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Comparisons of established risk prediction models for cardiovascular disease: systematic review

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Abstract

Objective To evaluate the evidence on comparisons of established cardiovascular risk prediction models and to collect comparative information on their relative prognostic performance.

Design Systematic review of comparative predictive model studies.

Data sources Medline and screening of citations and references.

Study selection Studies examining the relative prognostic performance of at least two major risk models for cardiovascular disease in general populations.

Data extraction Information on study design, assessed risk models, and outcomes. We examined the relative performance of the models (discrimination, calibration, and reclassification) and the potential for outcome selection and optimism biases favouring newly introduced models and models developed by the authors.

Results 20 articles including 56 pairwise comparisons of eight models (two variants of the Framingham risk score, the assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network to assign preventative treatment (ASSIGN) score, systematic coronary risk evaluation (SCORE) score, Prospective Cardiovascular Münster (PROCAM) score, QRESEARCH cardiovascular risk (QRISK1 and QRISK2) algorithms, Reynolds risk score) were eligible. Only 10 of 56 comparisons exceeded a 5% relative difference based on the area under the receiver operating characteristic curve. Use of other discrimination, calibration, and reclassification statistics was less consistent. In 32 comparisons, an outcome was used that had been used in the original development of only one of the compared models, and in 25 of these comparisons (78%) the outcome-congruent model had a better area under the receiver operating characteristic curve. Moreover, authors always reported better area under the receiver operating characteristic curves for models that they themselves developed (in five articles on newly introduced models and in three articles on subsequent evaluations).

Conclusions Several risk prediction models for cardiovascular disease are available and their head to head comparisons would benefit from standardised reporting and formal, consistent statistical comparisons. Outcome selection and optimism biases apparently affect this literature.

Introduction

Cardiovascular disease carries major morbidity and mortality.[1] To effectively implement prevention strategies clinicians need reliable tools to identify individuals without known cardiovascular disease who are at high risk of a cardiovascular event.[2][3] For this purpose, multivariable risk assessment tools, such as the Framingham risk score, are recommended for clinical use.[4] Besides the Framingham risk score, several other risk prediction tools combining different sets of variables have been developed and validated.[5][6] Some investigators have evaluated the performance of two or more risk prediction models in the same populations.

We evaluated the evidence on comparisons of established cardiovascular risk prediction models. We systematically collected comparative information on discrimination, calibration, and reclassification performance and evaluated whether specific biases may have affected the inferences of studies comparing such models.

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Methods

Eligible models and literature search

We assessed prediction models for the risk of cardiovascular disease in general populations that were considered in two recent expert reviews[5][6]: the Framingham risk score[7-9] (and the national cholesterol education program–adult treatment panel III version[10]), the assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network to assign preventative treatment (ASSIGN) score,[11] systematic coronary risk evaluation (SCORE) score,[12] Prospective Cardiovascular Münster (PROCAM) score,[13] QRESEARCH cardiovascular risk (QRISK1 and QRISK2) algorithms,[14][15] Reynolds risk score,[16][17] and the World Health Organization/International Society of Hypertension score.[18] Different versions of the Framingham risk score were categorised as Framingham risk score (including the Framingham risk score described by Anderson et al for risk of coronary heart disease and stroke[7] and the Framingham risk score proposed by Wilson et al[8]) (also proposed by National Institute for Health and Clinical Excellence guidelines) and as FRS (CVD) (which included the global Framingham risk score equations to predict cardiovascular disease[9]). See supplementary table 1 for additional details.

Medline (last update July 2011) was searched for articles with data on the performance of at least two of these models. We also scrutinised the received citations (through SCOPUS) and the references of all eligible papers for any additional relevant studies (see appendix for primary screening algorithm). Titles and abstracts were screened first and potentially eligible articles scrutinised in full text. No year or language restrictions were applied.

Study eligibility

Articles were eligible if they examined at least two pertinent risk models for the prediction of cardiovascular disease in populations without cardiovascular disease or general populations. We included original articles irrespective of sample size and duration of follow-up. Eligible outcomes were cardiovascular disease (and any composite cardiovascular disease end point), cardiovascular disease mortality, and coronary heart disease, including stable disease and acute coronary syndromes. When different published data on identical comparisons were identified comparing the same models, in the same cohort, and for the same outcome, we kept only the data that included the largest number of events. We excluded cross sectional studies, studies where all cause mortality was the only outcome, studies that used models to calculate the baseline risk without providing outcome data, and studies including exclusively patients with specific morbidities—that is, patients with known cardiovascular disease, diabetes, or other diseases.

Two investigators (GCMS, KCS) independently carried out the literature searches and assessed the studies for eligibility. Discrepancies were resolved by consensus and arbitration by two other investigators (IT, JPAI).

Data extraction

Two investigators independently extracted data from the main paper (GCMS, IT) and any accompanying supplemental material. The following items of interest were recorded in standardised forms: study design (prospective or retrospective), year of publication, sample size, type of population, percentage of baseline population with pre-existing cardiovascular disease, and reported risk models. We recorded the clinical end points assessed in each study (cardiovascular disease, cardiovascular disease mortality, coronary heart disease) and the respective number of events. When multiple different eligible outcomes or populations were identified in the same model comparison, we considered each outcome or cohort separately. Similarly, when more than two prognostic models were presented in an article, we considered all possible pairwise comparisons as eligible. Whenever a study also examined subgroups, such as males and females, we focused on the whole population unless only data per subgroup were provided; in those cases, we extracted data for each eligible subgroup separately.

Moreover, for each study we also captured whether the authors reported the presence of missing data on examined outcomes and on variables included in risk prediction models; and, if so, we recorded how missing data were managed (with imputation and by which methods, exclusion of missing observations, or other). We further extracted information on the geographical origin of each study and noted whether it was the same country to the one in which one (or both) of the compared models was initially developed.

For each model in each article we extracted metrics on discrimination (area under the receiver operating characteristic curve (or the equivalent C statistic), D statistic, R^2 statistic, and Brier score), their 95% confidence intervals, and the P value for comparison between models when available.[19][20] We also captured calibration[21] and reclassification[22][23] metrics. We extracted information on whether the observed versus predicted ratio and lack of fit statistics were reported, and whether the calibration plot was shown. Finally, we extracted information on reclassification statistics, such as the net reclassification index, and on the classification percentages of each model along with the thresholds used by each study.

Data analysis and evaluation of biases

We analysed each risk model pairwise comparison separately. For each comparison we noted the model with a numerically higher area under the receiver operating characteristic curve estimate, and whether there was formal statistical testing of the difference in areas under the receiver operating characteristic curve. When confidence intervals were not available, we estimated them as previously proposed.[24] We also recorded separately which pairwise comparisons had a relative difference in area under the receiver operating characteristic curve exceeding 5% (for example, if the worse score had an area under the receiver operating characteristic curve of 0.70, the better score had one >0.70×1.05=0.735). The choice of a 5% threshold was chosen for descriptive purposes only. Furthermore, we noted whether models differed in other performance metrics. Calibration was considered better when the observed to predicted ratio was closer to 1.

We also evaluated the potential for outcome selection and optimism biases. Some of the examined risk scores have been originally developed for different cardiovascular outcomes (see supplementary table 1). We evaluated whether the examined outcome in each comparison was used in the original development of only one of the two compared models and, if so, whether the outcome-congruent model showed better performance. Owing to optimism bias, a new model may have better performance than the competing standard model when it is first presented, but not in subsequent comparisons. Therefore we noted whether each article described the application of previously established models or was the first to describe or validate a specific model or models. Moreover, authors who developed one model may favour publishing results that show its superiority against competing models. We thus noted whether

any of the study authors had been involved in the development of any of the assessed models. Finally, we recorded the authors' comments on the relative performance of the model and examined whether these were affected by such potential biases.

Analyses were done in Stata 10.1 (College Station, TX). P values are two tailed.

Results

Inclusion of studies

Of 672 published articles screened at title and abstract level, 74 were identified as potentially eligible for inclusion in the review. Of these, 58 articles were excluded because they only compared models using a baseline risk calculation without association with outcomes (n=20); assessed only patients with specific conditions (diabetes (n=11), HIV infection (n=4), known cardiovascular disease (n=3), liver transplantation (n=1), schizoaffective disorder (n=1), systemic lupus erythematosus or rheumatoid arthritis (n=1)); or had ineligible model comparisons (n=10), ineligible outcomes (non-cardiovascular disease outcomes) (n=6), or duplicate comparisons (n=1). (See supplementary web figure). Searches of references and citations yielded another four eligible articles. Overall, 20 articles[11 13-16 25-39] were analysed (table 1⇓).

Characteristics of eligible studies and risk models

All articles were published after 2002 (table 1). All but two[25 27] studies had prospective designs. Most (n=17) articles assessed populations of European descent. The median sample size was 8958 (interquartile range 2365-327 136).

Eight different risk models were evaluated (all of those considered upfront eligible, except the World Health Organization/International Society of Hypertension score). Of the 28 possible types of pairwise comparisons of these eight risk scores, 14 existed in the literature. After excluding overlapping data (same models compared, same outcome, same cohort), independent data were available on 56 individual comparisons of risk models. Eight articles reported data for men and women separately (44 comparisons), four reported overall data (four comparisons), seven assessed only males (seven comparisons), and one assessed only women (one comparison, table 2⇓). The Framingham risk score or FRS (CVD) were involved in 50 of 56 comparisons (tables 1 and 2). In four articles (eight comparisons) the authors reported information on missing data on the examined outcomes, and in all cases the investigators excluded the respective participants (see supplementary table 2). Information on missing data for variables included in risk models was reported in 11 articles (44 comparisons). Different strategies were implemented to deal with missing data and sometimes different strategies were applied to different predictors: exclusion of participants with missing data[14 15 28-32 38] (27 comparisons), multiple imputation technique[14 15 28] (16 comparisons), value generation by multivariate regression methods[25] (10 comparisons), replacement by the mean value of the variable[26 31 36] (nine comparisons), and assumption that participants without information on smoking were non-smokers[26 31] (eight comparisons, also see supplementary table 2). In 25 comparisons, the geographical origin of the study population was the same as the origin of the population in which at least one of the examined models was initially developed (see supplementary table 3).

Discrimination performance

Area under the receiver operating characteristic curve estimates were available for all 56 pairwise comparisons (table 2). Confidence intervals were given for only 20 pairs and P values for the comparison of area under the receiver operating characteristic curve were available for only two comparisons (in a single study[11]).

The relative difference between the area under the receiver operating characteristic curve estimates exceeded 5% in only 10 (18%) comparisons, but even these differences were inconsistent: compared with SCORE, the Framingham risk score was worse in two cases but better in another two; compared with PROCAM, the Framingham risk score was worse in one case but better in another three; finally, FRS (CVD) was worse than SCORE in two cases.

Among the 50 comparisons that included variants of the Framingham risk score, in 37 (74%) the area under the receiver operating characteristic curve estimate was higher for the comparator model.

Use of other discrimination metrics (D statistic, R^2 statistic, Brier score) was inconsistent. At least one of these metrics was available for 26 comparisons (see supplementary table 4).

Calibration

Calibration performance was reported in 38 comparisons (see supplementary table 5). Observed versus predicted ratio estimates were available for 23 comparisons and results were quite inconsistent. The Framingham risk score was better than FRS (CVD) in one comparison but worse in another. The Framingham risk score was worse than ASSIGN in two comparisons, SCORE in two, QRISK1 in five, and PROCAM in one comparison, but it was better than ASSIGN in two comparisons, PROCAM in two, and QRISK1 in one comparison. FRS (CVD) was worse than ASSIGN in two comparisons and QRISK1 in one comparison, but it was better than QRISK1 in another comparison. Finally, QRISK1 was better than ASSIGN in two comparisons.

The 95% confidence intervals of the observed to predicted ratio were available in only two comparisons, so we could not tell whether differences were beyond chance.

Risk reclassification

Reporting of risk classification and reclassification was uncommon; information was available for 10 comparisons. In nine comparisons a dichotomous cut-off point of 20% 10 year risk was used; one study used 0-5, 5-10, 10-20, >20% as risk thresholds. All comparisons reported the number of participants reclassified with use of alternative models along with the predicted and observed risk in each risk category. The net reclassification index was calculated for six comparisons between non-nested models, all using the 20% threshold: ASSIGN versus Framingham risk score (n=2, net reclassification index 4%, 16%), ASSIGN versus FRS (CVD) (n=2, 0%, 12%), and FRS (CVD) versus Framingham risk score (n=2, 4% for both).

Outcome selection bias

In 13 comparisons the examined outcome was the one for which both compared models had been developed and validated, whereas in 32 comparisons only one of the compared models had been originally developed for that outcome, and in the other 11 comparisons none of the compared models had been developed originally for that outcome. When an outcome was

used that had been used in the original development of only one of the compared models, it was more common for the outcome-congruent model to have a better area under the receiver operating characteristic curve than the comparator (25 *v* 7, P<0.001, based on point estimates).

Optimism bias

Five articles[11 13-16] (12 comparisons) described a model for the first time (table 3⇓). In all 12 comparisons, the new model had a higher area under the receiver operating characteristic curve estimate than Framingham risk score versions, although the relative improvement exceeded 5% only for one model[13] (PROCAM better than Framingham risk score). Ten subsequently published articles addressed one or more of these same comparisons (table 3). In three[14 15 32] articles at least one of the authors had been previously involved in the development of one of the compared models, and that model continued to have a better area under the receiver operating characteristic curve. Conversely, two[35 39] of the seven[26 28 35 36-39] articles published by entirely independent authors showed the older model to have a better area under the receiver operating characteristic curve.

Author interpretation

Overall, the authors claimed superiority of one model in 31 of 56 comparisons (see supplementary table 3). In 25 of these 31 comparisons a Framingham risk score version was one of the models compared and in all 25 cases the comparator model was claimed to be superior: SCORE>Framingham risk score (n=3), ASSIGN>Framingham risk score (n=6), PROCAM>Framingham risk score (n=1), QRISK1>Framingham risk score (n=4), QRISK2>Framingham risk score (n=4), FRS (CVD)>Framingham risk score (n=2), ASSIGN>FRS (CVD) (n=2), QRISK1>FRS (CVD) (n=2), and Reynolds risk score>Framingham risk score (n=1). The other six pairs where superiority was claimed were QRISK2>QRISK1 (n=4) and QRISK1>ASSIGN (n=2). For 22 comparisons the authors either claimed that both models had good or equal discriminatory ability or did not comment on their relative performance. In eight articles the authors favoured models they had themselves developed (five first publications, three subsequent publications). Authors involved in the development of a model never favoured a comparator.

Discussion

Comparative studies on the relative performance of established risk models for prediction of cardiovascular disease often suggest that one model may be better than another. In particular, the Framingham risk score usually had inferior performance compared with other models, but the results were sometimes inconsistent across studies, and inferences may be susceptible to potential biases and methodological shortcomings. Most studies did not compare statistically the models that they examined. Models were usually reported to be superior against comparators when the examined outcome was the one that the model was developed for but not the one for which the comparator was developed. Articles presenting new models or including authors involved in the original development of a model favoured the model that the authors had developed.

Comparison with other studies

Head to head comparisons of emerging risk models are important to perform so as to document improvements in risk prediction. We showed that such data are limited and, when

available, difficult to interpret. Discrimination, the ability of a statistical model to distinguish those who experience cardiovascular disease events from those who do not, was presented for all comparisons but the differences were usually small. Only in 18% of the comparisons did the relative difference between the two areas under the receiver operating characteristic curve exceed 5%. Most studies did not report the confidence intervals of the area under the receiver operating characteristic curve or the P values for the comparison between models. Calibration, which assesses how closely predicted estimates of absolute risk agree with actual outcomes, was reported in two thirds of the comparisons, but again formal statistical testing was lacking. Although the area under the receiver operating characteristic curve is the most commonly used discrimination metric, it has limitations.[40] Similarly, assessment of model calibration by the Hosmer-Lemeshow goodness of fit test is sensitive to sample size and gives no information on the extent or direction of miscalibration.[41 42] Evaluating calibration graphically either by 10ths of predicted risk or by key prognostic variables, such as age, is more informative than a single P value.

Assessment of risk reclassification was sparse and, when assessed, it was suboptimally described, in agreement with previous empirical evaluations.[43 44] Reclassification is a clinically useful concept. It makes most sense when the categories of risk are clearly linked to different indications for interventions. It may be informative to report the percentage of patients changing risk categories and their direction of change. However, summary metrics such as the net reclassification index are problematic, especially when the compared models are non-nested (that is, they include different predictors and are derived from different datasets), and the problems are even worse when at least one model is poorly calibrated.[45]

Choices of comparators and outcomes are particularly important in such studies. Models were often claimed to be superior when the outcome examined was different from what the comparator model had been developed for. In those cases, the comparator is disadvantaged and becomes a strawman comparator towards which superiority can easily be claimed; a phenomenon analogous to that observed in clinical trial studies where an intervention is compared against a placebo or ineffective intervention.[46] In addition, we observed some evidence of potential optimism bias, with potentially unwarranted belief in the predictive performance of newer models[47] by the scientists developing them. Authors consistently claimed superiority of the models that they have developed versus comparators. While genuine progress in predictive ability is a possible explanation for this pattern, it is worthwhile to ensure that such favourable results are also validated by completely independent investigators.

Limitations of the study

Our study has limitations. Firstly, most of the analysed studies and models pertained to populations of European descent. Risk models may, however, perform differently in populations of different racial or ethnic backgrounds.[48 49] Systematic efforts for model validation in other populations are essential.[50] Secondly, most confidence intervals of area under the receiver operating characteristic curve estimates were unavailable and were derived as previously described.[24] We examined whether 95% confidence intervals did or did not overlap. A more formal statistical testing would have required access to individual level data to account for the fact that models were evaluated in the same population in each comparison using the pairwise individual level correlation in the calculations.[51]

Conclusions

Current studies comparing predictive models often have limitations or are missing information, which makes it difficult to reach robust conclusions about the best model or the ranking of performance of models. It should also be acknowledged that the answers to these questions may be different in different populations and settings. The box shows several items and pieces of information that would be useful to consider in the design and reporting of results in studies comparing different predictive models to make these evaluations more useful, unbiased, and transparent, and to allow a balanced interpretation of the relative performance of these models.

The clinical usefulness of these models should be ultimately established on the basis of their potential for affecting decisions on treatment and prevention and improving health outcomes.[52] Ideally, this would require randomised trials where patients are allocated to being managed using information from different predictive models. Given that such trials are difficult to perform and costly, evidence from well conducted studies of comparative predictive performance will remain important. Our empirical evaluation suggests that such studies may benefit from using standardised reporting of discrimination, calibration, and reclassification metrics with formal statistical comparisons; and standardised outcomes that are clinically appropriate and, whenever possible, relevant to both compared models. Finally, improved performance of new models versus established ones should ideally be documented in several studies carried out by independent investigators.

1 Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association. *Circulation* 2010;121:e46-215.
2 National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III): third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report. *Circulation* 2002;106:3143-421.
3 Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, et al. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;115:1481-501.
4 Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002;106:388-91.
5 Cooney MT, Dudina A, D'Agostino R, Graham IM. Cardiovascular risk-estimation systems in primary prevention: do they differ? Do they make a difference? Can we see the future? *Circulation* 2010;122:300-10.
6 Berger JS, Jordan CO, Lloyd-Jones D, Blumenthal RS. Screening for cardiovascular risk in asymptomatic patients. *J Am Coll Cardiol* 2010;55:1169-77.
7 Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293-8.
8 Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
9 D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743-53.
10 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2486-97.
11 Woodward M, Brindle P, Tunstall-Pedoe H; SIGN group on risk estimation. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007;93:172-6.
12 Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987-1003.
13 Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. *Circulation* 2002;105:310-5.
14 Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007;335:136.
15 Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;336:1475-82.
16 Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611-9.
17 Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation* 2008;118:2243-51.
18 Prevention of cardiovascular disease: guidelines for assessment and management of cardiovascular risk. World Health Organization; 2007.
19 Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007;115:928-35.
20 Zou KH, O'Malley AJ, Mauri L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. *Circulation* 2007;115:654-7.
21 Hosmer DW, Hjort NL. Goodness-of-fit processes for logistic regression: simulation results. *Stat Med* 2002;21:2723-38.
22 Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157-72; discussion 207-12.
23 Cook NR, Ridker PM. Advances in measuring the effect of individual predictors of cardiovascular risk: the role of reclassification measures. *Ann Intern Med* 2009;150:795-802.
24 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29-36.
25 Pandya A, Weinstein MC, Gaziano TA. A comparative assessment of non-laboratory-based versus commonly used laboratory-based cardiovascular disease risk scores in the NHANES III population. *PLoS One* 2011;6:e20416.
26 De la Iglesia B, Potter JF, Poulter NR, Robins MM, Skinner J. Performance of the ASSIGN cardiovascular disease risk score on a UK cohort of patients from general practice. *Heart* 2011;97:491-9.
27 Barroso LC, Muro EC, Herrera ND, Ochoa GF, Hueros JI, Buitrago F. Performance of the Framingham and SCORE cardiovascular risk prediction functions in a non-diabetic population of a Spanish health care centre: a validation study. *Scand J Prim Health Care* 2010;28:242-8.
28 Collins GS, Altman DG. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. *BMJ* 2010;340:c2442.
29 Van der Heijden AA, Ortegon MM, Niessen LW, Nijpels G, Dekker JM. Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: the Hoorn Study. *Diabetes Care* 2009;32:2094-8.
30 Chen L, Tonkin AM, Moon L, Mitchell P, Dobson A, Giles G, et al. Recalibration and validation of the SCORE risk chart in the Australian population: the AusSCORE chart. *Eur J Cardiovasc Prev Rehabil* 2009;16:562-70.
31 Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. *BMJ* 2009;339:b2584.
32 Woodward M, Tunstall-Pedoe H, Rumley A, Lowe GD. Does fibrinogen add to prediction of cardiovascular disease? Results from the Scottish Heart Health Extended Cohort Study. *Br J Haematol* 2009;146:442-6.
33 Scheltens T, Verschuren WM, Boshuizen HC, Hoes AW, Zuithoff NP, Bots ML, et al. Estimation of cardiovascular risk: a comparison between the Framingham and the SCORE model in people under 60 years of age. *Eur J Cardiovasc Prev Rehabil* 2008;15:562-6.
34 Mainous AG 3rd, Koopman RJ, Diaz VA, Everett CJ, Wilson PW, Tilley BC. A coronary heart disease risk score based on patient-reported information. *Am J Cardiol* 2007;99:1236-41.
35 Störk S, Feelders RA, van den Beld AW, Steyerberg EW, Savelkoul HF, Lamberts SW, et al. Prediction of mortality risk in the elderly. *Am J Med* 2006;119:519-25.
36 Cooper JA, Miller GJ, Humphries SE. A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the Second Northwick Park Heart Study. *Atherosclerosis* 2005;181:93-100.
37 Ferrario M, Chiodini P, Chambless LE, Cesana G, Vanuzzo D, Panico S, et al. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. *Int J Epidemiol* 2005;34:413-21.
38 Dunder K, Lind L, Zethelius B, Berglund L, Lithell H. Evaluation of a scoring scheme, including proinsulin and the apolipoprotein B/apolipoprotein A1 ratio, for the risk of acute coronary events in middle-aged men: Uppsala Longitudinal Study of Adult Men (ULSAM). *Am Heart J* 2004;148:596-601.
39 Empana JP, Ducimetière P, Arveiler D, Ferrières J, Evans A, Ruidavets JB, et al. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. *Eur Heart J* 2003;24:1903-11.
40 Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem* 2008;54:17-23.
41 Bertolini G, D'Amico R, Nardi D, Tinazzi A, Apolone G. One model, several results: the paradox of the Hosmer-Lemeshow goodness-of-fit test for the logistic regression model. *J Epidemiol Biostat* 2000;5:251-3.
42 Marcin JP, Romano PS. Size matters to a model's fit. *Crit Care Med* 2007;35:2212-3.
43 Tzoulaki I, Liberopoulos G, Ioannidis JP. Assessment of claims of improved prediction beyond the Framingham risk score. *JAMA* 2009;302:2345-52.
44 Tzoulaki I, Liberopoulos G, Ioannidis JP. Use of reclassification for assessment of improved prediction: an empirical evaluation. *Int J Epidemiol* 2011;40:1094-105.

Suggestions for studies comparing risk prediction models

- Comparative studies should be carried out in independent samples from those where each model was originally developed, and ideally by investigators other than those who originally proposed these models

- The study setting, country, and type of population should be described; it should also be recognised whether these characteristics are expected to offer any clear advantage to one of the compared models

- The main outcome of the study should be clearly defined and clinically relevant; it should be recognised that models originally developed to predict other outcomes may exhibit inferior predictive performance

- Models should be calculated using the same exact predictors and coefficients as when they were originally developed and validated

- The follow-up time should correspond to the same follow-up as when the models were developed (for example, 10 year risk); deviations should be clarified and an explanation about choice given

- The discrimination of each model should be given with point estimates and confidence intervals; differences between the discrimination of compared models should be formally tested, reporting the magnitude of the difference and the accompanying uncertainty

- The calibration of each model may be assessed with statistical tests, but there is no good formal test for comparing calibration performance; it is useful to also show graphically the expected versus predicted risk for different levels of risk or levels of predictors

- Examination of reclassification performance of examined risk scores is meaningful when there are well established clinically relevant risk thresholds; it is useful to provide information on the number of correct and incorrect classifications; avoid using the net reclassification improvement for non-nested models

- The extent of missing information for outcomes and predictors should be described, also explaining how missing information was handled

What is already known on this topic

Several risk prediction models for cardiovascular disease are recommended for clinical use; these models have often been developed and validated in different populations and for different outcomes

The comparative prognostic performance of the most popular and widely used risk models in terms of discrimination, calibration, and reclassification is largely unknown

What this study adds

Data from 20 studies (56 model comparisons) show limited evidence and inconsistent results about the relative prognostic ability of the most popular risk prediction models for cardiovascular disease

The literature seems to be affected by optimism and outcome selection biases

Standardised methodology and reporting could improve the quality of comparative studies of predictive models and guide future efforts towards meaningful prognostic research

45   Pencina MJ, D'Agostino RB Sr, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. *Stat Med* 2012;31:101-13.

46   Ioannidis JP. Perfect study, poor evidence: interpretation of biases preceding study design. *Semin Hematol* 2008;45:160-6.

47   Chalmers I, Matthews R. What are the implications of optimism bias in clinical research? *Lancet* 2006;367:449-50.

48   Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA* 2004;291:2591-9.

49   D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;286:180-7.

50   Hurley LP, Dickinson LM, Estacio RO, Steiner JF, Havranek EP. Prediction of cardiovascular death in racial/ethnic minorities using Framingham risk factors. *Circ Cardiovasc Qual Outcomes* 2010;3:181-7.

51   Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839-43.

52   Ioannidis JP, Tzoulaki I. What makes a good predictor?: the evidence applied to coronary artery calcium score. *JAMA* 2010;303:1646-7.

Tables

Table 1| Characteristics of included studies

Study	Year	Data collection period	Study design	Study population	Sample size (men/women)	Models	Outcomes	No of events (men/women)
Pandya et al[25]	2011	1988-94	Retrospective	National health and nutrition examination survey III cohort	5999 (3501/2498)	Framingham risk score, FRS (CVD)*, SCORE (low and high risk)	Cardiovascular disease mortality	176 (118/58)
De la Iglesia et al[26]	2011	1995-2006	Prospective	The Health Improvement Network cohort	1 072 289 (529 506/542 783)	Framingham risk score, FRS (CVD)*, ASSIGN	Cardiovascular disease (myocardial infarction, coronary heart disease, stroke, transcient ischaemic attack)	44 375 (26 202/18 173)
Barroso et al[27]	2010	No data	Retrospective	Cohort in Spain	608 (263/345)	Framingham risk score, SCORE	Coronary heart disease (angina, fatal and non-fatal myocardial infarction), cardiovascular disease mortality	57 (41/16)
Collins et al[28]	2010	1993-2008	Prospective	The Health Improvement Network cohort	1 583 106 (785 733/797 373)	Framingham risk score, QRISK1, QRISK2	Cardiovascular disease (angina, myocardial infarction, coronary heart disease, stroke, transcient ischaemic attack)	71 465 (42 408/29 057)
Van der Heijden et al[29]	2009	1989-92	Prospective	Cohort in Netherlands	1125 (509/616)†	Framingham risk score, SCORE	Coronary heart disease, coronary heart disease mortality	108 (coronary heart disease), 27 (fatal coronary heart disease)
Chen et al[30]	2009	2003-05	Prospective	Cohort in Australia	1998 (808/1190)	Framingham risk score, SCORE (low and high risk)	Cardiovascular disease mortality	62 (36/26)
Collins et al[31]	2009	1995-2006	Prospective	The Health Improvement Network cohort	1 072 800 (529 813/542 987)	FRS (CVD)*, QRISK1	Cardiovascular disease (myocardial infarction, coronary heart disease, stroke, transcient ischaemic attack)	43990 (25 963/18 027)
Woodward et al[32]	2009	1984-87, 1989, 1992, 1995	Prospective	Scottish Heart Health Extended Cohort Study cohort	13 060 (6509/6551)	Framingham risk score, ASSIGN	Cardiovascular disease mortality, coronary heart disease or cerebrovascular disease, CABG or PTCA	2626 (1634/992)
Scheltens et al[33]	2008	1987-92	Prospective	Cohort in Netherlands	40 316 (18 814/21 502)	Framingham risk score, SCORE	Cardiovascular disease mortality	256 (189/67)
Hippisley-Cox et al[15]	2008	1993-2008	Prospective	QRESEARCH cohort	750232 (374 469/375 763)‡	Framingham risk score, QRISK1, QRISK2	Cardiovascular disease (coronary heart disease, stroke, transcient ischaemic attack)	No data§
Hippisley-Cox et al[14]	2007	1995-2007	Prospective	QRESEARCH cohort	614 553 (305 140/309 413)	Framingham risk score, QRISK1, ASSIGN	Cardiovascular disease (myocardial infarction, coronary heart disease, stroke, transcient ischaemic attack)	30812 (17 705/13 107)
Mainous et al[34]	2007	1987-89	Prospective	Atherosclerosis risk In communities study	14 343 (6239/8104)	Framingham risk score, SCORE	Coronary heart disease (myocardial infarction, fatal coronary heart disease, cardiac procedure)	1108
Ridker et al[16]	2007	1992-2004	Prospective	Women's Health Study cohort	8158	Framingham risk score, Reynolds risk score	Cardiovascular disease (myocardial infarction, ischemic stroke, coronary revascularisation, cardiovascular disease mortality)	262

Table 1 (continued)

Study	Year	Data collection period	Study design	Study population	Sample size (men/women)	Models	Outcomes	No of events (men/women)
Woodward et al[11]	2007	1984-87, 1989, 1992, 1995	Prospective	Cohort in Scotland	13 297 (6540/6757)	Framingham risk score, ASSIGN	Cardiovascular disease mortality, coronary heart disease or cerebrovascular disease, CABG or PTCA	1165 (743/422)
Störk et al[35]	2006	No data	Prospective	Cohort in Netherlands	403¶	Framingham risk score, PROCAM	Cardiovascular disease and all cause mortality	31¶
Cooper et al[36]	2005	No data	Prospective	Cohort in United Kingdom	2732¶	Framingham risk score, PROCAM	Coronary heart disease	219¶
Ferrario et al[37]	2005	1982-96	Prospective	Cuore study	6865¶	Framingham risk score, PROCAM	Fatal and non-fatal major coronary heart disease	312¶
Dunder et al[38]	2004	1970-73	Prospective	Uppsala Longitudinal Study of Adult Men cohort	534¶‡	Framingham risk score, PROCAM	Fatal and non-fatal myocardial infarction	116¶
Empana et al[39]	2003	1991-93	Prospective	Prospective Epidemiological Study of Myocardial Infarction cohorts: Northern Ireland; France	2399¶; 7359¶	Framingham risk score, PROCAM	Coronary heart disease (angina, fatal coronary heart disease, myocardial infarction)	120¶; 197¶
Assmann et al[13]	2002	1979-85	Prospective	PROCAM cohort	5389¶	Framingham risk score, PROCAM	Myocardial infarction or coronary heart disease mortality	325¶

SCORE=systematic coronary risk evaluation; ASSIGN=assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network to assign preventative treatment score; QRISK1 and QRISK2=QRESEARCH cardiovascular risk algorithms; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; PROCAM=Prospective Cardiovascular Münster.

*Global Framingham risk score for total cardiovascular disease prediction.[9]

†Cohort subpopulation with normal glucose tolerance.

‡Derived from validation cohort.

§Data available from corresponding author.

¶Only males.

Table 2| Discrimination performance according to area under the receiver operating characteristic curve (AUC) metric

Study	Year	Outcome	Model	AUC (95% CI)		
				Men	Women	Overall
Pandya et al[25]	2011	Cardiovascular disease mortality	Framingham risk score	0.781 (0.738 to 0.823)	0.821 (0.766 to 0.876)	No data
			FRS (CVD)*	0.776 (0.733 to 0.819)	0.834 (0.782 to 0.885)	No data
			SCORE	Low risk: 0.785 (0.743 to 0.826), high risk: 0.785 (0.743 to 0.826)	Low risk: 0.792 (0.730 to 0.854), high risk: 0.792 (0.731 to 0.854)	No data
De la Iglesia et al[26]	2011	Cardiovascular disease (myocardial infarction, coronary heart disease, stroke, transient ischaemic attack)	Framingham risk score	0.740 (0.736 to 0.744)†	0.765 (0.761 to 0.769)†	No data
			FRS (CVD)*	0.752 (0.749 to 0.755)†	0.771 (0.767 to 0.775)†	No data
			ASSIGN	0.756 (0.753 to 0.759)†	0.792 (0.788 to 0.796)†	No data
Barroso et al[27]	2010	Coronary heart disease (angina, fatal and non-fatal myocardial infarction), cardiovascular disease mortality	Framingham risk score	—	—	0.70 (0.63 to 0.78)
			SCORE	—	—	0.86 (0.77 to 0.96)
Collins et al[28]	2010	Cardiovascular disease (angina, myocardial infarction, coronary heart disease, stroke, transient ischaemic attack)	Framingham risk score	0.75 (0.747 to 0.753)†	0.774 (0.771 to 0.777)†	No data
			QRISK1	0.771 (0.768 to 0.774)†	0.799 (0.796 to 0.802)†	No data
			QRISK2	0.773 (0.770 to 0.776)†	0.801 (0.798 to 0.804)†	No data
Van der Heijden et al[29]	2009	Coronary heart disease, coronary heart disease mortality	Framingham risk score	No data	No data	0.68 (0.63 to 0.74)
			SCORE	No data	No data	0.71 (0.66 to 0.76)
			Framingham risk score	No data	No data	0.71 (0.61 to 0.82)
			SCORE	No data	No data	0.79 (0.70 to 0.87)
Chen et al[30]	2009	Cardiovascular disease mortality	Framingham risk score	0.72 (0.65 to 0.80)	0.72 (0.64 to 0.80)	No data
			SCORE	Low risk: 0.75 (0.68 to 0.83), high risk: 0.75 (0.68 to 0.82)	Low risk: 0.70 (0.62 to 0.79), high risk: 0.70 (0.62 to 0.79)	No data
Collins et al[31]	2009	Cardiovascular disease (myocardial infarction, coronary heart disease, stroke, transient ischaemic attack)	FRS (CVD)*	0.752 (0.749 to 0.755)†	0.770 (0.766 to 0.774)†	No data
			QRISK1	0.762 (0.759 to 0.765)†	0.789 (0.785 to 0.793)†	No data
Woodward et al[32]	2009	Cardiovascular disease mortality, coronary heart disease or cerebrovascular disease, CABG or PTCA	Framingham risk score	0.7183 (0.7154 to 0.7213)	0.737 (0.7331 to 0.741)	No data
			ASSIGN	0.7248 (0.7216 to 0.7279)	0.7618 (0.7574 to 0.7662)	No data
Scheltens et al[33]	2008	Cardiovascular disease mortality	Framingham risk score	No data	No data	0.86 (0.84 to 0.88)
			SCORE	No data	No data	0.85 (0.83 to 0.87)
Hippisley-Cox et al[15]	2008	Cardiovascular disease (coronary heart disease, stroke, transient ischaemic attack)	Framingham risk score	0.779 (0.776 to 0.782)	0.800 (0.797 to 0.803)	No data
			QRISK1	0.788 (0.786 to 0.791)	0.814 (0.811 to 0.817)	No data
			QRISK2	0.792 (0.789 to 0.794)	0.817 (0.814 to 0.820)	No data
Hippisley-Cox et al[14]	2007	Cardiovascular disease (myocardial infarction, coronary heart disease, stroke, transient ischaemic attack)	Framingham risk score	0.7598 (0.756 to 0.764)†	0.7744 (0.771 to 0.778)†	No data
			QRISK1	0.7674 (0.763 to 0.772)†	0.7879 (0.785 to 0.791)†	No data
			ASSIGN	0.7644 (0.760 to 0.769)†	0.7841 (0.781 to 0.787)†	No data
Mainous et al[34]	2007	Coronary heart disease (myocardial infarction, fatal coronary heart disease, cardiac procedure)	Framingham risk score	0.691 (0.670 to 0.712)	0.808 (0.792 to 0.823)	No data
			SCORE	0.619 (0.597 to 0.641)	0.687 (0.668 to 0.705)	No data

Table 2 (continued)

Study	Year	Outcome	Model	AUC (95% CI) Men	AUC (95% CI) Women	AUC (95% CI) Overall
Ridker et al[16]	2007	Cardiovascular disease (myocardial infarction, ischaemic stroke, coronary revascularisation, cardiovascular disease mortality)	Framingham risk score	NA	0.787 (0.754 to 0.820)†	NA
			Reynolds risk score	NA	0.808 (0.776 to 0.840)†	NA
Woodward et al[11]	2007	Cardiovascular disease mortality, coronary heart disease or cerebrovascular disease, CABG or PTCA	Framingham risk score	0.716 (0.694 to 0.738)†	0.741 (0.720 to 0.762)†	No data
			ASSIGN	0.727 (0.706 to 0.748)†	0.765 (0.744 to 0.786)†	No data
Störk et al[35]	2006	Cardiovascular disease and all cause mortality	Framingham risk score	0.60 (0.49 to 0.69)	NA	NA
			PROCAM	0.55 (0.45 to 0.65)	NA	NA
Cooper et al[36]	2005	Coronary heart disease	Framingham risk score	0.62 (0.58 to 0.66)	NA	NA
			PROCAM	0.63 (0.59 to 0.67)	NA	NA
Ferrario et al[37]	2005	Fatal and non-fatal major coronary heart disease	Framingham risk score	0.723 (0.670 to 0.779)	NA	NA
			PROCAM	0.735 (0.678 to 0.790)	NA	NA
Dunder et al[38]	2004	Fatal and non-fatal myocardial infarction	Framingham risk score	0.61 (0.55 to 0.67)†	NA	NA
			PROCAM	0.63 (0.57 to 0.69)†	NA	NA
Empana et al[39]	2003	Coronary heart disease (angina, fatal coronary heart disease, myocardial infarction)	Framingham risk score‡	0.66 (0.606 to 0.714)†	NA	NA
			PROCAM‡	0.61 (0.555 to 0.665)†	NA	NA
			Framingham risk score§	0.68 (0.638 to 0.722)†	NA	NA
			PROCAM§	0.64 (0.598 to 0.682)†	NA	NA
Assmann et al[13]	2002	Myocardial infarction or cardiovascular disease mortality	Framingham risk score	0.778 (0.748 to 0.808)†	NA	NA
			PROCAM	0.824 (0.796 to 0.852)†	NA	NA

SCORE=systematic coronary risk evaluation; ASSIGN=assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network to assign preventative treatment score; CABG=coronary artery bypass graft; PTCA=percutaneous transluminal coronary angioplasty; NA=not applicable; PROCAM=Prospective Cardiovascular Münster score.

*Global Framingham risk score for total cardiovascular disease prediction.[9]

†Confidence intervals calculated as described in Hanley and McNeil.[24]

‡Northern Ireland cohort.

§France cohort.

Table 3| Potential optimism bias

| Study | First description of a model | | | Subsequent comparisons* | |
	Model	Comparator	Performed better than comparator(s)*	Involving some of same authors	Involving independent authors
Hippisley-Cox et al[15]	QRISK2	Framingham risk score, QRISK1	Yes	None	QRISK2>Framingham risk score and QRISK1[28]
Hippisley-Cox et al[14]	QRISK1	Framingham risk score, ASSIGN	Yes	QRISK1>Framingham risk score[15]	QRISK1>Framingham risk score[28]
Ridker et al[16]	Reynolds risk score	Framingham risk score	Yes	None	None
Woodward et al[11]	ASSIGN	Framingham risk score	Yes	ASSIGN>Framingham risk score[14 32]	ASSIGN>Framingham risk score[26]
Assmann et al[13]	PROCAM	Framingham risk score	Yes	None	PROCAM<Framingham risk score[35 39]; PROCAM>Framingham risk score[36-38]

QRISK1 and QRISK2=QRESEARCH cardiovascular risk algorithms; ASSIGN=assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network to assign preventative treatment score; PROCAM=Prospective Cardiovascular Münster score.

*Better performance of models is based on point estimates for area under the receiver operating characteristic curve.