter | 1194 (7.6) | 1.73 (1.44–2.07) | <0.0001 | 34 |
| MI | 10 028 (63.6) | 1.42 (1.21–1.66) | <0.0001 | 19 |
| PAD | 1624 (10.3) | 1.50 (1.26–1.79) | <0.0001 | 21 |
| Admission for CHF | 950 (6.0) | 1.97 (1.64–2.38) | <0.0001 | 51 |
| eGFR (mL/min/1.73 m<sup>2</sup>) | <30 | 225 (1.4) | 2.64 (2.94–3.58) | <0.0001 | <0.0001 |
| Referent: ≥60 | 30–44.99 | 839 (5.3) | 1.62 (1.30–2.01) | <0.0001 |
| LVEF (%) | 45–59.99 | 2383 (15.1) | 1.29 (1.09–1.55) | 0.0035 |
| Referent: >40 | 1232 (7.8) | 2.79 (2.30–3.38) | <0.0001 | <0.0001 |
| SBP ≥160 mmHg | 3728 (23.6) | 1.64 (1.40–1.93) | <0.0001 |
| 40–50 | 1154 (7.3) | 1.61 (1.30–1.99) | <0.0001 | 20 |

Hazard ratios and P-values for the variables included in the model. Statistics are n (%) with the exception of age which is summarized as mean (SD). All binary HRs have referent of not having the characteristic specified. For categorical variables with more than two categories, overall P-values for the variables are also given. Conditional \( \chi^2 \) statistics are given for each variable.

AF, atrial fibrillation; CI, confidence interval; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure; PAD, peripheral arterial disease; SD, standard deviation.

### External validation

In the CORONAR validation set, for Model 1, 318 of 4075 patients died from CV causes [c-statistic 0.80, 95% CI (0.77–0.82)]. The corresponding result for Model 2 was 291 events in 3622 patients [c-statistic 0.81, 95% CI (0.78–0.83)]. The P-values for the assessment of calibration-in-the-large were 0.136 and <0.001 for Models 1 and 2, respectively.
Figure 1  (A) Cumulative incidence of cardiovascular death as first event for Model 1, by fifths of the risk score distribution in the CLARIFY population. (B) Cumulative incidence of cardiovascular death as first event for Model 2, by fifths of the risk score distribution in the CLARIFY population.

Figure 2  (A) Calibration chart for Model 1 in the CLARIFY study dataset, comparing observed and expected numbers of events split by tenths of the distribution of the estimated risk with $P$-value for lack of fit. The mean estimated 5-year risks in the tenths are 1.03%, 1.71%, 2.28%, 2.86%, 3.51%, 4.31%, 5.32%, 6.76%, 9.26%, and 19.42%. (B) Calibration chart for Model 2 in the CLARIFY study dataset, comparing observed and expected numbers of events split by tenths of the distribution of the estimated risk with $P$-value for lack of fit. The mean estimated 5-year risks in the tenths are 1.07%, 1.65%, 2.15%, 2.65%, 3.24%, 3.99%, 5.01%, 6.55%, 9.53%, and 22.96%.
respectively, with the lack of fit for Model 2 suggesting that the model significantly underestimated the risk of patients in the CORONOR study. The REACH risk score for CV death within 20 months was calculated within CLARIFY. This score yielded a creditable c-statistic of 0.72. However, the estimated 20 months event rate of 1.99% overestimated the observed CLARIFY risk by ~28% indicating a lack of calibration, P-value <0.001.

Discussion

Summary and discussion of the findings

We have created simple risk models within a large international registry of patients with stable CAD. We have validated the discriminatory power of the models in an unselected registry of patients from the north of France (CORONOR). We describe in detail two risk models, based on restriction to the top 10 predictors of outcome, with and without the exclusion of measures of LVEF and laboratory parameters. Further models based on all predictors included in the stepwise regression models are described in the Supplementary material online, Appendix. All models performed well in terms of discrimination. Despite this, the models excluding LVEF and laboratory parameters were the only models that showed no evidence of lack of calibration-in-the-large in external validation, an important property of any prognostic model. Although the formal test for lack of calibration in CLARIFY for Model 1 is borderline significant, we note that this result is likely due to the high power in a very large study to detect small discrepancies which were evident only for patients at very low risk. Hence, our strong recommendation is that the Model 1 should be used because of its simplicity, good discrimination and calibration. Although Model 2 has a good c-statistic in CLARIFY and, in CORONOR, the lack of evidence that this model is well calibrated in an external dataset suggests that it should not be used. The explanation for the lack of calibration of Model 2 in CORONOR is unclear. However, this could be due to the fact that Model 2 could only be fitted in <50% of the participants in CLARIFY, a subset that might not be representative of the typical patients with stable CAD. The additional models in the Supplementary material online, Appendix, including all predictors in the stepwise models, do not provide any major improvement over the simpler models including only the top 10 predictors.

The directions of the hazard ratios for factors in the risk model are consistent with previous studies, with history of PCI and low systolic blood pressure (in a model containing raised systolic blood pressure as a risk factor) being the only medical history variables associated with lower risk. There has been variation in the hazard ratio associated with previous coronary revascularization in other studies. This likely depends on the underlying population studied and other factors included in the model and on whether coronary artery bypass graft is included or is the variable studied. In patients with previous MI, including those with events in the 3 months prior to inclusion, previous revascularization was associated with increased risk, while in more general populations with stable CAD like CLARIFY, previous revascularization was associated with lower risk. A likely explanation is the well-documented selection bias, whereby patients selected for revascularization, particularly PCI, tend to be younger and lower risk, whereas older more severe patients, with more advanced comorbidities can be recused by heart teams and managed conservatively.

Strengths of the approach

Given the improvement in outcomes in patients with acute coronary syndromes, CV mortality has decreased relative to non-CV causes of death. It was therefore important to exclude non-CV causes of death from the primary outcome and focus on CV death. The strengths of the models include their simplicity, the facts that they are more contemporary than previous models and that they were derived from a large heterogeneous international registry of consecutively recruited patients, with successful validation of two of the models in an external cohort study. CLARIFY and CORONOR had high rates of use of evidence-based secondary prevention therapies and were not restricted to the highly selected patient populations from randomized clinical trials.

Limitations of the research

There are limitations to the present analysis: events in CLARIFY were not adjudicated but investigator reported, and there may be some uncertainty about the reliability of the diagnosis of CV death in studies of outpatients. However, all data were monitored in 5% of the sites, which were randomly selected throughout the study with no major discrepancies detected. We expect that information regarding causes of death from volunteer investigators would be at least as good as and probably much better than information collected from death certificates. The discriminatory powers of our models are good, with particularly strong external validation of three of the models in the CORONOR study. However, there is always room for improvement. It seems likely that improvements in the discriminatory power would require either inclusion of a greater number of variables, including socioeconomic (e.g. social deprivation, attained educational level or other surrogates) or psychological variables (e.g. anxiety, depression) which may be difficult to measure or define, or the inclusion of more sophisticated imaging or biomarker data that may not currently be routinely available in patients’ records. In the near future, automated availability of a greater number of variables via electronic health records will likely allow easy access to more refined risk stratification, as already demonstrated. However, at present, the information required for the CLARIFY risk score is readily available to most physicians caring for patients with stable CAD. It is also true that c-statistics are driven not just by the model, but also by the heterogeneity of risk in the population studied. This is likely the explanation of the improved c-statistics in CORONOR, a study based on a less selected group of patients than CLARIFY. CLARIFY represents a more homogeneous group of patients with stable CAD, excluding those who are frail or at very high risk of future events. C-Statistics can be manipulated by including unstable patients who are patently at high risk without the need for evaluation with a risk model. The LVEF measurement used in CLARIFY was not standardized and could be collected by echocardiography, nuclear imaging, magnetic resonance imaging or angiography. Standardized measurements would likely have reduced variability and may have improved some of the models. However, this is often impossible to achieve in
Other approaches

To put our preferred model into context, as noted in the introduction, previous models have been based on specific subpopulations such as patients with angina\textsuperscript{5–7} or have focused on a complex set of variables collected in primary care\textsuperscript{12} or have been based on populations including unstable patients\textsuperscript{10} or patients without CAD.\textsuperscript{16} More recently two models focusing on patients with stable CAD have been developed that incorporate specific biomarkers such as NT-proBNP or hs-cTnT. A four variable model, including these variables, for the outcome of CV death, non-fatal MI, or stroke was developed that achieved modest c-statistics of 0.73 and 0.65 in the derivation and validation cohorts, respectively, with evidence of overestimation of risk in the top three tenths of the distribution of risk in the validation cohort.\textsuperscript{17} A second model for the outcome of CV death, incorporating seven variables, achieved c-statistics of 0.81 and 0.78. However, in the derivation cohort there was evidence of an increasing magnitude of overestimation of risk for annual risks $>1\%$.\textsuperscript{13} A weakness of this study in predicting outcomes with stable CAD is that the derivation study included patients as early as 1 month post-MI. Although these models show promise, they also illustrate the challenges of validating models in external populations. On this basis, we feel that the CLARIFY risk model makes an important contribution to risk prediction in patients with stable CAD.

We assessed the performance of the REACH risk score in CLARIFY. This model had reasonable discriminatory power but overestimated the risk in the CLARIFY population indicating a lack of calibration to a more contemporary population. While other models are available, there is no established model that is widely or preferentially used at present. In addition, several of the models require variables that were not available in the CLARIFY registry. In the future, availability of rich datasets may allow head-to-head comparisons of models and selection of the most parsimonious and effective ones. Nevertheless, our simple models, not requiring a measurement of LVEF or laboratory parameters, and yet achieving c-statistics $>0.8$ in external validation, set a high threshold to improve upon.

Concluding remarks

Any risk model cannot of course be the sole basis of decision-making for the treatment of individual patients. Rather, risk estimation should be used to form an overall clinical decision, together with an assessment of the individual levels of available risk factors included and not included in the model along with comorbidities and the potential for adverse effects of any treatment being considered. We do not recommend the use of our preferred risk model in patients with unstable CAD or in high risk patients with HF.

Declarations

Ethics approval and consent to participate

The participants provided written informed consent for participation in the study.

Consent for publication

Not applicable.

Availability of data and material

Participants in the study did not provide consent for their data to be made widely available. Because of the large number of countries involved and the very large number of sites and ethical review committees, it is not feasible to respectively obtain permission to make the dataset available. However, the authors will consider reasonable requests for access to summary information.

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References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017;135:e146–e603.

2. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949–3003.

3. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Apostolos P et al. American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/ST/SOS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2012;126:3097–3137.

4. Pylypchuk R, Wells S, Kerr A, Poppe K, Riddell T, Harwood M et al. Cardiovascular disease risk prediction equations in 400000 primary care patients in New Zealand: a derivation and validation study. Lancet 2018;391:1897–1907.

5. Clayton TC, Lubsen J, Pocock S, Yokai Z, Kirwan B-A, Fox KAA et al. Risk score for predicting death, MI, and stroke in patients with stable angina, based on a large randomised trial cohort of patients. BMJ 2005;331:869.

6. Daly CA, De Stavola B, Sendon JLL, Tavazzi L, Boersma E, Clemens F et al. Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study. BMJ 2006;332:262–267.

7. Kahan T, Forslund L, Held C, Billing E, Eriksson SV et al. Risk prediction in stable angina pectoris. Eur J Clin Invest 2013;43:141–151.

8. Søkhri N, Perel P, Clayton T, Feder GS, Hemingway H, Timmis A. A 10-year prognostic model for patients with suspected angina attending a chest pain clinic. Heart 2016;102:869–875.

9. Muncher JC, Colquhoun D, Simes RJ, Glasziou P, Harris P, Singh BB et al. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. LIPID Study Investigators. J Am Coll Cardiol 2001;38:56–63.

10. Bohula EA, Bonaca MP, Braunwald E, Aylward PE, Corbalan R, De Ferrari GM et al. Atherosclerotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous MI. Circulation 2016;134:304–313.

11. Bates L, Barendse R, Steyerberg EW, Simsoms ML, Decker JS, Nieboer D et al. Development and validation of a cardiovascular risk assessment model in patients with established coronary artery disease. Am J Cardiol 2013;112:27–33.

12. Rapsomaniki E, Shah A, Perel P, Denaxas S, George J, Nicholus O et al. Prognostic models for stable coronary artery disease based on electronic health record cohort of 102 023 patients. Eur Heart J 2014;35:844–852.

13. Lindholm D, Lindback J, Armstrong PW, Budaj A, Cannon CP, Granger CB et al. Biomarker-based risk model to predict cardiovascular mortality in patients with stable coronary disease. J Am Coll Cardiol 2017;70:813–826.

14. Bauters C, Deeneve M, Tricot O, Meurice T, Lamblin N; CORONOR Investigators. Prognosis of patients with stable coronary artery disease (from the CORONOR Study). J Am Coll Cardiol 2014;63:1142–1145.

15. Bauters C, Tricot O, Meurice T, Lamblin N; CORONOR Investigators. Long-term risk and predictors of cardiovascular death in stable coronary artery disease: the CORONOR study. Coron Artery Dis 2017;28:636–641.

16. Wilson PW, D’Agostino R Sr, Bhatt DL, Eagle K, Pencina MJ, Smith SC et al. An international model to predict recurrent cardiovascular disease. Am J Med 2012;123:695–703.

17. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180–189.

18. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. BMJ 2009;338:b604.

19. Søkhri E, Greenlaw N, Ferrari R, Ford I, Fox KM, Tardif JC et al. on behalf of the CLARIFY Investigators. Rationale, design, and baseline characteristics of the CLARIFY registry of outpatients with stable coronary artery disease. Clin Cardiol 2017;40:797–806.

20. Harrell FE Jr. Lee KL, Mark DB. Multivariable prognostic models: issues in developing, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:371–387.

21. May S, Hosmer DW. A simplified method of calculating an overall goodness-of-fit test for the Cox proportional hazards model. Lifetime Data Anal 1998;4:109–120.

22. Crowson CS, Atkinson EJ, Therneau TM. Assessing calibration of prognostic scores. Stat Med 2016;35:1692–1706.

23. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P et al. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation 2017;136:1908–1919.

24. Spoon DB, Paolis P, Singh M, Holmes DR Jr. Gersh BJ, Rihal CS et al. Trends in cause of death after percutaneous coronary intervention. Circulation 2014;129:1286–1294.

25. Steg PG, Lopez Sendon J, Lopez de Sa E, Goodman SG, Gore JM, Anderson FA Jr et al. External validity of clinical trials in acute myocardial infarction. Arch Intern Med 2007;167:68–73.

26. Rothwell PM. External validity of randomised controlled trials: “to whom do the results of this trial apply?” Lancet 2005;365:82–93.

27. Beatty AL, Ku IA, Bibbins-Domingo K, Christenson RH, D, Filippi, R Ganz, P et al. Traditional risk factors versus biomarkers for prediction of secondary events in patients with stable coronary heart disease: from the heart and soul study. J Am Heart Assoc 2015;4:e001646.