ESC European Society of Cardiology

European Heart Journal (2018) **00**, 1–13
doi:10.1093/eurheartj/ehy653

CLINICAL RESEARCH
Prevention and epidemiology

Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies

Lisa Pennells[1†], Stephen Kaptoge[1†], Angela Wood[1], Mike Sweeting[1], Xiaohui Zhao[2], Ian White[3], Stephen Burgess[1,4], Peter Willeit[1,5], Thomas Bolton[1], Karel G.M. Moons[6], Yvonne T. van der Schouw[7], Randi Selmer[8], Kay-Tee Khaw[1], Vilmundur Gudnason[9,10], Gerd Assmann[11], Philippe Amouyel[12], Veikko Salomaa[13], Mika Kivimaki[14], Børge G. Nordestgaard[15], Michael J. Blaha[16], Lewis H. Kuller[17], Hermann Brenner[18,19], Richard F. Gillum[20], Christa Meisinger[21], Ian Ford[22], Matthew W. Knuiman[23], Annika Rosengren[24,25], Debbie A. Lawlor[26], Henry Völzke[27], Cyrus Cooper[28], Alejandro Marín Ibañez[29], Edoardo Casiglia[30], Jussi Kauhanen[31], Jackie A. Cooper[32], Beatriz Rodriguez[33], Johan Sundström[34], Elizabeth Barrett-Connor[35], Rachel Dankner[36,37], Paul J. Nietert[38], Karina W. Davidson[39], Robert B. Wallace[40], Dan G. Blazer[41], Cecilia Björkelund[42], Chiara Donfrancesco[43], Harlan M. Krumholz[44], Aulikki Nissinen[13], Barry R. Davis[45], Sean Coady[46], Peter H. Whincup[47], Torben Jørgensen[48,49,50], Pierre Ducimetiere[51], Maurizio Trevisan[52], Gunnar Engström[53], Carlos J. Crespo[54], Tom W. Meade[55], Marjolein Visser[56], Daan Kromhout[57], Stefan Kiechl[5], Makoto Daimon[58], Jackie F. Price[59], Agustin Gómez de la Cámara[60], J Wouter Jukema[61], Benoît Lamarche[62], Altan Onat[63], Leon A. Simons[64], Maryam Kavousi[65], Yoav Ben-Shlomo[66], John Gallacher[67], Jacqueline M. Dekker[68], Hisatomi Arima[69], Nawar Shara[70], Robert W. Tipping[71], Ronan Roussel[72], Eric J Brunner[73], Wolfgang Koenig[74,75], Masaru Sakurai[76], Jelena Pavlovic[65], Ron T. Gansevoort[77], Dorothea Nagel[78], Uri Goldbourt[37], Elizabeth L.M. Barr[79], Luigi Palmieri[43], Inger Njølstad[80], Shinichi Sato[81], W.M. Monique Verschuren[82], Cherian V. Varghese[83], Ian Graham[84], Oyere Onuma[83], Philip Greenland[85], Mark Woodward[86,87], Majid Ezzati[88], Bruce M. Psaty[89], Naveed Sattar[90], Rod Jackson[91], Paul M. Ridker[92], Nancy R. Cook[92], Ralph B. D'Agostino Sr[93],

* Corresponding author. Tel: 01223 748659, Fax: 01223 748658, Email: ed303@medschl.cam.ac.uk

† These authors contributed equally to this article.

‡ Investigators of the Emerging Risk Factors Collaboration are listed at the end of this manuscript.

© The Author(s) 2018. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

Simon G. Thompson[1], John Danesh[1†], and Emanuele Di Angelantonio[1*†]; on behalf of The Emerging Risk Factors Collaboration[‡]

[1]Department of Public Health and Primary Care, University of Cambridge, 2 Worts' Causeway, Cambridge CB1 8RN, UK; [2]Department of Physiology, Development and Neuroscience, University of Cambridge, Downing Street, Cambridge, CB2 3EG, UK; [3]MRC Clinical Trials Unit, University College London, 90 High Holborn, London WC1V 6LJ, UK; [4]MRC Biostatistics Unit, Cambridge Institute of Public Health, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 0SR, UK; [5]Department of Neurology and Neurosurgery, Medical University of Innsbruck, Anichstraße 35, Innsbruck 6020, Austria; [6]Epidemiology: Methodology, Julius Center Research Program Methodology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584, the Netherlands; [7]Department of Epidemiology, Julius Center Research Program Cardiovascular Epidemiology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584, the Netherlands; [8]Division of Epidemiology, Norwegian Institute of Public Health, Postboks 222 Skøyen, Oslo 0213, Norway; [9]Icelandic Heart Association, Hjartavernd Holtasmá¡ri 1, Kópavogur 201, Iceland; [10]Faculty of Medicine, University of Iceland, Vatnsmýrarvegur 16, Reykjavik 101, Iceland; [11]Assmann-Foundation for Prevention, Gronowskistraße 33, Münster 48161, Germany; [12]Institut Pasteur de Lille, 1 rue du Professeur Calmette, Lille 59019, France; [13]National Institute for Health and Welfare, Mannerheimintie 166, Helsinki 00271, Finland; [14]Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 7HB, UK; [15]Department of Clinical Medicine, Copenhagen University Hospital, Blegdamsvej 3, Copenhagen 2200, Denmark; [16]Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins Hospital, 1800 Orleans St, Baltimore, MD 21287, USA; [17]Department of Epidemiology, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15212, USA; [18]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Neuenheimer Feld 581, Heidelberg 69120, Germany; [19]University of Heidelberg, Grabengasse 1, Heidelberg 69117 Germany; [20]Department of Medicine, Howard University College of Medicine, 2041 Georgia Avenue, Washington, DC 20060, USA; [21]German Research Center for Environmental Health, Ingolstädter Landstraße 1, Neuherberg 85764, Germany; [22]Institute of Health & Wellbeing, University of Glasgow, Boyd Orr Building, University Avenue, Glasgow, G12 8QQ, UK; [23]Faculty of Health and Medical Sciences, School of Population and Global Health, University of Western Australia, 35 Stirling Highway, Perth 6009, Western Australia, Australia; [24]Sahlgrenska Academy, University of Gothenburg, Medicinaregatan 3, Gothenburg 41390, Sweden; [25]Wallenberg Laboratory, Sahlgrenska University Hospital, Blå stråket 5, Gothenburg 41345, Sweden; [26]Department of Social Medicine, University of Bristol, Bristol BS8 2PR, UK; [27]Institute of Community Medicine, University of Greifswald, Ellernholzstraße 1/2, Greifswald 17489, Germany; [28]MRC Lifecourse Epidemiology Unit, University of Southampton, Tremona Rd, Southampton SO16 6YD, UK; [29]San Jose Norte Health Centre, 16 Lugar De Santuario Cabañas, Zaragoza 50013, Spain; [30]Department of Medicine, University of Padova, 2 Via Giustiniani, Padova 35128, Italy; [31]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, 1 Yliopistonranta, Kuopio, Finland; [32]Centre for Cardiovascular Genetics, University College London, 5 University Street, London WC1E 6JF, UK; [33]Department of Geriatric Medicine, University of Hawaii, 1960 East-West Road, Honolulu, HI 96822, USA; [34]Department of Medical Sciences, Uppsala University, Ing 40, 5 tr, Uppsala 751 85, Sweden; [35]University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA; [36]Unit for Cardiovascular Epidemiology, The Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer 52621, Israel; [37]Department of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, School of Public Health, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel; [38]Department of Public Health Sciences, Medical University of South Carolina, 135 Cannon Street, Charleston, SC 29425, USA; [39]Department of Medicine, Columbia University Irving Medical Center, 622 West 168th Street, New York, NY 10032, USA; [40]College of Public Health, University of Iowa, 145 N. Riverside Drive, Iowa City, IA 52242, USA; [41]Department of Surgery, Duke University Medical Center, 2301 Erwin Rd, Durham, NC 27707, USA; [42]Department of Public Health and Community Medicine, University of Gothenburg, Medicinaregatan 16, Gothenburg 41390, Sweden; [43]Department of Cardiovascular, Dysmetabolic and Aging-Associated Diseases, Istituto Superiore di Sanità (ISS), 299 Viale Regina Elena, Rome 00161, Italy; [44]Yale School of Medicine, 1 Church Street, New Haven, CT 06510, USA; [45]Department of Biostatistics, The University of Texas School of Public Health, 1200 Pressler Street, Houston, TX 77030, USA; [46]Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, 31 Center Drive, Bethesda, MD 20892, USA; [47]Population Health Research Institute, St George's, University of London, Cranmer Terrace, London SW17 0RE, UK; [48]Research Centre for Prevention and Health, 5 Øster Farimagsgade, Copenhagen 1014, Denmark; [49]Department of Public Health, University of Copenhagen, 5 Øster Farimagsgade, Copenhagen 1014, Denmark; [50]Aalborg University, Fredrik Bajers Vej 5, Aalborg 9100, Denmark; [51]Faculté de Médecine, Université Paris Descartes, 12 Rue de l'Ecole de Médecine, Paris 75006, France; [52]CUNY School of Medicine, City College of New York, 160 Convent Ave, New York, NY 10031, USA; [53]Department of Clinical Sciences, Lund University, Jan Waldenströms gata 35, Malmö 20502, Sweden; [54]School of Community Health, Portland State University, 506 SW Mill St, Portland, OR 97201, USA; [55]Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK; [56]Department of Health Sciences, Vrije Universiteit Amsterdam, VU University Medical Center, De Boelelaan 1085, Amsterdam 1081, the Netherlands; [57]Department of Epidemiology, University Medical Centre Groningen, University of Grogingen, Hanzeplein 1, Groningen 9713, the Netherlands; [58]Faculty of Medicine, Yamagata University, 1-4-12 Kojirakawa-machi, Yamagata 990-8560, Japan; [59]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Old Medical School, Teviot Place, Edinburgh EH8 9AG, UK; [60]Department of Clinical Research, Hospital 12 de Octubre, Av. Cordoba, Madrid 28041, Spain; [61]Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, Leiden 2333, the Netherlands; [62]Pavillon Ferdinand-Vandry, Université Laval, 2440 Hochelaga, Quebec G1V 0A6, Canada; [63]Department of Cardiology, Cerrahpaşa Faculty of Medicine, Istanbul University, Beyazıt, Fatih, Istanbul 34452, Turkey; [64]Faculty of Medicine, UNSW, Sydney 2052, Australia; [65]Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Doctor Molewaterplein 40, Rotterdam 3015, the Netherlands; [66]Bristol Neuroscience, Bristol University, Queens Road, Bristol BS8 1QU, UK; [67]Department of Psychiatry, University of Oxford, Warneford Hospital, Warneford Lane, Oxford OX3 7JX, UK; [68]The Institute for Health and Care Research, VU University Medical Center, De Boelelaan 1085, Amsterdam 1081, the Netherlands; [69]Kyushu University, 744 Motooka Nishi-ku, Fukuoka 819-0395, Japan; [70]Department of Biostatistics and Bioinformatics, MedStar Health Research Institute, 6525 Belcrest Road, Hyattsville, MD 20782, USA; [71]Clinical Biostatistics, Merck, 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA; [72]Centre de Recherche des Cordeliers, INSERM, 15 rue de l'Ecole de Médecine, Paris 57006, France; [73]Institute of Epidemiology & Health, University College London, 1-19 Torrington Place, London WC1E 7HB, UK; [74]Deutsches Herzzentrum München, Technische Universität München, 21 Arcisstraße, Munich 80333, Germany; [75]DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Biedersteiner Str. 29, Munich 80802, Germany; [76]Department of Social and Environmental Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan; [77]Department of Internal Medicine, University Medical Centre Groningen, University of Grogingen, Hanzeplein 1, Groningen 9713, the Netherlands; [78]Klinikum der Universität München, Ludwig-Maximilians-Universität, 15 Marchioninistraße, Munich 81377, Germany; [79]Clinical Diabetes and Epidemiology, Baker Heart and Diabetes Institute, 75 Commercial Rd, Melbourne 3004, Australia; [80]Department of Public Health, University of Tromsø, Hansine Hansens veg 18, Tromsø 9019, Norway; [81]Chiba Prefectural Institute of Public Health, 666-2 Nito-no-machi Chuo-ku, Chiba 260-8715, Japan; [82]Department for Determinants of Chronic Diseases, National Institute for Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, Bilthoven 3721, The Netherlands; [83]Noncommunicable Diseases, Disability, Violence and Injury Prevention Department, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; [84]School of Medicine, Trinity College Dublin, The University of Dublin, College Green, Dublin 2, Ireland; [85]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 420 East Superior Street, Chicago, IL 60611, USA; [86]The George Institute for Global Health, University of Oxford, 75 George Street, Oxford OX1 2BQ, UK; [87]The George Institute for Global Health, University of New South Wales, 1 King Street Newtown, Sydney 2042, Australia; [88]Faculty of Medicine, School of Public Health, Norfolk Place, St Mary's Campus, Imperial College London, London W2 1PG, UK; [89]Cardiovascular Health Research Unit, University of Washington, 1730 Minor Avenue, Seattle, WA 98101-1466, USA; [90]Institute of Cardiovascular & Medical Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK; [91]Faculty of Medical and Health Sciences, University of Auckland, 261 Morrin Road, Auckland, New Zealand; [92]Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue, Boston, MA 02215, USA; and [93]Mathematics and Statistics Department, Boston University, 111 Cummington Mall, Boston, MA 02215, USA

Received 24 January 2018; revised 3 May 2018; editorial decision 31 July 2018; accepted 4 October 2018

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

Aims There is debate about the optimum algorithm for cardiovascular disease (CVD) risk estimation. We conducted head-to-head comparisons of four algorithms recommended by primary prevention guidelines, before and after 'recalibration', a method that adapts risk algorithms to take account of differences in the risk characteristics of the populations being studied.

Methods and results Using individual-participant data on 360 737 participants without CVD at baseline in 86 prospective studies from 22 countries, we compared the Framingham risk score (FRS), Systematic COronary Risk Evaluation (SCORE), pooled cohort equations (PCE), and Reynolds risk score (RRS). We calculated measures of risk discrimination and calibration, and modelled clinical implications of initiating statin therapy in people judged to be at 'high' 10 year CVD risk. Original risk algorithms were recalibrated using the risk factor profile and CVD incidence of target populations. The four algorithms had similar risk discrimination. Before recalibration, FRS, SCORE, and PCE over-predicted CVD risk on average by 10%, 52%, and 41%, respectively, whereas RRS under-predicted by 10%. Original versions of algorithms classified 29–39% of individuals aged ≥40 years as high risk. By contrast, recalibration reduced this proportion to 22–24% for every algorithm. We estimated that to prevent one CVD event, it would be necessary to initiate statin therapy in 44–51 such individuals using original algorithms, in contrast to 37–39 individuals with recalibrated algorithms.

Conclusion Before recalibration, the clinical performance of four widely used CVD risk algorithms varied substantially. By contrast, simple recalibration nearly equalized their performance and improved modelled targeting of preventive action to clinical need.

Keywords Cardiovascular disease • Risk prediction • Risk algorithms • Calibration • Discrimination

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

Introduction

A key strategy in the primary prevention of cardiovascular disease (CVD) is the use of risk prediction algorithms to target preventive interventions on people who should benefit from them most.[1,2] There is, however, debate about the optimum algorithm for CVD risk estimation. The 2013 guidelines of the American College of Cardiology/American Heart Association (ACC/AHA)[3,4] have recommended the Pooled cohort equations (PCE). By contrast, the 2016 guidelines of the European Society of Cardiology[5] have recommended the Systematic COronary Risk Evaluation (SCORE) algorithm.[6,7] The Framingham risk score (FRS)[8] and the Reynolds risk score (RRS)[9,10] have been recommended by other North American guidelines.[11,12] Additional algorithms have been recommended by further guidelines.[13,14]

Such contrasting recommendations may create confusion among practitioners, potentially reflecting uncertainty about the performance of different algorithms under different circumstances. For example, because CVD event rates and average risk factor levels vary over time and place, algorithms developed in one population may not predict the correct risk in the target population being screened (i.e. they may not be well 'calibrated'[15,16]). Furthermore, although most CVD risk algorithms include information on a common set of risk factors, algorithms can differ owing to differences in the exact set of risk factors included, mathematical formulations used, and definitions of CVD outcomes employed. Hence, use of different algorithms as currently recommended could lead to varying clinical performance and uneven efficiency in allocating preventive interventions. Only few and relatively small studies have, however, provided head-to-head comparisons of different risk prediction algorithms recommend by primary prevention guidelines for allocation of statin therapy.[17–19] Despite some previous attempts to adjust risk algorithms to local and/or contemporary circumstances (i.e. 'recalibration'),[17,20] few have compared recalibrated versions of algorithms systematically across many populations.

Our study, therefore, aimed to address two sets of questions. First, how do risk prediction algorithms differ in term of predictive accuracy and clinical performance when evaluated in the same population? We chose algorithms that have been recommended by a guideline statement and could be evaluated with the information available in our consortium dataset. Hence, we conducted head-to-head comparisons of original versions of four risk algorithms (FRS, SCORE, PCE, and RRS), evaluating them using measures of predictive accuracy (e.g. discrimination, calibration) as well as clinical performance (e.g. we modelled the potential impact of initiating statin therapy as recommended by primary prevention CVD guidelines[3,4]). The second set of questions is: what is the clinical impact of adjusting these algorithms to local and contemporary circumstances, and how do they then compare to each other? To address them, we recalibrated these algorithms using CVD event rates and risk factor values of the target populations, and compared the performance of the original and recalibrated versions of algorithms across multiple settings.

Methods

Data sources

We analysed data from the Emerging Risk Factors Collaboration (ERFC), a consortium of prospective cohort studies with information on a variety of risk factors.[21] Prospective cohort studies were included in this analysis if they met all the following criteria: (i) had not contributed data to the development of any of the risk prediction algorithms studied in this analysis[4,6,8–10]; (ii) had recorded information on risk factors necessary to calculate algorithms [i.e. age, sex, smoking status, history of diabetes, systolic blood pressure, total and high-density lipoprotein cholesterol,

ethnicity, and use of antihypertensive medications; Supplementary material online, *Table S1* and Supplementary material online, *Appendix S1*]; (iii) were approximately population based (i.e. did not select participants on the basis of having previous disease); (iv) had recorded cause-specific deaths and non-fatal CVD events [i.e. non-fatal myocardial infarction (MI) or stroke] using well-defined criteria; and (v) had at least 1 year of follow-up after baseline. Details of contributing studies are in Supplementary material online, *Table S2* and Supplementary material online, *Appendix S2*. All studies used definitions of non-fatal MI based on World Health Organization (or similar) criteria and of non-fatal stroke based on clinical and brain imaging features. In registering fatal outcomes, all contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause), and used *International Classification of Diseases*, revisions 8, 9, and 10, coding to at least three digits. Ascertainment of fatal outcomes was based on death certificates, with 56 studies also involving review of medical records, autopsy findings, and other supplementary sources. Supplementary material online, *Table S3* provides International Classification of Diseases (ICD) codes used to define outcomes used in each CVD risk prediction algorithm.

Statistical analysis

Analyses included participants aged between 40 and 79 years, excluding those with a known history of CVD at baseline [i.e. coronary heart disease (CHD), other heart disease, stroke, transient ischaemic attack, peripheral vascular disease, atrial fibrillation, heart failure, or any cardiovascular surgery], as defined by each study.[21,22] For each participant, we used original versions of FRS, SCORE, PCE, and RRS to calculate the predicted 10 year risk of CVD events (Supplementary material online, *Appendix S1*). To enable comparison with the three other risk prediction algorithms evaluated in this study, we used a rescaled version of the FRS algorithm which predicts non-fatal MI, fatal CHD, or any stroke (rather than the broader CVD outcome it was originally derived for).[8] For SCORE, we used relevant high or low-risk versions depending on the geographical location of the cohort as recommended by the ESC guidelines.[5] Analyses involving RRS were performed in a subset of participants who had information available on C-reactive protein, family history of premature MI, and HbA1c (if female and with diabetes) (Supplementary material online, *Table S1*).

To help provide systematic evaluation of the four risk algorithms to predict relevant CVD endpoints, we used the following outcome definitions. The principal outcome was the composite of CVD events during the initial 10 year period of follow-up as defined by each algorithm ('the algorithm-specific outcome'): first onset of non-fatal MI, fatal CHD, or any stroke for FRS and PCE; non-fatal MI, fatal CHD or any stroke, coronary revascularization, or any CVD death for RRS; fatal CVD for SCORE (Supplementary material online, *Table S3*). The secondary outcome was a 'common' CVD outcome, defined as the composite of non-fatal MI, fatal CHD, or any stroke, adopting the definition of the 2013 ACC/AHA guidelines (and used by PCE and FRS).[4] Outcomes were censored if a participant was lost to follow-up, died from non-CVD causes, or reached 10 years of follow-up. Participants contributed only the first non-fatal or fatal CVD outcome (i.e. deaths preceded by non-fatal CVD events were not included) except in the case of the SCORE-specific outcome, for which all fatal CVD events were included.

We assessed risk discrimination using the C-index which estimates the probability of correctly predicting who will have a CVD event first in a randomly selected pair of participants.[23] The C-index calculation was stratified by sex and involved a two-stage approach, with estimates calculated separately within each study before pooling across studies weighting by the number of contributing events.[24] We assessed calibration of risk algorithms for each algorithm-specific outcome by comparing predicted and observed risks calculated for groups of participants defined by 5 year age categories and calculating goodness of fit tests.[25] Supplementary material online, *Appendix S3* provides further details of the methods used to assess calibration. We recalibrated each algorithm as shown in Supplementary material online, *Figure S1* and Supplementary material online, *Appendix S3*. Our approach involved adaptation of original risk algorithms using the risk factor profile and CVD incidence of target populations. Recalibration to CVD incidence involved two approaches. First, we recalibrated each algorithm to predict incidence of the endpoint it was derived to predict (the algorithm-specific outcome). Second, to enable head-to-head comparisons, we recalibrated SCORE and RRS to the common CVD outcome used by FRS and PCE, as mentioned above. Only studies with at least 10 years of follow-up were used in analyses involving recalibration, or assessment of calibration.

To assess the clinical implications of using different algorithms to initiate statin therapy in those whose 10 year CVD risk exceeds a given threshold (as recommended by several CVD primary prevention guideline statements[1,3–5,12]), we estimated the number of individuals who would be eligible for treatment and the potential cases avoided. First, we assumed CVD risk assessment for a population of 100 000 men and women aged ≥40 years without CVD at baseline and not already taking statins or meeting guideline recommendations for statin treatment (i.e. people without a history of diabetes or CVD and with low-density lipoprotein (LDL) cholesterol <190 mg/dL).[3] Second, we assumed the same age structure of a standard population of the United States. Third, we assumed age- and sex-specific incidence rates for CVD events as in the current study. Fourth, we assumed statin allocation according to the threshold of predicted 10 year CVD risk recommended by 2013 ACC/AHA guidelines[4] for first-onset fatal and non-fatal CVD events (i.e. ≥7.5%), or by the 2016 ESC Guidelines for fatal CVD (i.e. ≥5%).[5] Fifth, we assumed CVD risk reductions of 20% with statin treatment in people without a history of CVD, as reported by the Cholesterol Treatment Trialists' Collaboration.[26] We also compared categorization of participants across different algorithms before and after their recalibration using the net reclassification improvement (NRI).[27]

Analyses were performed using Stata version 14. *P*-values are two-sided. The study was designed and conducted by this collaboration's academic coordinating centre, and was approved by the Cambridgeshire Ethics Review Committee. The funders had no scientific role in the study.

Results

We analysed data on 360 737 participants without prior CVD who were recruited into 86 prospective cohorts between the years 1963 and 2003 (Supplementary material online, *Table S2*). The mean (standard deviation) age at baseline was 59 (8) years; 53% were male. Sixty-nine percent of the participants were recruited in European countries, 18% in North America, and the remainder mostly in Japan and Australia. Median (5^{th}–95^{th} percentile) follow-up was 10.2 (3.4–21.3) years, and during the initial 10 years of follow-up (3.1 million person-years at risk), 14 564 incident CVD events were recorded according to our common and FRS/PCE CVD definition, including 9259 CHD events and 5305 stroke events. At baseline, the median (5^{th}–95^{th} percentile) predicted 10 year CVD risks were 5.54% (1.02–23.34%) using FRS, 2.49% (0.13–23.25%) using SCORE, and 6.43% (0.69–33.33%) using PCE (*Table 1*). Baseline characteristics for the subset of participants with information on the RRS are presented in Supplementary material online, *Table S4*.

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

Table 1 Baseline characteristics and predicted 10 year cardiovascular disease risk relevant to assessed algorithms

Baseline characteristic	Mean (SD) or *n* (%)
Age at survey (years)	59 (8.0)
Males	189 342 (52.5%)
Current smoking	98 593 (27.3%)
History of diabetes	16 758 (4.6%)
Systolic blood pressure (mmHg)	132 (19)
Total cholesterol (mmol/L)	5.83 (1.08)
HDL cholesterol (mmol/L)	1.33 (0.38)
Total/HDL cholesterol ratio	4.50 (1.61)
Hypertension medication	37 960 (10.5)
Lipid lowering medication	7929 (5.1)
Predicted 10 year risk (%)	**median (5^{th}–95^{th} percentiles)**
Framingham risk score (FRS)	5.54% (1.02–23.34)
Systematic COronary Risk Evaluation (SCORE)	2.49% (0.13–23.25)
Pooled cohort equations (PCE)	6.43% (0.69–33.33)

Data are from 86 cohorts with 360 737 participants and 23 563 CVD events (14 538 occurring within 10 years). Versions of FRS and PCE used predict risk of fatal or non-fatal CVD, SCORE predicts risk of fatal CVD.
HDL, high-density lipoprotein.

Discrimination and calibration

When using algorithm-specific CVD outcomes, each algorithm provided broadly similar discrimination, with absolute C-index values ranging from 0.7010 to 0.7605. The pooled cohort equations provided somewhat greater risk discrimination than FRS or SCORE for all algorithm-specific outcomes, with differences in overall C-index compared with FRS between 0.0039 and 0.0131 ($P < 0.001$ when testing the null hypothesis of no difference between C-indices; *Figure 1*). Differences were greater for women than men, but similar among participants from European and North American cohorts (Supplementary material online, *Figure S2*). A similar pattern was observed in analyses restricted to participants with complete data enabling calculation of RRS (Supplementary material online, *Figure S3*). Differences in the C-index among algorithms were not affected by study recruitment periods (Supplementary material online, *Figure S4*).

For each algorithm-specific outcome, on average across cohorts the predicted 10 year risk was 1.10 times observed risk for FRS, 1.52 for SCORE, 1.41 for PCE, and 0.90 for RRS ($P < 0.0001$ for goodness of fit/calibration for all algorithms; *Figure 2* and Supplementary material online, *Figures S5* and *S6*). On average the extent of relative mis-calibration was similar in men and women, and across all ages for SCORE and PCE (Supplementary material online, *Figure S5*) which translated to greater discrepancy between absolute predicted and observed risks at older ages when using these algorithms (Supplementary material online, *Figure S6*). Framingham risk score tended to over-predict in men and younger women but to under-predict in older women. Reynolds risk score underestimated risk somewhat in men, but on average was well calibrated in women (*Figure 2*, Supplementary material online, *Figures S5* and *S6*). The extent and direction of mis-calibration varied substantially across individual cohorts, ranging from more than 50% underestimation to >400% overestimation of risk (Supplementary material online, *Figures S7* and *S8*). Heterogeneity in calibration could not be systematically explained by broad geographical region but was partially explained by year of baseline screening (Supplementary material online, *Figure S9*). After recalibration of algorithms to the incidence of the common CVD outcome and risk factor distribution of the cohorts contributing to the current analysis, the distribution of predicted 10 year CVD risk was similar across the four algorithms we studied (Supplementary material online, *Figure S10*), yielding good calibration for each algorithm (Supplementary material online, *Figure S11*). Risk discrimination did not change with recalibration since ranking of participant risk is unaffected by the recalibration methods used (Supplementary material online, *Figure S1* and *Appendix S3*).

Estimates of clinical performance

We initially conducted modelling that: employed original versions of the four CVD risk algorithms we studied; was weighted to represent the age and sex distribution of a standard US population ≥40 years; focused on individuals not already taking or eligible for statin treatment (i.e. people without a history of diabetes or CVD and with LDL <190 mg/dL)[3]; and defined the threshold for initiation of statin treatment as an absolute 10 year risk of ≥7.5% for FRS, PCE, and RRS, and ≥5% for SCORE ('high risk').

Under this scenario, we estimated that the proportion of individuals classified as high-risk (i.e. eligible for statin treatment) was 32% with FRS, 29% with SCORE, 39% with PCE, and 32% with RRS (Supplementary material online, *Table S5* and *Figure 3*). By contrast, after recalibration (using algorithmic-specific CVD endpoints), FRS, SCORE, PCE, and RRS predicted CVD outcomes more accurately, classified lower proportions of people as high risk, and identified higher proportions of CVD events among people classified as high risk. After further recalibration to the common CVD endpoint, the proportion of individuals classified as high risk lowered to a near uniform level (22%, 22%, 24%, and 23% with FRS, SCORE, PCE, and RRS, respectively). Of those classified as high risk by the original versions of algorithms, 11% later developed a first CVD event within 10 years (i.e. the positive predictive value was 11%, 11%, 10%, and 11%, respectively). By contrast, it was 13% with the recalibrated algorithms (Supplementary material online, *Table S5*).

Based on these estimates, we calculated that to prevent one CVD event when using original versions of FRS, SCORE, PCE, or RRS it would be necessary to initiate statin therapy in 46, 44, 51, or 45 individuals, respectively (following screening of 145, 150, 131, or 142 individuals, respectively; *Figure 3* and Supplementary material online, *Table S5*). By contrast, when using any of the recalibrated algorithms, one CVD event could be prevented by initiating statin therapy in 38 participants (following screening of 174, 171, 160, or 165 individuals, respectively). Similar findings to those observed above were noted in analyses that used a range of treatment thresholds different from those in current guidelines (*Figure 3*) with the divergent clinical performance of original algorithms converging to become almost identical at any treatment threshold after recalibration to a common CVD endpoint.

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

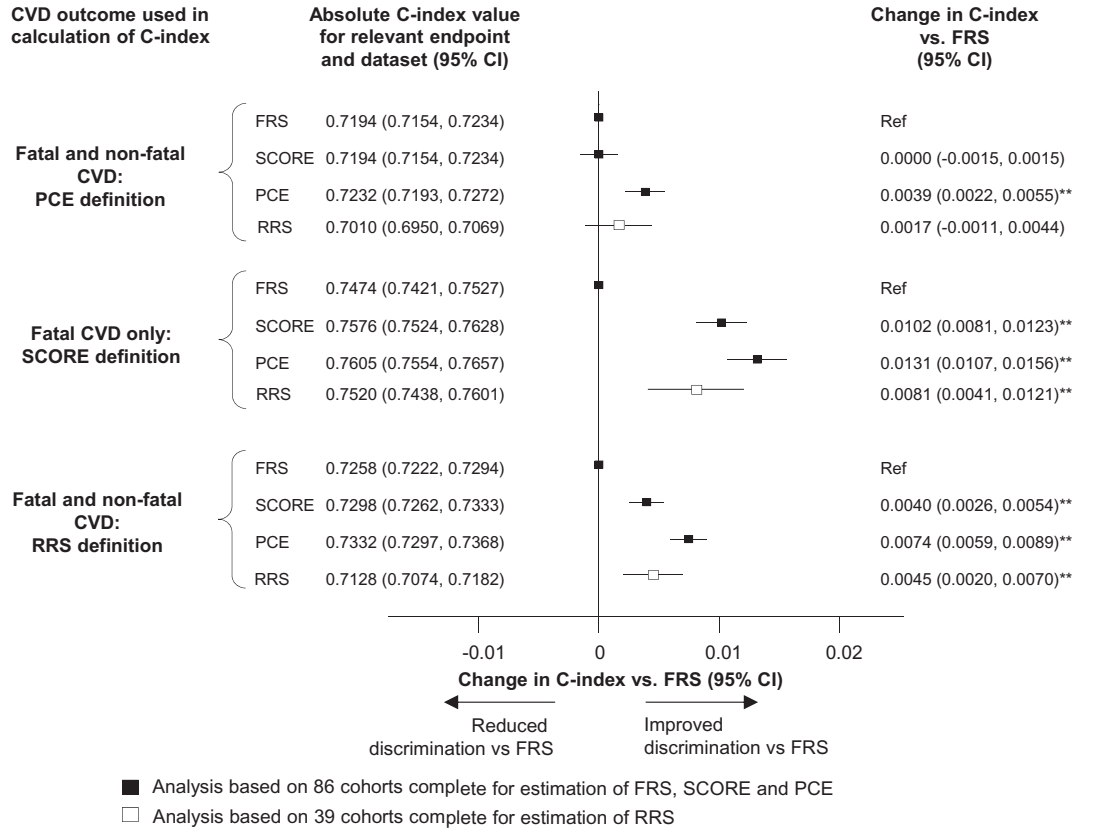


Figure 1 Discrimination abilities of original versions of three risk prediction algorithms compared with the Framingham risk score using alternative CVD definitions. Number of events observed according to CVD definitions used by the Pooled Cohort Equations, the Systematic COronary Risk Evaluation and the Reynolds Risk Score respectively were 14 564, 7433 and 17 642. Equivalent event numbers in the subset of participants with complete data for estimation of the Reynolds Risk Score were 6670, 2966 and 7953 respectively. FRS, Framingham risk score; PCE, pooled cohort equations; RRS, Reynolds risk score; SCORE, Systematic COronary Risk Evaluation. *$P < 0.05$; **$P < 0.001$.

We then modelled the concordance of statin treatment decisions based on use of these algorithms. Before recalibration, 41% of all individuals were at high risk with at least one of the four algorithms and 58% of these (24% of all individuals) were at high risk with all four. By contrast, after recalibration to our common CVD outcome, 28% of individuals were at high risk with at least one algorithm and 63% of these (18% of all individuals) were at high risk with all four (Supplementary material online, *Figure S12*). Discordance in treatment decisions before recalibration tended to be greatest when comparing SCORE to the other algorithms (*Figure 4*). For example, in pairwise comparisons between FRS and SCORE, in every 100 000 people screened 36 794 would be classified as high risk with either FRS or SCORE and 24 157 (66% of these) would be classified as high risk with both FRS and SCORE. By contrast, after recalibration, 18 716 (76%) of the 24 708 individuals at high risk with either FRS or SCORE would be at high risk with both algorithms (*Figure 4*). This greater concordance between algorithms in identifying those at high risk was also illustrated by a decrease in the NRI among both cases and event-free participants after recalibration (Supplementary material online, *Table S6*) and greater agreement between the absolute risk predictions (Supplementary material online, *Figure S13*).

Discussion

In an analysis of individual-participant data on over 350 000 people without a history of CVD at baseline, we systematically evaluated several risk algorithms recommended by North American and European guidelines for primary prevention of CVD. Our study's main finding was that the clinical performance of four widely used risk algorithms varied substantially, predominantly due to differing extent of calibration. By contrast, we observed only slight differences among the algorithms in relation to risk discrimination (a measure of predictive accuracy that is not influenced by the extent of model calibration). After recalibration, however, the performance of the four algorithms was essentially equalized. Our modelling suggested, therefore, that targeting of CVD preventive action to clinical need would improve considerably due to higher accuracy of individual risk predictions. A key implication of these results is that CVD primary prevention guidelines should shift away from debates about the relative merits of particular risk algorithms and, instead, achieve consensus about the need for more widespread use of *any* recalibrated algorithm.

Our findings have suggested that effective recalibration can be achieved through the use of simple methods that can be applied using

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

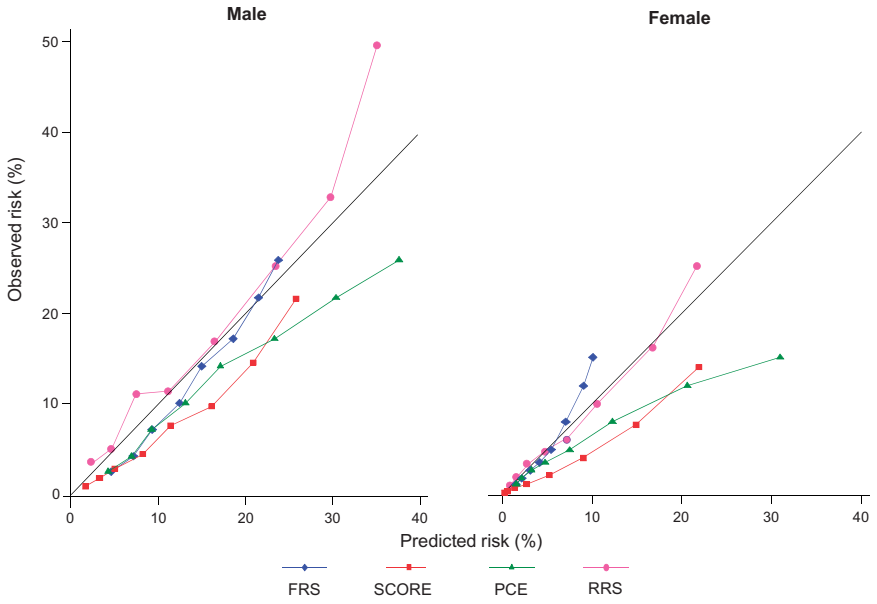


Figure 2 Observed and predicted 10-year cardiovascular risk using original version of prediction algorithms. Points presented in each plot are for each 5-year age group between 40–44 to 75–79 years. Observed risk was calculated according to the CVD definition specific to each algorithm. Assessment of the Framingham Risk Score, the Systematic COronary Risk Evaluation and the Pooled Cohort Equations was based on 223 663 participants from 47 cohorts with at least 10 years of follow-up. Assessment of the Reynolds Risk Score was based on 91 008 participants from 27 cohorts with at least 10 years of follow-up. FRS, Framingham risk score; PCE, pooled cohort equations; RRS, Reynolds risk score; SCORE, Systematic COronary Risk Evaluation.

aggregate level data on CVD event rates and average risk factor values for a target population to be screened. To scale this approach for clinical and public health purposes, cardiovascular bodies might facilitate the collation and regular updating of national and regional age- and sex-specific CVD event rates and risk factor data, including for particular geographical areas and ethnic groups with distinctive CVD event rates and risk factors values. This information could then be embedded in user-friendly risk prediction tools (e.g. online risk calculators or electronic health records systems), enabling regular and simple recalibration, as previously described.[28,29] An alternative approach is the periodic development of new risk algorithms, although it would be more costly and time-consuming than recalibration because it entails launch of large new cohort studies and their long-term follow-up.

In contrast with previous analyses of simulated data, studies in single populations, or comparisons of risk scores without recalibration,[17–20,30–35] our study directly compared original and recalibrated versions of four algorithms used across many different populations, providing the first demonstration of the extent of CVD risk prediction improvement achievable through recalibration. For example, following recalibration we observed that the proportion of individuals classified as high risk reduced from about 40% to 23%, and the number of individuals needed to initiate statin therapy to prevent one event reduced from between 44–51 to around 38. However, our modelling reflects the average improvement that can be achieved by recalibration across a set of different populations in which the initial extent and direction of mis-calibration varied substantially, partly due to differences in baseline study year. Therefore, the clinical improvement that could be achieved in countries or regions where mis-calibration is more extreme could potentially be much greater.

Our approach to recalibration was distinctive in two ways. First, it extended previous recalibration methods[36] by using age groups instead of categories of predicted risk, which allows direct application to population data that are routinely recorded. Second, it differed from other recalibration methods proposed for specific CVD risk algorithms[28,29] by providing a simpler procedure applicable to algorithms derived using any type of statistical model. Because we studied participant-level data from cohorts with prolonged follow-up, we could adopt a uniform approach to statistical analyses and conduct time-to-event analyses. To avoid providing over-optimistic assessment of algorithm performance, we omitted cohorts that had previously contributed data to the derivation of the risk algorithms we studied. Our clinical modelling was robust to different scenarios. The generalizability of our findings was enhanced by inclusion of several dozen population cohorts in 22 countries, mostly in Europe and North America, and the broad range in baseline year of recruitment across studies.

Our study had potential limitations. Because we used data from the target cohorts themselves to recalibrate algorithms, the benefits of recalibration could have been exaggerated (albeit in a manner that would have affected each algorithm identically). Conversely, inaccuracy in CVD ascertainment in contributing cohorts would tend to worsen the apparent performance of algorithms (again, affecting each algorithm identically).[37] Our modelling could have over-estimated potential benefits of statin therapy because not all people eligible for statins will receive them or be willing or able to take them. On the

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

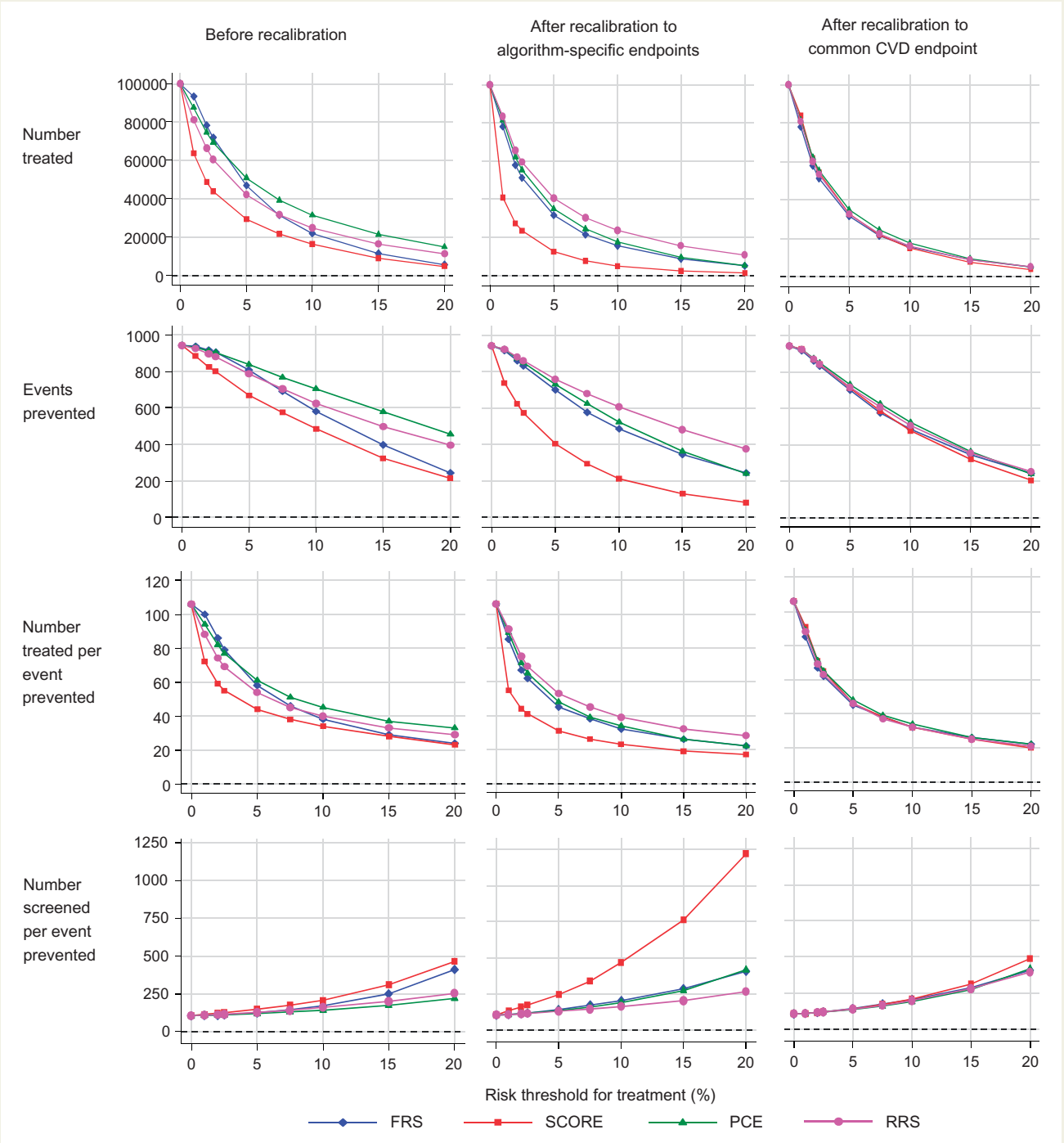


Figure 3 Estimated public health impact with screening using original and recalibrated cardiovascular disease risk prediction algorithms over a range of risk thresholds in a standard US population of 100 000 people aged over 40 years. Cardiovascular disease includes fatal coronary heart disease, fatal, and non-fatal myocardial infarction and any stroke. FRS, Framingham risk score; PCE, pooled cohort equations; RRS, Reynolds risk score; SCORE, Systematic COronary Risk Evaluation.

other hand, greater clinical impact than suggested by our modelling would be estimated if we had used less conservative assumptions (e.g. use of more efficacious statin regimens or additional treatments; longer time horizons; and lifestyle changes). We did not formally incorporate the impact of the potential hazards of statins into our modelling. We had incomplete information on medication use (such as statins and antihypertensive drugs) or cardiovascular intervention (such as coronary revascularization) during follow-up, which may have influenced our estimates of the observed CVD risk. Revascularization endpoints may have been differentially recorded

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018



Figure 4 Pairwise overlap in those classified at high risk when applying CVD risk prediction algorithms to a US standard population of 100 000 individuals. Risk thresholds to define high risk were set at 7.5% for Framingham risk score, pooled cohort equations and Reynolds risk score and 5% for Systematic COronary Risk Evaluation before recalibration. After to recalibration to our common CVD endpoint a risk threshold of 7.5% was used for all algorithms. *n* represents the number of individuals classified at high risk with either algorithm. FRS, Framingham risk score; PCE, pooled cohort equations; RRS, Reynolds risk score; SCORE, Systematic COronary Risk Evaluation.

across studies, which may have impacted on our assessment of calibration of the original RRS. There is, as yet, no randomized evidence that CVD risk assessment translates into CVD prevention.[38]

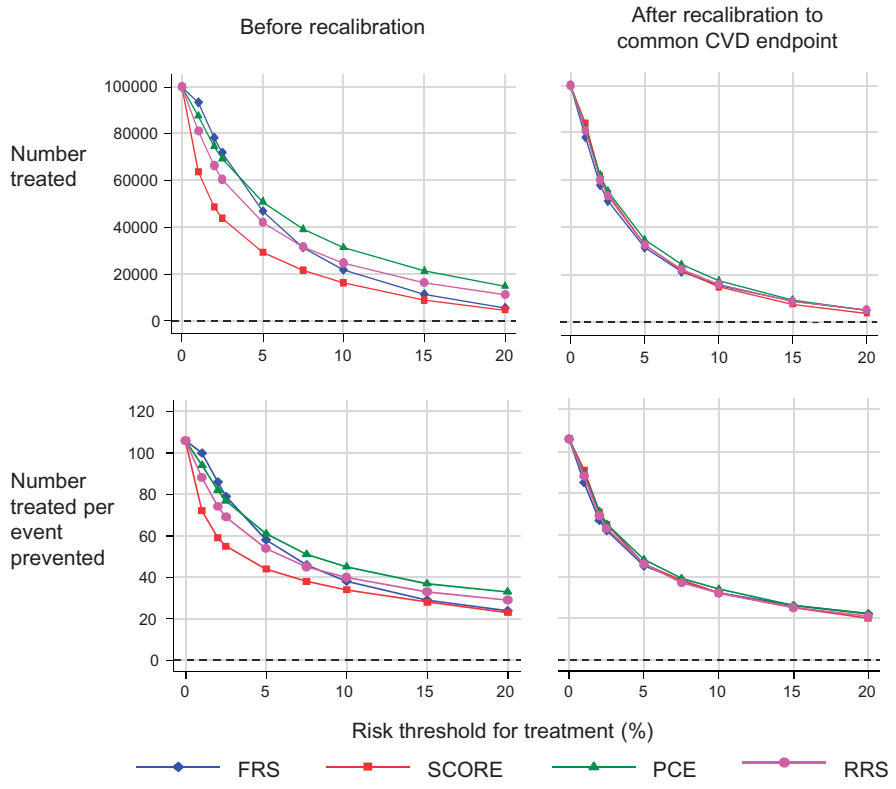
Conclusion

Whereas the performance of the original versions of four widely used CVD risk algorithms varied substantially, simple recalibration essentially equalized them and improved targeting of CVD preventive action to clinical need. This study supports the concept of using regularly recalibrated risk algorithms in routine clinical practice.

Investigators of the Emerging Risk Factors Collaboration

AFTCAPS: Robert W. Tipping; ALLHAT: Lara M. Simpson, Sara L. Pressel; ARIC: David J. Couper, Vijay Nambi, Kunihiro Matsushita, Aaron R. Folsom; AUSDIAB: Jonathan E. Shaw, Dianna J. Magliano, Paul Z. Zimmet; BHS: Matthew W. Knuiman; BRHS: Peter H. Whincup, S. Goya Wannamethee; BRUN: Johann Willeit, Peter Santer, Georg Egger; BWHHS: Juan Pablo Casas, Antointtte Amuzu; CAPS: Yoav Ben-Shlomo, John Gallacher; CASTEL: Valérie Tikhonoff, Edoardo Casiglia; CHARL: Susan E. Sutherland, Paul J. Nietert; CHS: Mary Cushman, Bruce M. Psaty; CONOR: Anne Johanne Søgaard, Lise Lund Håheim, Inger Ariansen; COPEN: Anne Tybjærg-Hansen, Gorm B. Jensen, Peter Schnohr; CUORE: Simona Giampaoli, Diego Vanuzzo, Salvatore Panico, Luigi Palmieri; DESIR: Beverley Balkau, Fabrice Bonnet, Michel Marre; DRECE: Agustin Gómez de la Cámara, Miguel Angel Rubio Herrera; DUBBO: Yechiel Friedlander, John McCallum; EAS: Stela McLachlan; EPESEBOS: Jack Guralnik, Caroline L. Phillips; EPESEIOW: Jack Guralnik; EPESENCA: Jack Guralnik; EPESENHA: Jack Guralnik; EPICNOR: Kay-Tee Khaw, Nick Wareham; ESTHER: Ben Schöttker, Kai-Uwe Saum, Bernd Holleczek; FINE_FIN: Aulikki Nissinen, Hanna Tolonen; FINE_IT: Simona Giampaoli, Chiara Donfrancesco; FINRISK 92/97: Erkki Vartiainen, Pekka Jousilahti, Kennet Harald; FRAM: Ralph B. D'Agostino Sr, Joseph M. Massaro, Michael Pencina, Ramachandran Vasan; FRAMOFF: Ralph B. D'Agostino Sr, Joseph M. Massaro, Michael Pencina, Ramachandran Vasan; FUNAGATA: Takamasa Kayama, Takeo Kato, Toshihide Oizumi; GLOSTRUP: Jørgen Jespersen, Lars Møller, Else Marie Bladbjerg; GOH: A. Chetrit; GOTO43: Annika Rosengren, Lars Wilhelmsen; GOTOW: Cecilia Björkelund, Lauren Lissner; GRIPS: Dorothea Nagel; HCS: Elaine Dennison; HISAYAMA: Yutaka Kiyohara, Toshiharu Ninomiya, Yasufumi Doi; HONOL: Beatriz Rodriguez; HOORN: Giel Nijpels, Coen D.A. Stehouwer; IKNS: Shinichi Sato, Yamagishi Kazumasa, Hiroyasu Iso; ISRAEL: Uri Goldbourt; KAREL72: Veikko Salomaa, Erkki Vartiainen; KIHD: Sudhir Kurl, Tomi-Pekka Tuomainen, Jukka T.

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018



Take home figure Recalibration equalizes the potential public health impact of different guideline recommended cardiovascular disease risk algorithms and should be regularly applied to improve targeting of intervention. Cardiovascular disease includes fatal coronary heart disease, fatal, and non-fatal myocardial infarction and any stroke. FRS, Framingham risk score; PCE, pooled cohort equations; RRS, Reynolds risk score; SCORE, Systematic COronary Risk Evaluation.

Salonen; LASA: Marjolein Visser, Dorly J.H. Deeg; LEADER: Tom W. Meade; MPP: Peter M. Nilsson, Bo Hedblad, Olle Melander; MESA: Ian H. De Boer, Andrew Paul DeFilippis; MCVDRFP: W.M. Monique Verschuren; MIDFAM: Naveed Sattar, Graham Watt; MONICA_KORA2: Christa Meisinger, Wolfgang Koenig; MONICA_KORA3: Wolfgang Koenig, Christa Meisinger; MORGEN: W.M. Monique Verschuren; MOSWEGOT: Annika Rosengren; MRFIT: Lewis H. Kuller; NCS: Aage Tverdal; NHANES III: Richard F. Gillum; NPHSII: Jackie A. Cooper; NSHS: Susan Kirkland; Daichi Shimbo, Jonathan Shaffer; OSAKA: Shinichi Sato, Yamagishi Kazumasa, Hiroyasu Iso; PARIS1: Pierre Ducimetiere; PREVEND: Stephan J.L. Bakker, Pim van der Harst, Hans L. Hillege; PRHHP: Carlos J. Crespo; PRIME: Philippe Amouyel, Jean Dallongeville; PROCAM: Gerd Assmann, Helmut Schulte; PROSPER: Stella Trompet, Roelof A.J. Smit, David J. Stott; ProspectEPIC: Yvonne T. van der Schouw; QUEBEC: Jean-Pierre Després, Bernard Cantin, Gilles R. Dagenais; RANCHO: Gail Laughlin, Deborah Wingard, Kay-Tee Khaw; RIFLE: Maurizio Trevisan; REYK: Thor Aspelund, Gudny Eiriksdottir, Elias Freyr Gudmundsson; RS_I: Arfan Ikram, Frank J.A. van Rooij, Oscar H. Franco; RS_II: Oscar L. Rueda-Ochoa, Taulant Muka, Marija Glisic; SHHEC: Hugh Tunstall-Pedoe; SHIP: Henry Völzke; SHS: Barbara V. Howard, Ying Zhang, Stacey Jolly; SPEED: John Gallacher, George Davey-Smith; TARFS: Günay Can, Hüsniye Yüksel; TOYAMA: Hideaki Nakagawa, Yuko Morikawa, Katsuyuki Miura; TROMSØ: Inger Njølstad; ULSAM: Martin Ingelsson, Vilmantas Giedraitis; USPHS2: Paul M. Ridker, J. Michael Gaziano; WHITE I: Mika Kivimaki, Martin Shipley; WHITE II: Eric J. Brunner, Martin Shipley; WCWC: Volker Arndt, Hermann Brenner; WHS: Nancy Cook, Paul M. Ridker; WOSCOPS: Ian Ford, Naveed Sattar; ZARAGOZA: Alejandro Marín Ibañez; ZUTE: Johanna M. Geleijnse.

Data Management Team

Thomas Bolton, Sarah Spackman, and Matthew Walker.

Co-ordinating Centre

Thomas Bolton, Stephen Burgess, Adam S. Butterworth, Emanuele Di Angelantonio, Pei Gao, Eric Harshfield, Stephen Kaptoge, Lisa Pennells, Sarah Spackman, Simon G. Thompson, Matthew Walker, Angela M. Wood, and John Danesh (principal investigator).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

The work of the co-ordinating centre was funded by the UK Medical Research Council (G0800270), British Heart Foundation (SP/09/

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

002), British Heart Foundation Cambridge Cardiovascular Centre of Excellence, UK National Institute for Health Research Cambridge Biomedical Research Centre, European Research Council (268834), and European Commission Framework Programme 7 (HEALTH-F2-2012-279233). The Emerging Risk Factor Collaboration's website https://www.phpc.cam.ac.uk/ceu/erfc/list-of-studies/ has compiled a list provided by investigators of some of the funders of the component studies in this analysis. I.W. was supported by the Medical Research Council Unit Programme MC_UU_12023/21. M.K. is supported by the Netherlands Organization for Scientific Research (NWO) Veni grant (Veni, 91616079). J.P. is supported by Erasmus Mundus Western Balkans (ERAWEB), a project funded by the European Commission.

Conflict of interest: H.A. reports personal fees from Bayer, Daiichi-Sankyo, Fukuda Denshi and Takeda, outside the submitted work; P.A. reports personal fees from Servier, Total, Genoscreen, Takeda, Fondation Alzheimer, outside the submitted work; M.J.B. reports grants and personal fees from National Institute of Health, American Heart Association, FDA, Aetna Foundation, Amgen, Novartis, MedImmune, Sanofi/Regeneron, outside the submitted work; C.C. reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB; E.D.A. reports grants from European Commission Framework 7, the European Research Council, the British Heart Foundation, the UK Medical Research Council, National Institute for Health Research, and NHS Blood and Transplant, outside the submitted work; J.D. reports grants from the UK Medical Research Council, the British Heart Foundation, the UK National Institute of Health Research, and the European Commission, during the conduct of the study; personal fees and non-financial support from Merck Sharp and Dohme UK Atherosclerosis, personal fees and non-financial support from Novartis Cardiovascular and Metabolic Advisory Board, grants from the British Heart Foundation, European Research Council, Merck, the National Institute of Health Research, NHS Blood and Transplant, Novartis, Pfizer, the UK Medical Research Council, the Wellcome Trust, and AstraZeneca, and personal fees and non-financial support from Pfizer Population Research Advisory Panel, outside the submitted work; M.E. reports grant from Young Health Programme of AstraZeneca, and personal fees from Prudential, Scor, and Third Bridge, all outside the submitted work; M.K. reports grant from the Medical Research Council; H.M.K. reports personal fees from UnitedHealth, Hugo, IBM Watson Health, Element Science, Aetna, Centers for Medicare & Medicaid Services, and grants from Medtronic, and FDA, outside the submitted work; S.Ki reports grants from the Austrian Research Promotion Agency FFG, outside the submitted work; S.Ka reports grants from UK Medical Research Council, and British Heart Foundation, during the conduct of the study; W.K. reports personal fees from AstraZeneca, Novartis, Pfizer, The Medicines Company, DalCor, Sanofi, Berlin-Chemie, Kowa, Amgen, grants and non-financial support from Roche Diagnostics, Beckmann, Singulex, Abbott, outside the submitted work; P.J.N. reports grants from National Institutes of Health, during the conduct of the study; B.M.P. reports that he serves on the DSMB of a clinical trial funded by Zoll LifeCor and on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson; P.M.R. reports grants from Novartis, Kowa, Pfizer, NHLBI, outside the submitted work; he is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneka and Seimens; R.R. reports grants, personal fees and non-financial support from Sanofi, MSD, Amgen, Physiogenex, AstraZeneca, Novo Nordisk, Janssen, Eli Lilly, Abbott, Medtronic, Servier, outside the submitted work; V.S. reports personal fees from Novo Nordisk outside the submitted work; N.S. reports grants and personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, Sanofi, outside the submitted work; S.G.T. reports grants from UK Medical Research Council, and British Heart Foundation, during the conduct of the study; P.W. reports personal fees from Novartis Pharmaceuticals, outside the submitted work; M.W. reports personal fees from Amgen, outside the submitted work. The other authors declare no competing interests.

References

1. US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US preventive services task force recommendation statement. *JAMA* 2016;**316**:1997–2007.
2. 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**:300–310.
3. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**129**: S1–S45.
4. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**:S49–S73.
5. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S, De BG, Roffi M, Aboyans V, Bachl N, Bueno H, Carerj S, Cho L, Cox J, De SJ, Egidi G, Fisher M, Fitzsimons D, Franco OH, Guenoun M, Jennings C, Jug B, Kirchhof P, Kotseva K, Lip GYH, Mach F, Mancia G, Bermudo FM, Mezzani A, Niessner A, Ponikowski P, Rauch B, Rydén L, Stauder A, Turc G, Wiklund O, Windecker S, Zamorano JL, Zamorano JL, Aboyans V, Achenbach S, Agewall S, Badimon L, Barón EG, Baumgartner H, Bax JJ, Bueno H, Carerj S, Dean V, Erol Ç, FD, Gaemperli O, Kirchhof P, Kolh P, Lancellotti P, Lip GYH, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Roffi M, Torbicki A, Carneiro AV, Windecker S, Metzler B, Najafov R, Stelmashok V, De MC, Dilić M, Gruev I, Miličić D, Vaverkova H, Gustafsson I, Attia I, Duishvili D, Ferrières J, Kostova N, Klimiashvili Z, Hambrecht R, Tsioufis K, Szabados E, Andersen K, Vaughan C, Zafrir B, Novo S, Davletov K, Jashari F, Kerimkulova A, Mintale I, Saade G, Petrulioniene Z, Delagardelle C, Magri CJ, Rudi V, Oukerraj L, Çölkesen BE, Schirmer H, dos RRP, Gherasim D, Nedogoda S, Zavatta M, Giga V, Filipova S, Padial LR, Kiessling A, Mach F, Mahdhaoui A, Ural D, Nesukay E, Gale C. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
6. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De BG, De BD, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall PH, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; SCORE project Group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
7. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Z, Riccardi G,

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

Taskinen MR, Tokgozoglu L, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT; Group ESCSD. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.
8. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743–753.
9. 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**:611–619.
10. 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**:2243–2251.
11. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010;**56**:e50–e103.
12. Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest J Jr, Grover S, Gupta M, Hegele RA, Lau DC, Leiter LA, Lonn E, Mancini GB, McPherson R, Ngui D, Poirier P, Sievenpiper JL, Stone JA, Thanassoulis G, Ward R. 2016 Canadian Cardiovascular Society Guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2016;**32**:1263–1282.
13. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;**100**:ii1–ii67.
14. 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 Munster (PROCAM) study. *Circulation* 2002;**105**:310–315.
15. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. *J Am Coll Cardiol* 2009;**54**:1209–1227.
16. D'Agostino RB Sr, Pencina MJ, Massaro JM, Coady S. Cardiovascular disease risk assessment: insights from Framingham. *Global Heart* 2013;**8**:11–23.
17. Cook NR, Paynter NP, Eaton CB, Manson JE, Martin LW, Robinson JG, Rossouw JE, Wassertheil-Smoller S, Ridker PM. Comparison of the Framingham and Reynolds risk scores for global cardiovascular risk prediction in the multiethnic women's health initiative. *Circulation* 2012;**125**:1748.
18. Mortensen MB, Nordestgaard BG. Comparison of five major guidelines for statin use in primary prevention in a contemporary general population. *Ann Intern Med* 2018;**168**:85–92.
19. Simmonds MC, Wald NJ. Risk estimation versus screening performance: a comparison of six risk algorithms for cardiovascular disease. *J Med Screen* 2012;**19**:201–205.
20. Liu J, Hong Y, D'Agostino RB Sr, Wu Z, Wang W, Sun J, Wilson PW, Kannel WB, Zhao D. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA* 2004;**291**:2591–2599.
21. Danesh J, Erqou S, Walker M, Thompson SG, Tipping R, Ford C, Pressel S, Walldius G, Jungner I, Folsom AR, Chambless LE, Knuiman M, Whincup PH, Wannamethee SG, Morris RW, Willeit J, Kiechl S, Santer P, Mayr A, Wald N, Ebrahim S, Lawlor DA, Yarnell JW, Gallacher J, Casiglia E, Tikhonoff V, Nietert PJ, Sutherland SE, Bachman DL, Keil JE, Cushman M, Psaty BM, Tracy RP, Tybjaerg-Hansen A, Nordestgaard BG, Frikke-Schmidt R, Giampaoli S, Palmieri L, Panico S, Vanuzzo D, Pilotto L, Simons L, McCallum J, Friedlander Y, Fowkes FG, Lee AJ, Smith FB, Taylor J, Guralnik J, Phillips C, Wallace R, Blazer D, Khaw KT, Jansson JH, Donfrancesco C, Salomaa V, Harald K, Jousilahti P, Vartiainen E, Woodward M, D'Agostino RB, Wolf PA, Vasan RS, Pencina MJ, Bladbjerg EM, Jorgensen T, Moller L, Jespersen J, Dankner R, Chetrit A, Lubin F, Rosengren A, Wilhelmsen L, Lappas G, Eriksson H, Bjorkelund C, Cremer P, Nagel D, Tilvis R, Strandberg T, Rodriguez B, Bouter LM, Heine RJ, Dekker JM, Nijpels G, Stehouwer CD, Rimm E, Pai J, Sato S, Iso H, Kitamura A, Noda H, Goldbourt U, Salomaa V, Salonen JT, Nyyssonen K, Tuomainen TP, Deeg D, Poppelaars JL, Meade T, Cooper J, Hedblad B, Berglund G, Engstrom G, Doring A, Koenig W, Meisinger C, Mraz W, Kuller L, Selmer R, Tverdal A, Nystad W, Gillum R, Mussolino M, Hankinson S, Manson J, De SB, Knottenbelt C, Cooper JA, Bauer KA, Rosenberg RD, Sato S, Naito Y, Holme I, Nakagawa H, Miura H, Ducimetiere P, Jouven X, Crespo C, Garcia-Palmieri M, Amouyel P, Arveiler D, Evans A, Ferrieres J, Schulte H, Assmann G, Shepherd J, Packard C, Sattar N, Cantin B, Lamarche B, Despres JP, Dagenais GR, Barrett-Connor E, Wingard D, Bettencourt R, Gudnason V, Aspelund T, Sigurdsson G, Thorsson B, Trevisan M, Witteman J, Kardys I, Breteler M, Hofman A, Tunstall-Pedoe H, Tavendale R, Lowe GD, Ben-Shlomo Y, Howard BV, Zhang Y, Best L, Umans J, Onat A, Meade TW, Njolstad I, Mathiesen E, Lochen ML, Wilsgaard T, Gaziano JM, Stampfer M, Ridker P, Ulmer H, Diem G, Concin H, Rodeghiero F, Tosetto A, Brunner E, Shipley M, Buring J, Cobbe SM, Ford I, Robertson M, He Y, Ibanez AM, Feskens EJ, Kromhout D, Collins R, Di AE, Kaptoge S, Lewington S, Orfei L, Pennells L, Perry P, Ray K, Sarwar N, Scherman M, Thompson A, Watson S, Wensley F, White IR, Wood AM. The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. *Eur J Epidemiol* 2007;**22**:839–869.
22. Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, Freitag DF, Pennells L, Peters SA, Hart CL, Haheim LL, Gillum RF, Nordestgaard BG, Psaty BM, Yeap BB, Knuiman MW, Nietert PJ, Kauhanen J, Salonen JT, Kuller LH, Simons LA, van der Schouw YT, Barrett-Connor E, Selmer R, Crespo CJ, Rodriguez B, Verschuren WM, Salomaa V, Svardsudd K, van der Harst P, Bjorkelund C, Wilhelmsen L, Wallace RB, Brenner H, Amouyel P, Barr EL, Iso H, Onat A, Trevisan M, D'Agostino RB, Sr., Cooper C, Kavousi M, Welin L, Roussel R, Hu FB, Sato S, Davidson KW, Howard BV, Leening MJ, Rosengren A, Dorr M, Deeg DJ, Kiechl S, Stehouwer CD, Nissinen A, Giampaoli S, Donfrancesco C, Kromhout D, Price JF, Peters A, Meade TW, Casiglia E, Lawlor DA, Gallacher J, Nagel D, Franco OH, Assmann G, Dagenais GR, Jukema JW, Sundstrom J, Woodward M, Brunner EJ, Khaw KT, Wareham NJ, Whitsel EA, Njolstad I, Hedblad B, Wassertheil-Smoller S, Engstrom G, Rosamond WD, Selvin E, Sattar N, Thompson SG, Danesh J. Association of cardiometabolic multimorbidity with mortality. *JAMA* 2015;**314**:52–60.
23. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–387.
24. Pennells L, Kaptoge S, White IR, Thompson SG, Wood AM, Tipping RW, Folsom AR, Couper DJ, Ballantyne CM, Coresh J, Goya Wannamethee S, Morris RW, Kiechl S, Willeit J, Willeit P, Schett G, Ebrahim S, Lawlor DA, Yarnell JW, Gallacher J, Cushman M, Psaty BM, Tracy R, Tybjærg-Hansen A, Price JF, Lee AJ, McLachlan S, Khaw K-T, Wareham NJ, Brenner H, Schöttker B, Müller H, Jansson J-H, Wennberg P, Salomaa V, Harald K, Jousilahti P, Vartiainen E, Woodward M, D'Agostino RB, Bladbjerg E-M, Jørgensen T, Kiyohara Y, Arima H, Doi Y, Ninomiya T, Dekker JM, Nijpels G, Stehouwer CDA, Kauhanen J, Salonen JT, Meade TW, Cooper JA, Cushman M, Folsom AR, Psaty BM, Shea S, Döring A, Kuller LH, Grandits G, Gillum RF, Mussolino M, Rimm EB, Hankinson SE, Manson JE, Pai JK, Kirkland S, Shaffer JA, Shimbo D, Bakker SJL, Gansevoort RT, Hillege HL, Amouyel P, Arveiler D, Evans A, Ferrières J, Sattar N, Westendorp RG, Buckley BM, Cantin B, Lamarche B, Barrett-Connor E, Wingard DL, Bettencourt R, Gudnason V, Aspelund T, Sigurdsson G, Thorsson B, Kavousi M, Witteman JC, Hofman A, Franco OH, Howard BV, Zhang Y, Best L, Umans JG, Onat A, Sundström J, Michael Gaziano J, Stampfer M, Ridker PM, Michael Gaziano J, Ridker PM, Marmot M, Clarke R, Collins R, Fletcher A, Brunner E, Shipley M, Kivimäki M, Ridker PM, Buring J, Cook N, Ford I, Shepherd J, Cobbe SM, Robertson M, Walker M, Watson S, Alexander M, Butterworth AS, Angelantonio ED, Gao P, Haycock P, Kaptoge S, Pennells L, Thompson SG, Walker M, Watson S, White IR, Wood AM, Wormser D, Danesh J. Assessing risk prediction models using individual participant data from multiple studies. *Am J Epidemiol* 2014;**179**:621–632.
25. Parzen M, Lipsitz SR. A global goodness-of-fit statistic for Cox regression models. *Biometrics* 1999;**55**:580–584.
26. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;**388**:2532–2561.
27. Pencina MJ, D' Agostino RB, D' Agostino RB, 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**:157–172; discussion 207–12.
28. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;**286**:180–187.
29. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, Azizi F, Cifkova R, Di CM, Eriksen L, Farzadfar F, Ikeda N, Khalili D, Khang YH, Lanska V, Leon-Munoz L, Magliano D, Msyamboza KP, Oh K, Rodriguez-Artalejo F, Rojas-Martinez R, Shaw JE, Stevens GA, Tolstrup J, Zhou B, Salomon JA, Ezzati M, Danaei G. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol* 2015;**3**:339–355.

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018

30. Cook NR, Ridker PM. Calibration of the pooled cohort equations for atherosclerotic cardiovascular disease: an update. *Ann Intern Med* 2016;**165**: 786–794.
31. DeFilippis AP, Young R, Carrubba CJ, McEvoy JW, Budoff MJ, Blumenthal RS, Kronmal RA, McClelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;**162**:266–275.
32. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, Ikram MA, Stricker BH, Hofman A, Franco OH. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA* 2014;**311**:1416–1423.
33. Mortensen MB, Falk E, Limitations of the SCORE-guided European guidelines on cardiovascular disease prevention. *Eur Heart J* 2017;**38**:2259–2263.
34. Muntner P, Colantonio LD, Cushman M, Goff DC Jr, Howard G, Howard VJ, Kissela B, Levitan EB, Lloyd-Jones DM, Safford MM. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. *JAMA* 2014;**311**: 1406–1415.
35. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, Williams K, Neely B, Sniderman AD, Peterson ED. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med* 2014;**370**:1422–1431.
36. van Houwelingen HC. Validation, calibration, revision and combination of prognostic survival models. *Stat Med* 2000;**19**:3401–3415.
37. Psaty BM, Prentice RL. Variation in event rates in trials of patients with type 2 diabetes. *JAMA* 2009;**302**:1698–1700.
38. Usher-Smith JA, Silarova B, Schuit E, Moons GM, Griffin K. Impact of provision of cardiovascular disease risk estimates to healthcare professionals and patients: a systematic review. *BMJ Open* 2015;**5**:SJ.

Downloaded from https://academic.oup.com/eurheartj/advance-article-abstract/doi/10.1093/eurheartj/ehy653/5198769 by University of Leicester user on 06 December 2018